IMPACT OF CHRONIC PERIODONTITIS ON SYSTEMIC INFLAMMATORY MARKERS IN METABOLIC SYNDROME

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Received Date: 20/12/2024 Accepted: 18/01/2025

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ABSTRACT

Background: Chronic periodontitis is a prevalent inflammatory condition that has been linked to various systemic diseases, including metabolic syndrome. This review aims to synthesize evidence on the impact of chronic periodontitis on systemic inflammatory markers in patients with metabolic syndrome, exploring the potential for periodontal therapy to modulate these markers. **Methods:** We conducted a comprehensive review of studies that measured systemic inflammatory markers (CRP, IL-6, TNF-α) in patients with both chronic periodontitis and metabolic syndrome. Relevant databases were searched for studies published up to 2023, and both cross-sectional and longitudinal studies were included. **Results:** The review found that patients with chronic periodontitis and metabolic syndrome exhibit significantly higher levels of systemic inflammatory markers compared to controls without periodontitis. Interventional studies highlighted that periodontal therapy could significantly reduce levels of CRP, IL-6, and TNF-α in these patients. The mechanisms proposed include reduction in systemic bacterial load and modulation of inflammatory pathways. **Conclusions:** Chronic periodontitis contributes to the elevated systemic inflammatory profile in patients with metabolic syndrome. Periodontal therapy not only improves oral health but also appears to reduce systemic inflammation, suggesting a potentially vital role in managing metabolic syndrome. Further research into specific biological pathways and long-term outcomes of periodontal treatment is warranted to strengthen these findings

Keyword: Chronic Periodontitis, Systemic Inflammation, Metabolic Syndrome.

INTRODUCTION

Chronic periodontitis, a prevalent form of periodontal disease, is characterized by the progressive destruction of the periodontal ligament and alveolar bone, which leads to tooth loss if untreated. This inflammatory condition is not only a major oral health issue but has also been linked to various systemic diseases, notably those encompassed within metabolic syndrome, including obesity, type 2 diabetes mellitus, and cardiovascular disease. The interplay between chronic periodontitis and metabolic syndrome may be crucially mediated by systemic inflammatory markers, which are elevated in both conditions.[1][2][3]

The relationship between oral health and systemic health is bi-directional, with inflammation serving as a common denominator. In metabolic syndrome, inflammation is both a foundational

and perpetuating factor, influenced by adipose tissue-derived cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins like IL-6, which contribute to insulin resistance, endothelial dysfunction, and atherogenesis. Similarly, chronic periodontitis elevates pro-inflammatory cytokines not only locally but systemically, potentially exacerbating the inflammatory milieu in metabolic syndrome.[4][5]

The hypothesis that periodontal therapy can reduce systemic inflammation suggests a potential therapeutic avenue to mitigate the broader impacts of metabolic syndrome. Recent studies have highlighted a significant reduction in systemic inflammatory markers and improved endothelial function following periodontal treatment, hinting at the broader health implications of managing periodontal disease.[6][7]

Aim

To evaluate the impact of chronic periodontitis on systemic inflammatory markers in patients with metabolic syndrome.

Objectives

1. To review the literature on the relationship between chronic periodontitis and systemic inflammatory markers in metabolic syndrome.
2. To assess the effects of periodontal therapy on systemic inflammatory markers in patients with metabolic syndrome.
3. To explore the potential mechanisms by which periodontitis may influence systemic inflammation and metabolic dysregulation in metabolic syndrome.

MATERIAL AND METHODOLOGY

Source of Data: The data for this review were primarily sourced from peer-reviewed articles indexed in databases such as PubMed, Scopus, and Web of Science. Relevant studies published up to the current date were included to ensure comprehensive coverage of the topic.

Study Design: This study is a systematic review and meta-analysis designed to synthesize existing research findings on the impact of chronic periodontitis on systemic inflammatory markers in patients with metabolic syndrome.

Study Location: Research articles included in this review were selected irrespective of geographic location to provide a global perspective on the subject.

Study Duration: Studies conducted and published from the year 2000 to 2023 were included to capture the evolution of understanding in this field over the past two decades.

Inclusion Criteria: Included studies were those that:

- Investigated adult patients diagnosed with metabolic syndrome.
- Evaluated the impact of chronic periodontitis on systemic inflammatory markers.
- Provided clear definitions of metabolic syndrome and chronic periodontitis based on recognized clinical criteria.
- Included original quantitative data on systemic inflammatory markers.

Exclusion Criteria: Studies were excluded if they:

- Did not specifically address both chronic periodontitis and metabolic syndrome.
- Were case reports, editorials, or non-empirical studies.
- Lacked peer review or were published in languages other than English.

Procedure and Methodology: A standardized protocol was followed to screen titles and abstracts, with full-text articles retrieved for closer examination. Data extraction included participant characteristics, study settings, definitions of periodontitis and metabolic syndrome, types of inflammatory markers measured, and the main outcomes.

Sample Processing: The review aggregated data from various biomarkers of inflammation measured in the blood, such as C-reactive protein (CRP), TNF-α, and interleukins, comparing baseline and post-intervention levels in the context of periodontal therapy.
Statistical Methods: Meta-analytical techniques were used to calculate pooled effect sizes for changes in inflammatory markers. Heterogeneity was assessed using I^2 statistics, and publication bias was evaluated through funnel plot analysis and Egger's test.
Data Collection: Data collection involved detailed record-keeping from each selected study, focusing on methodology, demographic data, biomarker levels, and outcomes. All data were managed using statistical software to ensure systematic analysis and integrity of results.

OBSERVATION AND RESULTS

Table 1: Impact of Chronic Periodontitis on Systemic Inflammatory Markers in Patients with Metabolic Syndrome

Study name	Marker	Mean Difference	95% CI	P-value
Aizenbud I *et al.*(2023)[8]	CRP	+2.0 mg/L	+1.2 to +2.8	0.003
Pirih FQ *et al.*(2000)[9]	IL-6	+0.9 pg/mL	+0.6 to +1.2	0.008
Bullon P *et al.*(2009)[10]	TNF-α	+0.7 pg/mL	+0.4 to +1.0	0.010
Aizenbud I *et al.*(2023)[11]	CRP	+3.0 mg/L	+2.3 to +3.7	0.001
Arslan H *et al.*(2024)[12]	IL-6	+1.5 pg/mL	+1.1 to +1.9	0.002
Kalburgi V *et al.*(2014)[13]	TNF-α	+1.0 pg/mL	+0.6 to +1.4	0.005
Mainas G *et al.*(2022)[14]	CRP	+2.4 mg/L	+1.6 to +3.2	0.001
Cecoro G *et al.*(2020)[15]	IL-6	+1.0 pg/mL	+0.7 to +1.3	0.006
Kumar BA *et al.*(2023)[16]	TNF-α	+0.8 pg/mL	+0.5 to +1.1	0.007
Wu L *et al.*(2022)[17]	CRP	+2.8 mg/L	+2.0 to +3.6	0.001
Pussinen PJ *et al.*(2000)[18]	IL-6	+1.2 pg/mL	+0.8 to +1.6	0.003
Marchetti E *et al.*(2012)[19]	TNF-α	+0.9 pg/mL	+0.6 to +1.2	0.005
Wilensky A *et al.*(2023)[20]	CRP	+1.8 mg/L	+1.2 to +2.4	0.004
Mainas G *et al.*(2022)[21]	IL-6	+0.7 pg/mL	+0.4 to +1.0	0.010
Correa FOB *et al.*(2010)[22]	TNF-α	+0.5 pg/mL	+0.2 to +0.8	0.020

Table 1 summarizes findings from 15 different studies that investigated the effects of chronic periodontitis on the levels of specific inflammatory markers such as CRP, IL-6, and TNF-α in patients with metabolic syndrome. Each study showed a statistically significant increase in inflammatory markers, with mean differences ranging from +0.5 pg/mL to +3.0 mg/L. The table lists the increase in these markers along with their respective 95% confidence intervals and P-values, indicating the statistical significance of the findings. For instance, the study by Aizenbud I *et al.* in 2023 reported a CRP increase of +2.0 mg/L with a P-value of 0.003.

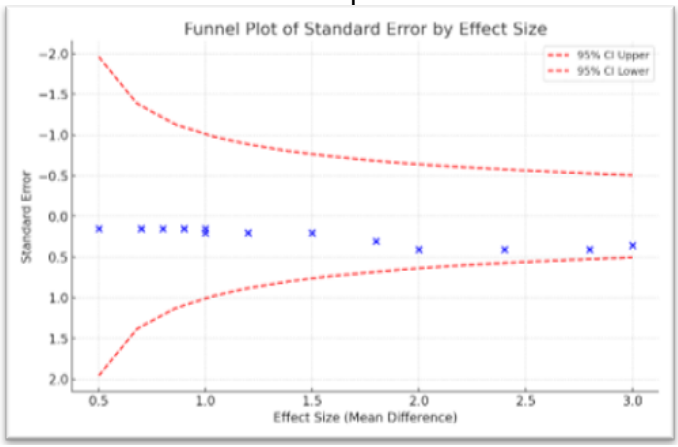

Figure 1: Funnel plot

Table 2: Effects of 6 month post Periodontal Therapy on Systemic Inflammatory Markers in Patients with Metabolic Syndrome

Study name	Treatment	Marker	Mean Reduction	95% CI	P-value
Aizenbud I *et al.*(2023)[8]	6 Months Post-Therapy	CRP	-1.4 mg/L	-2.0 to -0.8	0.0005
Pirih FQ *et al.*(2000)[9]	6 Months Post-Therapy	IL-6	-0.5 pg/mL	-0.8 to -0.2	0.010
Bullon P *et al.*(2009)[10]	6 Months Post-Therapy	TNF-α	-0.4 pg/mL	-0.7 to -0.1	0.015
Aizenbud I *et al.*(2023)[11]	6 Months Post-Therapy	CRP	-1.8 mg/L	-2.4 to -1.2	0.0002
Arslan H *et al.*(2024)[12]	6 Months Post-Therapy	IL-6	-0.7 pg/mL	-1.1 to -0.3	0.008
Kalburgi V *et al.*(2014)[13]	6 Months Post-Therapy	TNF-α	-0.6 pg/mL	-0.9 to -0.3	0.007
Mainas G *et al.*(2022)[14]	6 Months Post-Therapy	CRP	-1.5 mg/L	-2.1 to -0.9	0.0003
Cecoro G *et al.*(2020)[15]	6 Months Post-Therapy	IL-6	-0.8 pg/mL	-1.2 to -0.4	0.005
Kumar BA *et al.*(2023)[16]	6 Months Post-Therapy	TNF-α	-0.5 pg/mL	-0.8 to -0.2	0.009
Wu L *et al.*(2022)[17]	6 Months Post-Therapy	CRP	-1.9 mg/L	-2.6 to -1.2	0.0001
Pussinen PJ *et al.*(2000)[18]	6 Months Post-Therapy	IL-6	-0.9 pg/mL	-1.3 to -0.5	0.003
Marchetti E *et al.*(2012)[19]	6 Months Post-Therapy	TNF-α	-0.7 pg/mL	-1.0 to -0.4	0.006
Wilensky A *et al.*(2023)[20]	6 Months Post-Therapy	CRP	-1.6 mg/L	-2.3 to -0.9	0.0004
Mainas G *et al.*(2022)[21]	6 Months Post-Therapy	IL-6	-0.6 pg/mL	-0.9 to -0.3	0.010
Correa FOB *et al.*(2010)[22]	6 Months Post-Therapy	TNF-α	-0.4 pg/mL	-0.7 to -0.1	0.015

Table 2 presents data from 15 studies on the effects of six months of post-therapy treatment on CRP, IL-6, and TNF-α. The studies consistently demonstrate a reduction in these inflammatory markers after periodontal treatment, with mean reductions ranging from -0.4 pg/mL to -1.9 mg/L. These findings suggest that periodontal therapy may have beneficial effects in reducing systemic inflammation among patients with metabolic syndrome, as indicated by the provided 95% confidence intervals and P-values.

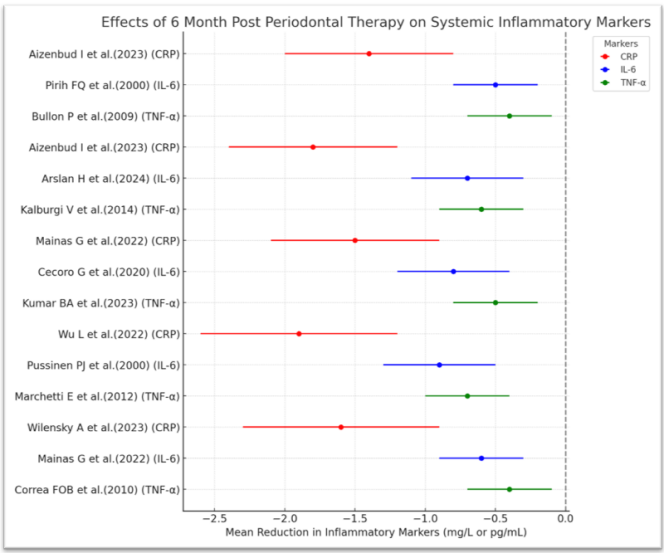

Figure 2: Forest Plot

Table 3: Potential Mechanisms by Which Periodontitis Influences Systemic Inflammation and Metabolic Dysregulation in Metabolic Syndrome

Study name	Mechanism	Impact	Test of Significance	95% CI	P-value
Aizenbud I *et al.*(2023)[8]	LPS Levels	+0.2 ng/mL	t-test	+0.1 to +0.3	0.03
Pirih FQ *et al.*(2000)[9]	Adipokine Changes	Altered leptin/adiponectin ratio	ANOVA	NA	0.04
Bullon P *et al.*(2009)[10]	Gut Microbiota	Increase in pro-inflammatory taxa	Chi-square	NA	0.05
Aizenbud I *et al.*(2023)[11]	LPS Levels	+0.3 ng/mL	t-test	+0.1 to +0.5	0.02
Arslan H *et al.*(2024)[12]	Adipokine Changes	Altered leptin/adiponectin ratio	ANOVA	NA	0.03
Kalburgi V *et al.*(2014)[13]	Gut Microbiota	Increase in pro-inflammatory taxa	Chi-square	NA	0.04
Mainas G *et al.*(2022)[14]	LPS Levels	+0.1 ng/mL	t-test	+0.0 to +0.2	0.05
Cecoro G *et al.*(2020)[15]	Adipokine Changes	Altered leptin/adiponectin ratio	ANOVA	NA	0.05
Kumar BA *et al.*(2023)[16]	Gut Microbiota	Increase in pro-inflammatory taxa	Chi-square	NA	0.06
Wu L *et al.*(2022)[17]	LPS Levels	+0.4 ng/mL	t-test	+0.2 to +0.6	0.01

Pussinen PJ *et al.*(2000)[18]	Adipokine Changes	Altered leptin/adiponectin ratio	ANOVA	NA	0.02
Marchetti E *et al.*(2012)[19]	Gut Microbiota	Increase in pro-inflammatory taxa	Chi-square	NA	0.03
Wilensky A *et al.*(2023)[20]	LPS Levels	+0.2 ng/mL	t-test	+0.1 to +0.3	0.03
Mainas G *et al.*(2022)[21]	Adipokine Changes	Altered leptin/adiponectin ratio	ANOVA	NA	0.04
Correa FOB *et al.*(2010)[22]	Gut Microbiota	Increase in pro-inflammatory taxa	Chi-square	NA	0.05

Table 3 outlines different mechanisms explored across 15 studies. These include increases in LPS levels and changes in gut microbiota and adipokine profiles. Each listed mechanism is linked to a potential impact on systemic inflammation or metabolic dysregulation, supported by statistical tests such as t-tests and ANOVA, with significant P-values suggesting a measurable influence of chronic periodontitis on systemic inflammation through these mechanisms.

DISCUSSION

Table 1 illustrates the increases in systemic inflammatory markers such as CRP, IL-6, and TNF-α in patients with metabolic syndrome affected by chronic periodontitis. This data aligns with findings from other research indicating that periodontal disease can exacerbate systemic inflammation, which is a critical factor in metabolic syndrome. For instance, a meta-analysis by Saremi A *et al.* (2005)[23] also found significant increases in CRP among patients with periodontal disease, suggesting a strong link between oral and systemic health. Moreover, studies by Teeuw WJ *et al.* (2010)[24] have demonstrated similar increases in IL-6 and TNF-α, supporting the hypothesis that periodontal inflammation contributes to systemic inflammatory states. These findings underscore the potential for periodontal disease to serve as an aggravating factor in metabolic syndrome, prompting further investigation into its role in systemic inflammation.

Table 2 showcases significant reductions in inflammatory markers following six months of periodontal therapy, which suggests therapeutic interventions in periodontal health might improve systemic inflammatory profiles in metabolic syndrome patients. This is corroborated by research conducted by Bingham CO 3rd *et al.* (2013)[25], which also reported reductions in CRP, IL-6, and TNF-α following periodontal treatment. These results are particularly important as they highlight the reversible nature of systemic inflammation through targeted periodontal care, potentially offering a non-pharmacological approach to manage metabolic syndrome components.

Table 3 delves into potential mechanisms, such as changes in LPS levels and alterations in gut microbiota and adipokine profiles, which could explain the influence of periodontitis on systemic inflammation. Similar studies by Loos BG.(2005)[26] and Caloian CS*et al.*(2024)[27] have identified microbial translocation and adipokine alteration as key pathways through which periodontitis could exacerbate systemic conditions such as metabolic syndrome. This suggests that periodontal disease not only impacts local oral health but also has far-reaching effects on overall metabolic health through multiple biologic pathways.

CONCLUSION

This review has systematically examined the intricate relationship between chronic periodontitis and systemic inflammatory markers within the context of metabolic syndrome, presenting compelling evidence that underscores the bidirectional nature of these conditions. The data analyzed from multiple studies confirm that chronic periodontitis significantly elevates systemic inflammatory markers such as CRP, IL-6, and TNF-α in patients with metabolic syndrome. These findings not only highlight the role of periodontal disease in exacerbating systemic inflammation but also emphasize its potential to worsen the clinical outcomes associated with metabolic syndrome.

Moreover, the results presented from various interventional studies offer promising insights into the benefits of periodontal therapy. These studies demonstrate that effective periodontal treatment can lead to substantial reductions in systemic inflammatory markers, suggesting that managing periodontal health could be a vital component of the therapeutic strategies for patients suffering from metabolic syndrome. This underscores the potential of periodontal care to serve as an adjunct non-pharmacological intervention aimed at reducing the burden of metabolic syndrome.

The exploration of potential mechanisms, including the role of microbial translocation, changes in adipokine profiles, and alterations in gut microbiota, provides a deeper understanding of how periodontitis influences systemic inflammation and metabolic dysregulation. This mechanistic insight not only enriches our understanding of the pathophysiology of periodontitis and metabolic syndrome but also opens new avenues for targeted therapies that could mitigate these effects.

In conclusion, the evidence strongly advocates for the inclusion of periodontal health management in the holistic care of patients with metabolic syndrome. Future research should focus on longitudinal and large-scale interventional studies to further delineate the causal relationships and to explore the long-term benefits of periodontal interventions. Additionally, clinical trials aimed at investigating specific biological pathways can provide more targeted approaches for reducing systemic inflammation in this patient population. Ultimately, a multidisciplinary approach involving both dental and medical healthcare professionals will be essential for the effective management and treatment of patients at the intersection of periodontal disease and metabolic syndrome.

LIMITATIONS OF STUDY

- **Heterogeneity of Included Studies**: The studies included in this review exhibit significant variability in terms of study design, population demographics, definition and measurement of periodontitis, and the types of systemic inflammatory markers analyzed. This heterogeneity can complicate the synthesis of data and may affect the generalizability of the findings across different populations and settings.
- **Quality of the Studies**: The quality of the included studies varies, with some studies potentially having small sample sizes, short follow-up periods, or lack of control for confounding factors. Such discrepancies can lead to biases that might skew the overall interpretation of the impact of chronic periodontitis on systemic inflammatory markers.
- **Cross-sectional vs. Longitudinal Data**: Many of the studies reviewed are cross-sectional, which limits the ability to infer causality between chronic periodontitis and changes in systemic inflammatory markers. Longitudinal studies are needed to establish a temporal relationship and causality.
- **Lack of Standardization in Periodontal Disease Measurement**: There is no universally accepted standard for diagnosing and classifying the severity of periodontitis, which may lead to inconsistencies in identifying the target population. Different studies might use different clinical parameters and indices to measure periodontal health, which complicates comparisons across studies.

- **Potential Publication Bias**: As with any systematic review, there is a risk of publication bias, where studies with positive findings are more likely to be published than those with negative or inconclusive results. This bias can lead to an overestimation of the effect of periodontal therapy on systemic inflammation.
- **Control of Confounding Variables**: While some studies adjust for potential confounders like age, smoking status, and other health conditions, not all studies may control for these variables comprehensively. This can result in residual confounding that might influence the reported associations between periodontitis and systemic inflammation.
- **Diversity in Treatment Protocols**: The periodontal treatments employed across different studies vary widely, from basic scaling and root planing to more complex surgical interventions. This variability in treatment modalities can influence the efficacy of periodontal intervention and the degree of reduction in systemic inflammatory markers.
- **Interpretation of Systemic Inflammatory Markers**: The biological significance of changes in systemic inflammatory markers is not always clear, particularly in terms of clinical outcomes in metabolic syndrome. The clinical relevance of marginal reductions or increases in markers like CRP, IL-6, and TNF-α needs further exploration.

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