

Efficacy of Non-Surgical Therapy on IL-6 Levels In Patients with Chronic Periodontitis: A Systematic Review

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ABSTRACT

Chronic periodontitis-affected tissues have an increased production of pro-inflammatory cytokines relative to anti-inflammatory counterparts, including IL-6. Therefore, this systematic review aimed to synthesize and appraise the available literature to provide a comprehensive analysis of the efficacy of non-surgical therapy, specifically focusing on the therapeutic effect of IL-6 in patients with chronic periodontitis. This review focused on seven studies including 308 patients with moderate to severe chronic periodontitis across five different countries. The RoB assessment showed a moderate to low risk of bias studies. Moreover, the studies found a statistically significant decrease in IL-6 levels in patients after receiving non-surgical therapy. There were statistically significant alterations in periodontal indices and IL-6 levels over time, which showed the efficacy of non-surgical treatment based on various literature. Hence, decreasing IL-6 could serve as a therapeutic indicator of inflammatory response.

Keywords: Chronic Periodontitis, Immune Host-Response, Inflammatory Marker, IL-6, Non-Surgical Therapy

ABSTRAK

Pada jaringan dengan periodontitis kronis peningkatan kecepatan produksi sitokin pro inflamasi dibandingkan dengan sitokin anti-inflamasi termasuk IL-6. Penulisan ini bertujuan untuk mensintesis dan menilai penelitian-penelitian yang ada serta memberikan analisis secara komprehensif mengenai manfaat dari terapi non bedah, terutama efek terapeutik dari jumlah IL-6 pada pasien dengan periodontitis kronis. Tinjauan ini mencakup tujuh penelitian yang melibatkan 308 pasien dengan periodontitis kronis sedang hingga berat pada lima negara yang berbeda. Penilaian *RoB* menunjukkan risiko sedang hingga rendah dari studi bias. Semua studi menunjukkan penurunan signifikan secara statistik kadar IL-6 pada pasien yang telah mendapatkan terapi non bedah. Perubahan yang signifikan secara statistik pada indeks periodontal dan kadar IL-6 dari waktu ke waktu menyatakan kemanfaatan dari perawatan non bedah berdasarkan berbagai penelitian, sehingga menurunkan IL-6 dapat digunakan sebagai indikator terapeutik dari respon inflamasi.

Kata Kunci : Periodontitis Kronis, Respon Imun Inang, Petanda Peradangan, IL-6, Terapi Non Bedah



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1. Introduction

Periodontitis is a persistent inflammatory condition due to the presence of microbial plaque that induces inflammation in periodontal tissues and subsequent loss of alveolar bone. Without proper treatment, this condition elevates the tendency for tooth mobility and eventual loss [1]. Global epidemiological research has shown a significant occurrence of periodontitis in various countries, such as China, the United States, and the United Kingdom [2,3]. In addition to initial interventions, comprehensive resolution of local inflammatory stimuli and restoration of the standard morphology of periodontal soft and hard tissues often necessitate periodontal surgery [4]. Nevertheless, patients with severe periodontitis frequently face a series of expensive procedures, constituting a financial burden. Studies have shown that professional mechanical plaque removal, such as subgingival SRP debridement followed by periodontal endoscopy (PE), can produce favorable results [5]. Chronic periodontitis-affected tissues have an increased production of pro-inflammatory cytokines relative to anti-inflammatory counterparts. Studies have shown that reduced levels of anti-inflammatory cytokines play a crucial role in the continuation of gingival inflammation. Among multifunctional cytokines, Interleukin (IL) 6 plays a crucial role in mediating the host's response to tissue destruction and preventing infection [6]. Stimulated by various factors, including, parathormone, lipopolysaccharides (LPS), tumor necrosis factor (TNF), transforming growth factor β , 1,25-dihydroxyvitamin D₃, and Interleukin-1, IL-6 is generated by stromal cells and osteoblasts. Furthermore, it is released by diverse cell types such as macrophages, neutrophils, keratinocytes, fibroblasts, and endothelial cells [7]. Apart from its effects on hepatocytes and lymphocytes, IL-6 has diverse impacts frequently observed in chronic inflammatory diseases [8].

The initial phase of periodontal therapy includes the removal of supragingival biofilm by professionals, followed by managing established risk factors in periodontal disease [9,10]. For patients diagnosed with gingivitis, this therapeutic stage suffices to arrest gingival inflammation following the removal of accumulated biofilm. However, for patients diagnosed with periodontitis, the initial step is the elimination of subgingival calculus and biofilm. Subgingival instrumentation may include the use of adjunctive antimicrobials, either local or systemic or anti-inflammatory medications. Non-surgical periodontal therapy (NSPT) is a broad term referring to subgingival mechanical instrumentation conducted as a part of the second phase of treatment. Standard NSPT, such as scaling and root planing (SRP), is the gold-standard intervention for treating patients with Stage I-III periodontitis [11]. Specific sites or individuals may show suboptimal reactions to conventional NSPT, potentially related to microbial factors. In cases where this treatment approach is unsuccessful in shifting the dysbiosis infection process toward homeostatic factors, such as lingering subgingival biofilm after SRP, invasion of periodontopathic bacteria into tissue, or the continuation of a non-resolving chronic inflammatory response despite subgingival debridement, alternative factors may be implicated [12,13]. Continuous efforts are directed toward identifying non-surgical therapies capable of enhancing the efficacy of chronic periodontitis therapy. Therefore, this systematic review aimed to synthesize and appraise the available literature for providing a comprehensive analysis of the efficacy of non-surgical therapy studies, specifically focusing on the therapeutic effect of IL-6 levels in patients with chronic periodontitis.

2. Method and materials

2.1. Literature search strategy

The literature search was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines using Patient, Intervention, Control, Outcome (PICO) based keywords in five electronic databases, namely ProQuest, Cochrane, PubMed, Embase, and EBSCO. The search included the period from inception to December 20th, 2023. The keywords were arranged with various synonyms, including both text words and medical subject headings (MeSH Terms) for each PICO component, namely "Chronic Periodontitis", "Non-surgical Therapy", "Control", and "Interleukin 6 level."

2.2. Eligibility criteria

The inclusion criteria included (1) Study design: Randomized controlled trials and non-randomized interventional studies; (2) Language: English; (3) Population: Adult chronic periodontitis patients; (4) Intervention: Non-surgical therapy (oral hygiene, scaling and root planing, supragingival polishing, systemic antimicrobial medication); (5) Outcome parameter: Interleukin 6 levels. Meanwhile, the exclusion criteria included (1) No available data for extraction; (2) Irretrievable full-text articles; (3) Review articles; (4) Case reports; (5) Patients with immunodeficient or immunocompromised comorbidities; (6) Patients with a history of autoimmune disease; (7) Non-clinical trials (in vivo and in vitro studies).

2.3. *Screening and study selection*

The eligibility of search results underwent a two-step screening process. Initially, screening included the examination of article titles and abstracts. When eligible, the screening process continued to a full-text examination of the article meeting the criteria. Three reviewers (AB, CD, EF) independently conducted the screening, resolving any inconsistencies through consensus among all authors.

2.4. *Quality assessment and data extraction*

Three independent reviewers (AB, CD, EF) performed the literature search and data extraction with disagreements being resolved through discussion. The extracted data included: author and publication year, study design, study location, subject characteristics, type of non-surgical therapy, interleukin 6 level, and statistical results. The quality assessment of the studies included in the analysis was conducted by three independent reviewers (AB, CD, EF), and any discrepancies were resolved through consensus among all authors. ROBIN-1 tool was used to evaluate the perceived RoB in non-randomized studies, while Cochrane Risk of Bias 2.0 tool was used for assessing the randomized literature.

3. **Results**

3.1. *Literature search*

A literature search across four databases produced 926 articles. After removing duplicates, 829 articles were screened based on title and abstract. This screening process identified 45 full-text articles, which were further assessed for eligibility. Subsequently, 38 articles were excluded due to the unavailability of extractable data, and 7 were included for systematic review. Figure 1 presents the process of literature searching and screening.

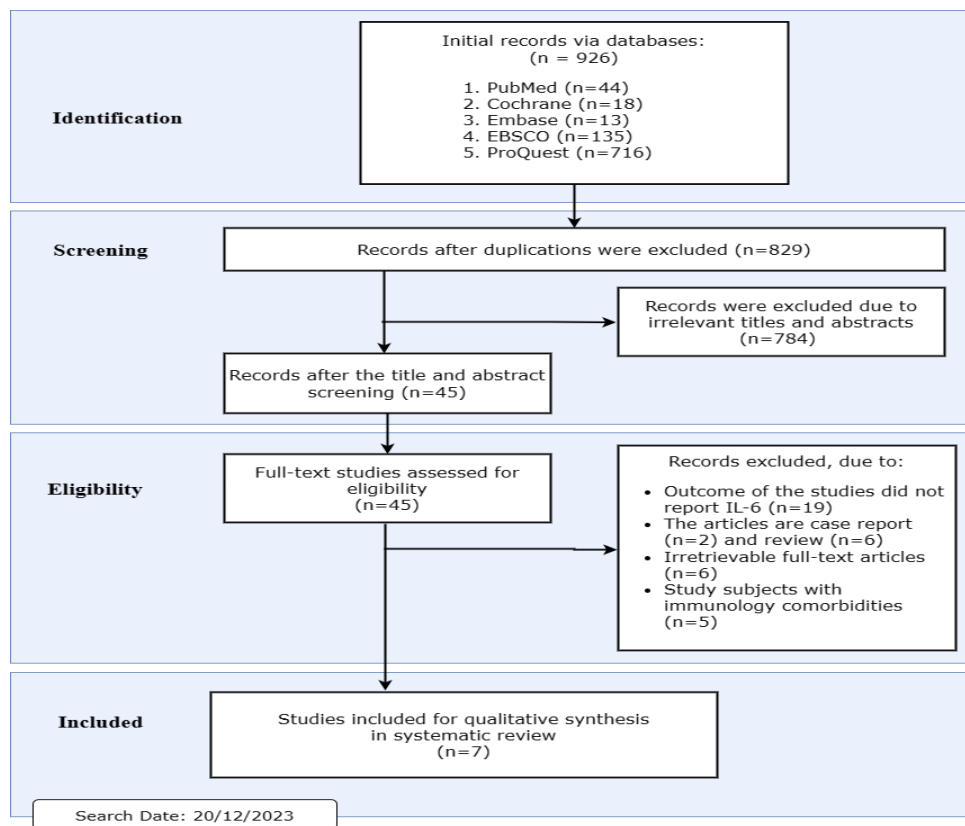


Figure 1. Literature searching and screening process

3.2. *Characteristics of included literature and risk of bias assessment*

This review included two randomized control trials and non-randomized literature published from 2010 to 2023. A total of 308 patients with moderate to severe chronic periodontitis from five different countries were included in this review. Tables 1 and 2 present the characteristics of the included literature. Risk of bias (RoB) examination showed moderate to low risk of bias literature, as presented in Tables 3 and 4.

Table 1.

Author & year	Study design	Study location	Total sample (n)	Groups		Participant characteristics
				Test (n, male/female)	Control (n, male/female)	
Erdemir et al (2010)[14]	NRCT	Turkey	23	23 (13/10)	23 (13/10)	Patients had moderate to severe periodontal disease, characterized by multiple sites with a probing depth of 5.0 mm or more, CAL (clinical attachment level) of 3.0 mm or more, and radiographic bone loss in at least two teeth per quadrant. Inclusion criteria specified the presence of teeth supporting a fixed partial denture on one posterior side of the maxilla, with natural teeth on the other posterior side. Patients were in good general health and no participant underwent periodontal therapy in the preceding three months, including root surface debridement or the adjunctive use of local or systemic antimicrobials. Samples were collected from two teeth with metal ceramic FPD and two contralateral teeth from each participant.
Luchesi et al (2013)[15]	RCT	Brazil	42	16 (n/a)	21 (n/a)	Patients were diagnosed with chronic periodontitis based on the 1999 AAP Classification, showing either buccal or lingual class II furcation with a PD of ≥ 5 mm and BOP.
Segarra-Vidal et al (2017)[16]	RCT	Spain	37	19 (5/14)	18 (5/13)	Patients with chronic generalized moderate to advanced periodontitis should have CAL of ≥ 3 mm, which is moderate (3-4 mm) and advanced (≥ 5 mm), and periodontal of at least 30%. Patients with healthy periodontal had CAL of < 1 mm.
Lobao et al (2019)[17]	NRCT	Brazil	62	33 (13/20)	29 (11/18)	Patients with at least two teeth, CAL of ≥ 6 mm, and PD of ≥ 5 mm in one or more sites.
Leite et al (2019) [18]	NRCT	Brazil	63	33 (13/20)	30 (12/18)	Patients with CAL of ≥ 6 mm and PD of ≥ 5 mm in one or more sites of BOP at the same site within 30 seconds after the removal of probe.
Lubis et al (2020) [19]	NRCT	Indonesia	21	7 (n/a)	14 (n/a)	Patients with a minimum of 10 teeth and pocket depth between 4 and 6 mm were included.
Khan et al (2023) [20]	NRCT	India	60	60 (n/a)	60 (n/a)	Severe periodontitis patients showed more than two interproximal sites with CAL of ≥ 6 mm, not on the same tooth, and the presence of more than one interproximal site with PD of ≥ 5 mm. Moderate periodontitis was defined as the presence of more than two interproximal sites with CAL of ≥ 4 mm occurring on two or more different teeth or more than two interproximal sites with PD of ≥ 5 mm, not on the same tooth.
Total			308	191	195	

Note: Std, standard deviation; n, number; M, male; F, female; FPD, fixed partial denture; mm, millimeter; s, seconds; RCT, randomized control trial; NRCT, non-randomized control trial.

Table 2. Characteristics of the included studies

Author, year	Patient group			Control group			Sample collections	Main findings
	Treatment	IL-6 (pg/μl)	Age (y, mean ± std)	Treatment	IL-6 (pg/μl)	Age (y, mean ± std)		
Erdemir et al (2010) [14]	PFM	Initial: 0.86 ± 1.21 1st mo: 0.99 ± 1.30 3rd mo: 0.57 ± 0.68	43.5 ± 7.22	No treatment (contralateral teeth)	Initial: 0.33 ± 0.19 1st mo: 0.37 ± 0.20 3rd mo: 0.53 ± 0.42	43.5 ± 7.22	GCF	The average total amount of Interleukin-6 showed a positive correlation only with the first month of Gingival Index values, with P<0.05.
Luchesi et al (2013) [15]	PDT +SRP	Initial: 1.24 ± 1.47 3rd mo: 0.52 ± 0.73 6th mo: 1.39 ± 1.97	50.75 ± 8.18	SRP	Initial: 1.95±2.70 3rd mo: 1.35±1.54 6th mo: 1.35±1.54	50.2± 10.89	GCF	Three months post-therapy, the PDT group showed a lower level of pro-inflammatory Interleukin-6 compared to the control group, with P<0.05.
Segarra-Vidal et al (2017) [16]	PDT +SRP	Initial: 3.40 ± 1.091 5th w: 3.20 ± 1.192 13th w: 3.17 ± 0.989 25th w: 3.00 ±1.082	55 ± 2	SRP	Initial: 3.118 ± 0.732 5th w: 2.703 ± 1.031 13th w: 2.922 ± 0.73 25th w: 2.666 ± 0.76	55 ± 2	GCF	Initially, Interleukin-6 levels in the periodontal disease group were higher than those in the control group (10.11 ± 5.94 pg/ml). Regardless of the treatment intervention, Interleukin-6 was elevated at the end of the treatment.
Lobao et al (2019) [17]	OHI	Initial: 1.597±0.858 3rd mo: 0.394±0.333 Δ = -1.202 ± 0.630	41.1 ± 7.8	Basic therapy	Initial: 1.458±0.518 3rd mo: 0.289 ± 0.113 Δ = -1.168 ± 0.547	39.6 ± 9.0	Serum	There was a significant decrease in Interleukin-6 levels in both groups after 90 days, with P values less than 0.001.
Leite et al (2019) [18]	SSRP +OHI	Initial: 1.60 ± 0.86 3rd mo: 0.39 ± 0.33 p<0.01	41.1 ± 7.8	SS	Initial: 1.46 ± 0.52 3rd mo: 0.29 ± 0.11 p<0.01	39.5 ± 8.9	GCF	The test group showed a statistically significant decrease in Interleukin-6 levels 90 days after scaling and root planing (P≤ 0.05)
Lubis et al (2020) [19]	SRP+ 1% Curcumin gel	Initial: 53.23 ± 0.23 1st w: 40.00 ± 0.04 % reduction: 14.96 ± 3.81	n/a	SRP	Initial: 53.00 ± 0.10 1st w: 47.31 ± 0.93 % reduction: 11.20 ± 2.28	n/a	GCF	The curcumin 1% gel group showed a statistically significant decrease in Interleukin-6 levels and a higher percentage reduction in CGF compared to the control group.
Khan et al (2023) [20]	SRP	Post-treatment 1st mo: 0.293±0.517	35.40 ± 5.22	No treatment	Pre-treatment: 0.578±0.826	35.40 ± 5.22	GCF	After scaling and root planing, the mean values of interleukin-6 showed a significant decrease following one month of treatment. The post-treatment group showed a statistically positive correlation between Interleukin-6, Gingival Index, Bleeding on Probing, and Probing Pocket Depth

Following SRP, mean values of IL-6 significantly decreased after one month of treatment. The post-treatment group showed a statistically modest positive relationship between IL-6 and GI, BOP, and PPD.

Note: std, standard deviation; n, number; y, years old; mo, month; PFM, porcelain fused to metal restoration; GCF, gingival crevicular fluid; GI, gingival index; SRP, scaling and root planing; PDT, photodynamic therapy; w, weeks; OHI, oral hygiene instruction; SSRP, sub-gingival and supra-gingival scaling, and root planing; SS, supra-gingival scaling; BOP, bleeding on probing; PPD, probing pocket depth.

Table 3. Risk of bias assessment of cohort study.

Item No.	Quality assessment criteria	Erdemir et al (2010)	Lobao et al (2019)	Leite et al (2019)	Lubis et al (2020)	Khan et al (2023)
1	Bias due to confounding	?	+	+	?	+
2	Bias in the selection of participants	+	+	+	+	+
3	Bias in the classification of intervention	?	+	+	?	+
4	Bias due to deviation from intended interventions	+	+	+	+	+
5	Bias due to missing data	+	+	+	+	+
6	Bias in measurement of outcomes	+	+	+	+	+
7	Bias in selection of the reported result	+	+	+	+	+
Study quality		Moderate	Low-risk	Low-risk	Moderate	Low-risk

Table 4. Risk of bias assessment of cross-sectional studies.

Item No.	Quality assessment criteria	Luchesi et al (2013)	Segarra-Vidal et al (2017)
1	Bias arising from the randomization process	+	+
2	Bias due to deviations from intended interventions	?	+
3	Bias due to missing outcome data	+	+
4	Bias in measurement of the outcome	+	+
5	Bias in selection of the reported result	+	+
Study quality		Some concerns	Low risk of bias

3.3. Study outcome

All studies showed a statistically significant decrease in IL-6 levels in patients after receiving non-surgical therapy [14–20]. Furthermore, a significant reduction in the amount of IL-6 occurred during the first three months and remained at the end of the treatment. Various types of non-surgical therapies were applied, namely porcelain fused to metal (PFM) restoration, oral hygiene instruction (OHI), supra-gingival scaling (SS), scaling and root planing (SRP), supra-gingival and sub-gingival scaling and root planing (SSRP), and photodynamic therapy (PDT). Some studies analyzed the therapeutic effect based on the correlation between diagnostic and prognostic biomarkers in periodontology, including probing pocket depth (PPD), bleeding on probing (BOP), and gingival index (GI) [14,17,20].

4. Discussion

The current review included three studies covering Asia, South America, and Europe, with a total of 308 patients and a female predominance. The mean age range was 30-55 years old, and all patients had moderate to severe chronic periodontitis with a standardized diagnosis protocol, showing the homogeneity of the recruited patients. Therefore, most of the included literature found a moderate to low risk of bias, showing a moderate study quality.

All studies consistently found a significant reduction in the amount of interleukin (IL) 6 during the first three months, which remained at the end of the treatment [14–20]. Prolonged follow-up showed the possibility of re-infection, which could dilute the systemic effect of periodontal therapy [20]. Erdemir et al examined the GCF contents, specifically IL-6 and IL-8, along with clinical parameters at the teeth supporting porcelain fused to metal (PFM) restorations and contralateral teeth in subjects. The effect of scaling and root planning (SRP) on IL-6 levels in GCF was evaluated as part of the treatment response in a group of chronic periodontitis patients who had not received any prior periodontal treatment [14]. Various combinations of non-surgical therapy were

found in the included studies. Luchesi et al. and Segarra-Vidal et al. combined the PDT and SRP treatments [15,16]. Furthermore, Lobao et al. and Leite et al. applied OHI therapy in the patient group and in combination with other therapies, specifically SSRP [17,18]. Others used only SRP as a test group [19,20], while studies before [15,16,19] classified SRP as the control. Lubis et al. showed the combination of 1% curcumin after SRP and the anti-inflammatory effect of curcumin as an adjunct therapy [19]. Regardless of these results, the limited number of samples should be considered.

5. Study limitations

The current study had several limitations due to the characteristics of the best currently available evidence. The literature included in this review used various statistical analyses, which might not be fully comparable to each other. Most of the literature were non-randomized with a limited number of samples, and showed variations in therapy. Therefore, further prospective and proper standardized studies with a relatively larger sample population are required to investigate the efficacy of non-surgical periodontal therapy (NSPT) on interleukin (IL) 6 levels in patients with chronic periodontitis and confirm the current findings.

6. Conclusion

In conclusion, statistically significant alterations in periodontal indices and Interleukin (IL) 6 levels showed the efficacy of non-surgical treatment based on various literature. Therefore, decreasing IL-6 could be used as a therapeutic indicator of inflammatory response.

7. Conflict of Interest

The authors declared no conflict of interest.

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