Review Article

Role of adjunct use of omega 3 fatty acids in periodontal therapy of periodontitis. A systematic review and meta-analysis

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ABSTRACT

Background: Host modulation therapy has emerged as a new concept for the treatment of periodontal disease. Recently, a lot of research is being done in product containing docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Omega-3 PUFA have therapeutic, anti-inflammatory and protective properties. This systematic review analysed the adjunctive use of omega-3 fatty acids in periodontal therapy of periodontitis patients.

Methods: PICO question (patient, intervention, comparison, and outcome) was formed. Keywords were generated and were fed in databases. The databases were Pubmed, Cochrane library and LIVIVO. Studies selected are Randomized clinical trial, clinical studies, and longitudinal studies. Meta-analysis were performed for Pocket depth (PD), Clinical attachment level (CAL), Gingival index (GI) and Plaque Index (PI). Risk of bias was also assessed.

Results: On analysis of all the 8 studies at 3 months showed significant effect of omega-3 fatty acid on clinical attachment level (CAL), Pocket depth (PD). There was significant effect of omega-3 fatty acids in 4 studies at 6 months.

Conclusion: Within the limitation of the review, omega-3 polyunsaturated fatty acids seems to have a positive effect on periodontal healing following periodontal therapy. Chronic periodontitis patient should be counselled to incorporate omega-3 fatty acid in their diet along with standard periodontal therapy.

1. Introduction

Periodontitis is a multifactorial disease. Periodontal inflammation causes tissue destruction, leading to tooth loss. Periodontitis is mainly caused by gram negative bacteria in the gingival sulcus which causes dysbiosis. This leads to activation of immune response resulting in a hyper inflammatory state against biofilm.¹

Regular removal of supra and sub gingival biofilm is crucial. Scaling and root planning is mechanical removal of biofilm and is still considered the gold standard.

Although plaque bacteria causes direct damage to the periodontal tissue. Most destructive events occurs from activation of destructive process as a part of host immune-inflammatory response to plaque bacteria.²

The host immune system is turned on by bacterial lipopolysaccharide (LPS), that leads to production of pro-inflammatory factors IL-1 β , IL-6, TNF, MMP. Moreover the inflammatory process modify the level of kappa- β nuclear actor receptor ligand, which is responsible for activation of osteoclast.³

Host modulating therapy means treating the host side of host-bacteria interaction. Host modulating therapy offers the opportunity for modulating or reducing this destruction by treating aspects of chronic inflammatory response. They involve NSAIDS, tetracycline, bisphosphonates. However they also have adverse effects. So the use of these medications is limited.^{4,5}

Recently polyunsaturated Ω -3 fatty acid is used as host modulating therapy in various chronic inflammatory diseases cardio vascular diseases and rheumatoid arthritis. Ω -3 fatty acids include DHA and EPA.

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They are essential fatty acids, as they are not synthesized in body and must be included in the diet.⁶ Current guidelines recommend a daily intake of 500 mg of EPA and DHA for people without cardiovascular disease, while those with a history of cardiovascular disorder should take 1 g of Ω -3 polyunsaturated fatty acid per day.⁷ Ω -3 fatty acids mechanism of action is attributed as EPA and DHA competes with arachadonic acid at two levels. First it gets integrate into cell membrane phospholipid, reducing the levels of AA-derived eicosanoid. Second by competing as substrate for COX and LOX pathway, leading to production of EPA and DHA derived eicosanoid. They are resolvins, protectins and maresins.⁸

These pro-resolution lipid mediators diminish the inflammatory process and minimizing tissue damage during inflammation and causing resolution of acute and chronic inflammation.⁹

Resolvins brings down neutrophil infiltration, inflates phagocyte removal of apoptotic neutrophil. Protectin inhibit T cell infiltration and increases their apoptosis. Maresins are synthesized by macrophages from DHA. They inhibit neutrophil recruitment and stimulate macrophage to scavenge apoptotic neutrophil.^{10,11, and 12}

In this paper we will review the role of Ω -3 fatty acid as an adjunct to periodontal therapy in treatment of Periodontitis along with meta - analysis.

2. Material and methods

2.1. Databases

The literature search for the present systematic review and meta-analysis was conducted using the following electronic databases and sources: Pubmed or medline (www.Pubmed.gov), Science –Direct (www.sciencedirect.com), Livivo (HYPERLINK "<http://www.livivo.de/>" \o "<http://www.livivo.de/>" "www.livivo.de"), Embase (www.Elsevier.com/online-tools/embase). A hand search was done in leading periodontal journal, followed by gray search (Fig. 1). The search was conducted till December 19, 2020.

The studies were assemble according to the search term were

analysed systematically. The studies were sorted according to inclusion and exclusion criteria.

Inclusion Criteria.

1. English language
2. Randomized, clinical Trial
3. Longitudinal Studies
4. Clinical Studies
5. Use of Omega-3 fatty acids in non-surgical and surgical periodontal therapy

Exclusion Criteria.

- 1) Absence of periodontitis
- 2) Gingivitis
- 3) Case-reports
- 4) Books

A search strategy was performed using the PICO model (patient, intervention, comparison, outcome) taking into consideration the following aspects: population/patient (patient), diagnostic/therapeutic procedure (intervention), comparison (comparison), and outcomes.

Consequently, the following search terms were defined: Patient: periodontitis or periodontal disease, Intervention: omega 3; fish oil; EPA; DHA, Comparison: placebo Outcomes: BOP; pocket depth; plaque.

2.2. Search results

Through database, 10 articles in pubmed and 7 articles in LIVIVO were found. In the chochrane library 5 articles were found. 3 articles were found by hand search. Abstract of the articles were analysed.

8 articles that were included are: N.M Elwakeel 2015,¹³ Hesham El-Sharkawy 2010¹⁴, Elkhoul AM 2011¹⁵, Nidia C Castro dos Santos 2020¹⁶, Mirella Stando 2020¹⁷, Girish D. Deore 2014¹⁸ Vanali Vinodbhai Umrana 2017¹⁹ and Rampally 2020²⁰ (Table 2).

The articles that were excluded were Naqvi et al.²¹ and Rosentein

Fig. 1. Systematic literature search in Pubmed, Cochrane library, Livivo and gray search.

Table 1
Filtering of the studies found according to the predetermined selection criteria.

studies	Clinical trial	RCT	periodontitis	Adjunctive Ω -3FS	Adjunctive aspirin	NSPT	Surgical Periodontal therapy	placebo	Probing depth	Clinical Attachment level	Gingival index	Plaque Index	IL-1 β
Elwakeel NM 2015	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	no	yes
El-Sharkawy 2010	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	no
Mirella stando 2020	yes	yes	yes	yes	no	yes	no	no	yes	yes	no	yes	no
Rampally 2019	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	no	no
Santos 2020	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	no	yes	no
Elkhouti AM 2011	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes
Vanali 2017	yes	yes	yes	yes	no	yes	no	no	yes	yes	yes	yes	yes
Umrانيا 2017	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes
Girish Deore 2014	yes	yes	yes	yes	no	yes	no	yes	yes	yes	yes	yes	no

Table 2

CAL compared at 3 months for all the 8 studies.

et²² because only oral hygiene instruction were provided, but any kind of periodontal therapy was not provided during the study. Study by Ahmad Zare Javid²³ was also excluded as only one clinical parameter was assessed that is pocket depth.

2.3. El Sharkawy 2010¹⁴

In this study, adjunctive treatment of chronic periodontitis with omega-3 fatty acid and low dose aspirin was investigated. There were two groups, 40 subjects in each. Control group received scaling and root planning and placebo. Test group received scaling and root planning along with 900 mg of omega 3 fatty acids and 81 mg of aspirin. Clinical parameters PI, GI, BOP, PD and CAL were measured at baseline, 3 months and 6 months. There was significant reduction in PD and CAL at 3 months and 6 months in test group compared to control group. With respect to PI and GI there was no significant difference between the two groups at 3 month and 6 month. Among bio chemical outcomes there was a statistically significant reduction in RANKL concentration in saliva in test group at 3 month and 6 month. However salivary MMP-8 levels were statistically lower in test group at 6 month compared to control group.

2.4. Girish D Deore 2014¹⁸

In this randomized double-blind, placebo – controlled clinical trial, effect of omega 3 fatty acids as a host modulator was evaluated in chronic periodontitis. There were two groups, 29 samples in each group. Control group was treated with scaling root planning and placebo. The treatment group was treated with scaling root planning and 300 mg of omega 3 fatty acids for 12 weeks. A significant reduction in the gingival index, pocket depth and Clinical attachment level was found in the treatment group compared to control at 12 weeks. In biochemical analysis of serum CRPs showed no statistically significant change between two groups at 12 weeks.

2.5. Santos 2020¹⁶

In this randomized clinical trial effect of omega 3 fatty acid and

aspirin as an adjunct to periodontal debridement in patients with periodontitis were evaluated. 75 patients were randomly assigned to three groups (25/group). CG received placebo and periodontal debridement. TG1 received 3 g of omega 3/day +100 mg of aspirin/day for 2 months after periodontal debridement. TG2 received 3 g of omega 3/day +100 mg of aspirin/day for 2 months before periodontal debridement. Periodontal parameters were collected at baseline, at 3 months and 6 months after debridement for CG and TG1. For TG2 parameters were collected before omega3 and aspirin therapy, after omega 3 and aspirin therapy/ before debridement and 6 months after debridement. Ten patients in TG1 and 9 patients in TG2 achieved clinical end point for treatment as opposed to 4 in CG. There was a clinical attachment gain in moderate and deep pockets for TG1.

2.6. Elwakeel NM 2015¹³

This randomized double blind placebo-controlled study investigated effect of omega 3 fatty acids plus low dose aspirin effect on clinical and biochemical profiles of patients with chronic periodontitis and type 2 diabetes 0.40 patients were randomly divided into two groups. Group 1 received omega –3 fatty acids (1 g three times a day) plus low dose aspirin (75 mg) followed by scaling root planing for 6 months and group 2 received placebo with scaling root planing for 6 months. Pocket depth, clinical attachment level, gingival index and plaque index, IL-1 β , monocyte chemo attractant protein –3 in GCF were investigated at baseline, 3 and 6 months after treatment. Pocket depth, clinical attachment level, gingival index and IL-1 β levels showed significant reduction in group 1 compared to group 2 after 3 and 6 months.

2.7. Stando 2020¹⁷

Effect of omega 3 fatty acids adjunct to nonsurgical treatment of periodontitis was evaluated in this randomized clinical trial. Test group (n = 16) patients were given 2.6 gm of EPA and 1.8 gm of DHA, along with scaling root planing. In the control group (n = 14), patients received only scaling root planing. There was statistically improvement in CAL at three months in the test group on intergroup comparison. Salivary samples of IL-1 β showed no difference between the two groups after 3 months.

2.8. Vanali Umrana 2017¹⁹

A randomized clinical trial evaluate the effect of omega 3 poly unsaturated fatty acids as an adjunct to scaling and root planning on clinical parameters PI, GI, PD, CAL and immunological parameters like IL-1 β after 3 months. Subjects were divided into two groups (20 patients each). Control patients received SRP alone, whereas test group received daily dose of 700 mg net fish oil (eicosapentanoic acid –180mg and docosahexanoic acid-120mg) with SRP. Improvements in clinical parameters were not statistically significant on intergroup comparison. However IL-1 β showed statistically reduction in test group.

2.9. Rampally 2019²⁰

In this study effectiveness of omega –3 fatty acid as adjuvants to nonsurgical periodontal therapy in Type II diabetic patients with chronic periodontitis was evaluated. Control patients (n = 14) received nonsurgical periodontal therapy along with placebo while test group (n = 14) received nonsurgical periodontal therapy with omega –3 fatty acid and clinical parameters recorded were GI, PPD, CAL. The intergroup comparison showed a significant improvement in pentraxin levels only.

2.10. Elkhoul AM 2011¹⁵

The efficacy of host response modulation therapy (omega –3 plus

low dose aspirin) as an adjunctive treatment of chronic periodontitis was evaluated in this study. 40 patients were randomly allocated in two groups. Experimental group received DFDBA and omega –3 PUFA combined with low dose aspirin while the control group received DFDBA with placebo. Clinical parameters that were monitored were GI, PPD, CAL and the biomarker assessed in GCF samples was interleukin –1B. There was statistically significant improvement in the clinical parameters and significant modulatory effect on the levels of IL-1B in the experimental group at 6 month.

2.11. Statistical analysis

Heterogeneity was assessed using Cochrane's Q and I² statistics. Constant continuity corrections of +1 were performed in case of no events in both test and control groups. Random-effect meta-analysis was performed using the Der Simonian-Laird estimator of variance. As sensitivity analysis, fixed-effect meta-analysis was performed using the Mantel-Haenszel method. SMD and 95% confidence intervals (95% CI) were calculated as effect estimates. Meta-analysis was performed using SPSS v 21.0 (IBM), Epi info v 7.1 (CDC, WHO), Medcalc v 12.5.0.0 (Osteend, Belgium), RevMan 5.4.1 & graph Pad Prism v. 6.1 & a few online available resources for measuring Heterogeneity & quality checks of individual articles, guidelines like Consort, PRISMA, QUOROM & MOOSE.

2.12. Outcome parameters

CAL, PD, PI and GI were recorded in all the 8 studies. Comparison was done for CAL, PD, PI and GI at 3 months and 6 months (Table 1). Study by Girish Deore 2014¹⁸ has recorded all the parameters at baseline and at 3 months after treatment in both the group. Vanali 2017¹⁹ has recorded all clinical parameters at baseline, 1 and 3 months. Elkhoul A. M 2011¹⁵ recorded all the clinical parameters and IL-1 β levels at baseline, 3 months and 6 months. In the study by El-Sharkawy 2010¹⁴ clinical assessment of PI, GI, PD and CAL was done at baseline, 3 months and 6 months. In study by Elwakeel N.M 2015¹³ GI, PD and CAL and immunological parameter IL-1 β was recorded at baseline, 3 months and 6 months, data of PI as not mentioned.

Clinical parameters CAL and PD and immunological parameters were measured at baseline, 3 months and 6 months by Castro dos Santos 2020¹⁶, however GI was not measured and PI was measured in percentage hence these two parameters were not analysed in this meta-analysis. There were three groups in study by Rampally 2019²⁰ group 1(NSPT + apirin), group 2 (NSPT+ Ω 3 fatty acids) and group 3 (NSPT + placebo). Clinical parameters GI, PD, CAL were recorded at baseline and 3 months. The parameters of group 1 were not included in the meta –analysis as there was no adjunctive use of Ω -3 fatty acids. Mirella Stando 2020¹⁷ recorded PD, CAL at baseline and at 3 months. PI was measured in percentage hence not included in meta-analysis and GI was not measured. IL-1 β assessment was done at baseline and at 3months.

Mirella Stando 2020¹⁷ recorded PD, CAL at baseline and at 3 months. PI was measured in percentage hence not included in meta-analysis and GI was not measured. IL-1 β assessment was done at baseline and at 3months.

2.13. Comparison of results

When CAL was compared at 3 months for all the 8 studies, only 3 studies have shown that SMD has crossed. The final SMD slightly favors experimental group (Table no2).

When CAL was compared at 6 months, for 4 studies El Sharkawy 2010¹⁴, Santos 2020¹⁶, Elkhoul 2011¹⁵, N.M Elwakeel 2015.¹³ One study have shown that SMD has crossed 0. The final SMD slightly favours experimental group (Table no3).

PPD was compared for all the 8 studies at 3 months, four studies have shown that SMD has crossed 0. The final SMD slightly favours

Table 3
CAL compared at 6 months for all the 4 studies.

experimental group (Table no 4).

PPD was compared at 6 months, for 4 studies El Sharkawy 2010¹⁴, Santos 2020,¹⁶ Elkhoully 2011¹⁵, N.M Elwakeel 2015.¹³ Rampally have shown that SMD has crossed 0. However the total random effects SMD obtained was -0.95 (95% -1.65 to -0.26). The final SMD slightly favours experimental group (Table no 5).

GI comparison at 3 and 6 months were non-conclusive (Tables 6 and 7). PI comparison at 3 and 6 months were also non-conclusive (table no 8, 9). IL -1 β comparison for two studies at 3 months favours experimental group but at 6 months is non-conclusive as there is high heterogeneity (Tables 10 and 11).

Table 4
PPD compared for all the 8 studies at 3 months.

Table 5
PPD compared at 6 months for all the 4 studies.

Table 6
GI compared at 3 months for all the 8 studies.

3. Risk of bias

Table 12 shows the risk of bias analysis. The bias those were considered selection bias, performance bias, attrition bias, detection bias, and reporting bias.

4. Discussion

The present systematic review and meta-analysis investigated the adjunctive role of omega 3 fatty acids in the periodontal therapy of periodontitis patient. On analysis of all the 8 studies at 3 months showed significant effect of omega 3 fatty acid on clinical parameters CAL and PPD and positive effect of omega-3 fatty acids in 4 studies at 6 months. This may be because of their anti-inflammatory effect.²⁴ Although there

Table 7
GI compared at 6 months for 3 studies.

Table 8
PI compared at 3 months for 6 studies.

Table 9
PI compared at 6 months for 2 studies.

Table 10
IL-1 β compared at 3 months for 2 studies.

Table 11
IL-1 β compared at 6 months for 2 studies.

was an overall positive effect, but study by Vanali 2017¹⁹ did not showed significant improvement on clinical parameters PI, GI, PD and CAL on intergroup comparison. Similarly Rampally in 2020²⁰, also reported no significant difference on intergroup comparison (Ω -3 and NSPT) and (placebo and NSPT). In study by Stando 2020¹⁷, there was no significant reduction in probing depth after 3 month on intergroup comparison, but there was statistically improvement in CAL in test group (Ω -3 and SRP) at 3 month on inter group comparison. On the contrary study by Girish D Deore¹⁸ GI, PD and CAL showed significant improvement in test group (Ω -3 and SRP) after 3 month. The molecular basis of anti-inflammatory effect of Ω -3 polyunsaturated fatty acid is by resolution of inflammatory pathway by inhibiting the production of nuclear transcription factors and cytokines.²⁵ EPA and DHA metabolizes into resolvins of the E and D series respectively. Hence there is reduction in pro-inflammatory cytokines like IL-8 and IL-6.²⁶

EL- Sharkawy 2010¹⁴ demonstrated, a significant reduction in probing depth and significant gain in Clinical attachment level in test group (SRP+ Ω -PUFA + aspirin) compared to control group (SRP + placebo) at 3 months and 6 months. Similar pattern was seen in Elwakeel NM 2015.¹³ There is a significant improvement in Probing depth, Clinical attachment level in test group (SRP + Ω -3 PUFA + Aspirin) compared to control group (SRP + placebo) after 3 months and 6 months. This clinical improvement is due to dietary supplementation with Ω -3 PUFA and Aspirin and is known to increase circulating levels of resolvins. This suggests a potential therapeutic benefit.

Elkhouli AM 2011¹⁵ reported improvement in Probing Depth reduction and CAL gain in test group (Ω -3 PUFA + DFDBA + Aspirin) compared to control group (DFDBA + placebo). This continual improvement of regenerative process around grafted material is due to helpful synergistic effect of Host Modulating agent and pro-resolving lipid mediators. These Pro-resolving lipid mediators shows powerful

Table 12
Risk of bias summary.

Elkhoul 2011	El Sharkawy 2010	Elwakeel NM 2015	Girish Deore 2014	Rampally 2018	Santos 2020	Shinde 2020	Vanali 2017
●	●	●	●	●	●	●	●
●	●	●	●	●	●	●	●
●	●	●	●	●	●	●	●
●	●	●	●	●	●	●	●
●	●	●	●	●	●	●	●
●	●	●	●	●	●	●	●
●	●	●	●	●	●	●	●

● High risk of bias
● Low risk bias

pro-resolution and anti-fibrotic activities to overcome the limitation of DFDBA which is fibrous tissue encapsulation.²⁷ The above three studies (EL- Sharkawy 2010¹⁴, Elwakeel NM 2015¹³, Elkhoul AM 2011¹⁵) demonstrated that the efficacy of dietary supplementation of Ω -3PUFA and aspirin in reducing alveolar bone resorption by reducing osteoclastic activity and tapering of gingival inflammation via their anti-inflammatory properties.²⁸ In EL-sharkawy 2010¹⁴ study there was no significant change in GI on inter group comparison at 3 months and 6 months. On the other hand Elkhoul¹⁵ there was reduction in mean gingival index and that were statistically significant in test group. Similar significant improvement was seen in GI in experimental group was seen in Elwakeel NM¹³ study at 6 months. In the above three studies Ω -3 PUFA was given in combination of aspirin. When administered together there is an enhanced anti-inflammatory effect by forming more robust resolvins and protectins.²⁹

In study by Rampally,²⁰ there was no significant difference in GI between test group and placebo group. Like wise in Vanali¹⁹ showed no improvement in GI on inter group comparisons. On contrast Girish Deore¹⁸ showed decrease in GI in test group compared to placebo. This difference could be due to bigger sample size in Girish Deore¹⁸ study compared to other two. In the above three studies solely Ω -3 PUFA was given.

In a review by Azzi et al.³⁰ determined the effect of omega – 3 ingestion on periodontal disease severity. The result of the review was there was no significant difference on the clinical severity of Periodontal disease, on comparison with control. However they reported a preventive effect of serum level of EPA and DHA on Periodontal disease progression.

A long term ingestion of Ω -3 PUFA is associated with a better periodontal condition. In a longitudinal study found that decrease intake of Ω -3 PUFA in diet is associated with greater intensity of periodontal disease.³¹ This study was supported by another study that patient who consumed DHA and EPA showed less prevalence of periodontitis.³² Cytokines produced by immune cell particularly interleukin. These cytokines promote lipogenesis and hyperlipidaemia, which contribute to cardiovascular disease and other inflammatory diseases including periodontal disease. Ω -3 PUFA reduces the level of these inflammatory cytokines.³³

In study by Elkhoul¹⁵ demonstrated significant reduction on IL-1 β levels following Ω -3 and aspirin at 6 months. Increased level of GCF IL-1 β is associated with variety of inflammatory disorder, particularly periodontitis. Hence down regulate of cytokines levels by concomitant administration of Ω -3 PUFA with low dose aspirin along with SRP, lead to significant improvement in periodontal condition. Similar phenomenon was seen in Elwakeel NM¹³ with significant reduction in GCF IL-1 β in experimental group after 6 months. Ω -3 PUFA causes resolution of inflammation, which is an active process. Process is mediated by

metabolism of arachidonic acid by lipooxygenase transformation circuit leading to production of lipoxins, a pro-resolution lipid mediator. These resolution pathways are intensified by the action of aspirin on COX-2.

As with other inflammatory diseases and condition, Ω -3 PUFA provide an appropriate, economical, safe health measure in modifying the course of inflammatory disease in susceptible individual. During the periodontal therapy the dental team can advise to incorporate dietary intake of omega 3 fatty acids after nutritional counselling.

5. Conclusion

Within the study limitations, role of adjunct use of omega-3 fatty acids appear to have a positive effect on periodontal wound healing with regard to reduction in CAL and PD.

Author contribution

Debopriya Chatterjee: Concepts, Design, Definition of intellectual content, Clinical studies, Experimental studies, Data analysis, Manuscript preparation, Manuscript editing, Manuscript review, Guarantor. Aishwarya Chatterjee: Concepts, Design, Definition of intellectual content, Literature search, Clinical studies, Experimental studies, Data acquisition, Data analysis, Manuscript preparation, Manuscript editing, Manuscript review, Guarantor. Dheeraj Kalra: Design, Definition of intellectual content, Clinical studies, Experimental studies, Data analysis, Statistical analysis, Manuscript editing, Manuscript review, Guarantor. Anjali Kapoor, Clinical studies, Experimental studies, Data analysis, Manuscript preparation, Manuscript editing, Manuscript review, Guarantor. Sharmistha Vijay, Clinical studies, Experimental studies, Data analysis, Manuscript preparation, Manuscript editing, Manuscript review, Guarantor. Saurabh Jain, Clinical studies, Experimental studies, Data analysis, Manuscript preparation, Manuscript editing, Manuscript review, Guarantor.

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