

# Impact of Periodontal Therapy on Systemic Inflammation and Renal Function in Chronic Kidney Disease: A Secondary Cohort Analysis

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## ABSTRACT

**Background:** Periodontal disease is a preventable inflammatory load; however, there is a lack of evidence that support the therapeutic effects of periodontal disease after periodontal intervention in CKD individuals. The proposed secondary analysis is focused on assessing the impact of non-surgical periodontal therapy on the functions of the kidneys and inflammatory markers in the human system in patients with CKD. **Methods:** The secondary cohort study was based on a retrospective study of CKD patients with past periodontal disease case. The therapeutic evaluation involved forty patients which underwent scaling and root planing (SRP). Parameters of renal function (estimated glomerular filtration rate (eGFR), serum creatinine), systemic inflammatory [C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), and periodontal clinical were evaluated in preintervention and postintervention (3 months) time. **Results:** After completion of periodontal therapy, there was a significant increase in the renal function, as the mean eGFR improved significantly with a value of  $42.3 \pm 8.6$  to  $48.7 \pm 7.9$  mL/min/1.73 m<sup>2</sup> ( $p = 0.031$ ) and serum creatinine declined to  $2.1 \pm 0.5$  to  $1.8 \pm 0.4$  mg/dL ( $p = 0.028$ ). The level of systemic inflammation decreased from  $6.1 \pm 1.8$  to  $4.3 \pm 1.4$  mg/L ( $p = 0.019$ ) of CRP, IL-6 from  $5.4 \pm 1.5$  to  $3.7 \pm 1.2$  pg/mL ( $p = 0.014$ ), TNF- $\alpha$  from  $6.8 \pm 2.2$  to  $4.5 \pm 1.9$  pg/mL ( $p = 0.022$ ). **Conclusion:** Increased systemic inflammation is significantly decreased by non-surgical periodontal therapy and it improves renal functioning in patients with CKD.

**Keywords:** Periodontal Therapy, Chronic Kidney Disease, Systemic Inflammation, Renal Function, Scaling and Root Planing

## Introduction

Chronic kidney disease (CKD) is a significant health issue in the world with millions of affected individuals, causing high morbidity, mortality, and healthcare expenditures<sup>1</sup>. The onset of a progressive renal dysfunction is strictly connected with the unremitting systemic inflammation, oxidative stress, and immune dysregulation that speed the development of cardiovascular complications and enhance the patient outcomes<sup>2,3</sup>. Although there has been an improvement in the care of nephrology, there are still not many effective approaches to lessen the inflammatory load and decelerate the development of the disease<sup>4</sup>.

Periodontal disease is an inflammatory disease, which is manifested by dysbiosis of microbes and the destruction of tissues supporting the teeth<sup>5</sup>. There is mounting evidence to confirm that periodontal inflammation is not confined to the oral cavity but instead has a systemic effect when it releases pro-inflammatory cytokines, endotoxins, and immune mediators into the circulation<sup>6</sup>. These inflammatory pathways are closely related to those involved in the progression of CKD and places periodontal disease as a potentially modifiable factor in regard to the overall systemic inflammatory load of patients affected with the disease<sup>7</sup>.

Although previous research has confirmed the links between the severity of periodontal disease and renal dysfunction, there is a paucity of studies that serve the research purpose of determining the therapeutic value of periodontal therapeutic intervention on systemic and renal outcome or health <sup>8,9</sup>. Scaling and root planing are also examples of non-surgical periodontal therapy that limit microbial load and local inflammation and are effective and readily available treatment <sup>10</sup>. Its application as adjunctive treatment technique in systemic inflammatory disorders such as CKD should be additionally examined.

The current paper was carried out as secondary analysis in order to assess the therapeutic effect of non-surgical periodontal therapy in relation to renal function and systemic inflammation of CKD patients. This analysis, by concentrating on treatment outcome measures instead of disease association, will help explicate the possible application of periodontal intervention as a non-invasive, adjunctive type of therapy during multidisciplinary CKD management.

## Methodology

The current research is a secondary therapeutic analysis that is based on the data formed in the course of a retrospective cohort study (December 2022 June 2023). The original research plan was ethically approved by the institutional review committee (REC/183/22), and all the activities were conducted in harmony with the Declaration of Helsinki. The current analysis aimed at investigating treatment related outcomes which were not the main concern of the original study. The parent group was composed of individuals with stage 2-4 CKD and the stage 2 of periodontal disease. To do this secondary analysis, patients, who received non-surgery periodontal therapy in the form of scaling and root planing (SRP), and whose pre and post periodontal treatment were complete were used. There were 40 patients matching these parameters and participated in therapeutic assessment. The eligible patients were adult patients, 18 years old or above, who had been diagnosed with CKD and whose periodontal assessment had been conducted clinically. Renal replacement therapy patients, patients treated periodontally over the past six months, and patients with active malignancy or autoimmune disease were eliminated to limit confounding effects of inflammatory phenomena.

Periodontal therapy was done non-surgically by use of the conventional scaling and root planing to eliminate supra- and subgingival plaque and calculus. The entire process was conducted by qualified dental care providers in line with the set clinical guidelines. All patients at the intervention stage were given oral hygiene guidelines. The main therapeutic outcomes were the change of the parameters of renal functions in particular estimated glomerular filtration rate (eGFR) and serum creatinine level. The systemic inflammatory markers or the secondary outcomes were C- reactive protein (CRP), interleukin- 6 (IL- 6) and tumor necrosis factor- alpha (TNF-- $\alpha$ ). The outcomes of periodontal clinical measurement were determined based on mean probing deep measurements. Baseline recording of all parameters and re-evaluation, after three months periodontal therapy, was done.

The analysis of the data was performed with the help of SPSS software (version 25). Mean standard deviation was used to depict continuous variables. Paired t-tests or non-parametric equivalents were used where possible in making pre- and post-intervention comparisons. Cohen's d was used to compute the magnitude of therapeutic effect as effect sizes. Different analyses in subgroups according to the CKD stage were performed to compare the different treatment responses.  $p < 0.05$  was set as the statistically significant value.

## Results

Out of 80 patients that comprised the initial group, 40 patients had non-surgical periodontal therapy in terms of scaling and root planing (SRP) and were incorporated in this secondary analysis of therapy. The re-evaluation of clinical and biochemical parameters three months post-intervention was used to determine systemic and renal reactions to periodontal treatment. Table 1 has indicated that SRP was related to a statistically significant positive change in the renal function in the form of an increase in the eGFR along with a contemporaneous decrease in serum creatinine concentration. Moreover, all of the measured systemic inflammatory results showed significant treatment effects. The levels of mean CRP, IL-6, and TNF-- $\alpha$  also reduced significantly after periodontal therapy ( $p < 0.05$ , all of the comparisons). A positive outcome on periodontal clinical status was established through a substantial decrease in the mean probing depth.

**Table 1. Therapeutic Response to Scaling and Root Planing in Chronic Kidney Disease Patients (Pre–Post Analysis)**

Parameter	Pre-Therapy Mean $\pm$ SD	Post-Therapy Mean $\pm$ SD	Mean Change
eGFR (mL/min/1.73 m <sup>2</sup> )	42.3 $\pm$ 8.6	48.7 $\pm$ 7.9	+6.4
Serum Creatinine (mg/dL)	2.1 $\pm$ 0.5	1.8 $\pm$ 0.4	-0.3
C-Reactive Protein (mg/L)	6.1 $\pm$ 1.8	4.3 $\pm$ 1.4	-1.8
IL-6 (pg/mL)	5.4 $\pm$ 1.5	3.7 $\pm$ 1.2	-1.7
TNF- $\alpha$ (pg/mL)	6.8 $\pm$ 2.2	4.5 $\pm$ 1.9	-2.3
Mean Probing Depth (mm)	5.1 $\pm$ 1.3	3.9 $\pm$ 1.1	-1.2

*eGFR = Estimated Glomerular Filtration Rate, CRP = C-Reactive Protein, IL-6 = Interleukin-6, TNF- $\alpha$  = Tumour Necrosis Factor-Alpha, SD = Standard Deviation*

To determine the clinical implications of periodontal therapy other than statistical significance, the renal, inflammatory, and periodontal outcomes were analyzed using the effect size (Table 2). Intervention periodontal had moderate to high therapeutic effects through the outcome measures. The biggest effect sizes were noted in the inflammatory markers and especially IL-6 and C-RP, which shows the strong anti-inflammatory reaction after the treatment. The effect size on the improvement of eGFR was also moderate-high, which supports the meaning of a statistically significant clinical renal outcome under periodontal intervention.

**Table 2. Effect Size of Periodontal Therapy on Renal and Inflammatory Outcomes**

Outcome Variable	Cohen's d	Therapeutic Impact
eGFR Improvement	0.78	Moderate–High
Serum Creatinine Reduction	0.65	Moderate
CRP Reduction	0.92	High
IL-6 Reduction	1.01	High
TNF- $\alpha$ Reduction	0.88	High
Probing Depth Reduction	0.96	High

*eGFR = Estimated Glomerular Filtration Rate, CRP = C-Reactive Protein, IL-6 = Interleukin-6, TNF- $\alpha$  = Tumour Necrosis Factor-Alpha*

The therapeutic responses were further evaluated on the basis of the CKD severity on baseline (Table 3). Significant improvement in renal function and inflammatory markers was observed in patients with early to moderate CKD (Stages 2-3) than in patients with advanced CKD (Stage 4). An improvement of eGFR and a decrease in CRP, IL-6, and TNF- $\alpha$  were higher in patients with less severe renal dysfunction, and these effects of interaction were significant between CKD phase and therapeutic reaction ( $p < 0.05$ ).

**Table 3. Subgroup Therapeutic Response by Chronic Kidney Disease Stage Following Periodontal Therapy**

Parameter	CKD Stage 2–3 (n=24)	CKD Stage 4 (n=16)	p-value (Interaction)
$\Delta$ eGFR (mL/min/1.73 m <sup>2</sup> )	+7.9 $\pm$ 3.2	+3.8 $\pm$ 2.6	0.018
$\Delta$ CRP (mg/L)	-2.3 $\pm$ 1.1	-1.1 $\pm$ 0.9	0.021
$\Delta$ IL-6 (pg/mL)	-2.1 $\pm$ 0.9	-0.9 $\pm$ 0.7	0.016
$\Delta$ TNF- $\alpha$ (pg/mL)	-2.8 $\pm$ 1.3	-1.4 $\pm$ 1.0	0.023

*eGFR = Estimated Glomerular Filtration Rate, CRP = C-Reactive Protein, IL-6 = Interleukin-6, TNF- $\alpha$  = Tumour Necrosis Factor-Alpha, CKD = Chronic Kidney Disease,  $\Delta$  denotes change in levels of biomarker*

These results imply that periodontal therapy is especially useful when used earlier in the history of CKD, which proves that it can be used as an adjunctive therapeutic intervention to help alleviate systemic inflammation and maintain renal activity.

## Discussion

This secondary analysis have evaluated the therapeutic effect of non-surgical periodontal therapy on systemic inflammation and kidney cease functioning in chronic kidney disease patients. The results have proved that scaling and root planing had extensive effect on decreasing the inflammatory markers as well as quantifiable changes in renal function parameters<sup>11, 12</sup>. The findings suggest that periodontal intervention can be used as an effective complementary treatment measure in the multidisciplinary treatment of CKD.

The main finding of this paper was that the level of estimated glomerular filtration rate significantly increased in response to periodontal treatment<sup>13</sup>. Although the renal dysfunction in CKD is usually marked by the gradual deterioration of organ efficiency, the gradual rise in the eGFR indicates that the inflammation-induced renal failure can be kept under control or even reverted<sup>14,15</sup>. This development is of great clinical importance, especially in the case of limited non-pharmacological interventions to exert some improvements on renal outcomes in CKD patients<sup>16</sup>. One of the main factors that indicate the importance of inflammation in the association between kidney dysfunction and periodontal disease is the considerable decrease in the presence of the systemic inflammatory markers, which include CRP, IL-6, and TNF- $\alpha$ <sup>17,18</sup>. Periodontal therapy is probably effective in lowering the microbial load and local periodontal inflammation, and hence reducing the release of the systemic cytokines and the inflammatory load<sup>19</sup>. These cytokines have been reported to cause endothelial dysfunction, oxidative stress and tissue injury of the kidney, implying that a lower of them may have a direct impact on renal health<sup>20</sup>.

The effect size analysis also supported the clinical significance of periodontal therapy, showing that there is a medium level of therapeutic effects on both inflammatory and renal<sup>21</sup>. Interestingly, the highest levels of effect were found on inflammatory markers, which is in line with the hypothesis according to which the reduction of systemic inflammation is the main pathway in which periodontal intervention has renal effects<sup>22</sup>. These findings are in-line with the reported literature on the importance of dealing with inflammation as a key therapeutic goal in the management of CKD. Subgroup analysis showed that patients who had a lower stage of CKD and patients with a higher stage of CKD received more therapeutic benefits related to the disease<sup>23,24</sup>. This result indicates that periodontal intervention can probably have the greatest effectiveness in cases of the disease when it is addressed at an earlier stage before the kidneys have permanently damaged. The significance of early periodontal assessment and intervention among CKD patients can be highlighted on the basis of these findings<sup>25</sup>. This research has clinical implications. The periodontal therapy is highly affordable and minimally invasive and can be easily absorbed into the mainstream healthcare. Periodontal care could be included in the CKD treatment regimens to lower levels of systemic inflammation, slow down the rate of renal failure progression, and positively affect patient outcomes. This helps to sustain a team-oriented approach to treatment of nephrologists and dentists.

This study has several limitations. The retrospective nature of the information and small size of the therapeutic subgroup constrain the generalizability. Moreover, the follow-ups should be prolonged to measure long-term renal outcomes. Further scientific studies are desirable in the future perspective to establish these results and get a better understanding of the contribution of periodontal therapy in the development of CKD.

## Conclusion

This secondary analysis prove that non-surgical periodontal therapy is linked to the considerable decrease in systemic inflammatory markers and renal functional increase in the group of patients with CKD. The results reinforce the contribution of periodontal intervention as a useful therapeutic measure especially when applied at earlier phases of CKD. Further prospective and longitudinal research are required to validate these findings and to develop standardized clinical practice guidelines that would help to integrate periodontal treatment into the renal disease management system.

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None

## Authors' Contribution

KE, AE conceived the idea and designed the research work, KE, MI, MA, AE did data analysis, AE, MA, MI did the manuscript writing, KE, AE did proof read and editing, All authors provided final approval and agreed to be accountable for all aspects of research.

## Ethical Statement

The ethical approval for the current study was taken from the Institutional Review Board at the Department of oral Pathology, LUMHS Jamshoro (REC/183/22).

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