ODOVTOS
International Journal of Dental Sciences

UNIVERSIDAD DE COSTA RICA FOd Facultad de Odontología

https://revistas.ucr.ac.cr/index.php/Odontos

LITERATURE REVIEW:

Effects of Surgical and Non-surgical Periodontal Therapy on Renal Function and Inflammatory Biomarkers and Mortality in Patients with Chronic Kidney Disease: An Umbrella Review

Efectos de la terapia periodontal quirúrgica y no quirúrgica sobre la función renal, los biomarcadores inflamatorios y la mortalidad en pacientes con enfermedad renal crónica: una revisión en paraguas

Anny Marcela Vivares-Builes DDS[1,5] https://orcid.org/0000-0002-8631-4910
María Teresa Pertúz-Rondón DDS[1] https://orcid.org/0000-0003-2024-0100
German Márquez-Toro MD, MSc[2] https://orcid.org/0009-0006-2330-6960
Carlos Pizarro-Herrera MD, MSc[2] https://orcid.org/0009-0003-8674-7382
Andrés Alonso Agudelo-Suarez MSc, PhD[3] https://orcid.org/0000-0002-8079-807X
Carlos M. Ardila DDS, PhD[4,5] https://orcid.org/0000-0002-3663-1416

[1]Department of Dentistry, Faculty of Dentistry, Institución Universitaria Visión de las Américas, Medellín, Colombia.
[2]Department of Nephrology, Nefrouros Renal Unit, Envigado, Antioquia, Colombia.
[3]Department of Basic Sciences, Faculty of Dentistry, Universidad de Antioquia, UdeA, Medellín, Colombia.
[4]Department of Periodontics, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India.
[5]Department of Basic Sciences, Faculty of Dentistry, Biomedical Stomatology Research Group, Universidad de Antioquia, UdeA, Medellín, Colombia.

Correspondence to: Carlos M. Ardila DDS, PhD - martin.ardila@udea.edu.co

Received: 4-XI-2025 Accepted: 4-XII-2025

ABSTRACT: Periodontitis and chronic kidney disease (CKD) share common pathophysiological mechanisms, with periodontitis acting as a chronic inflammatory comorbidity that exacerbates systemic inflammation in CKD patients. This study aimed to analyze the effect of surgical and non-surgical periodontal therapy on renal function, inflammatory biomarkers, and mortality in patients with CKD according to the available evidence. An umbrella review was conducted, including systematic reviews and meta-analyses from databases such as PubMed, Clinical Key, Scopus, Cochrane, Scielo, and Google Scholar. Methodological quality was assessed using AMSTAR-2, and reporting quality with PRISMA. Five systematic reviews and meta-analyses, encompassing 21 primary studies, were analyzed. The evidence indicates that periodontal therapy significantly reduces systemic inflammatory biomarkers like IL-6 and C-reactive protein, while also improving renal function markers, including an increased glomerular filtration rate. Non-surgical periodontal therapy was associated with a statistically significant reduction in mortality and cardiovascular-related morbidity, especially with intensive therapy and follow-up. These findings suggest that periodontal treatment may benefit renal health by reducing systemic inflammation and lowering mortality risks linked to cardiovascular complications. However, the heterogeneity of study designs and analyzed variables limits the ability to draw definitive conclusions. Future high-quality research is necessary to clarify these associations.

KEYWORDS: Biomarkers; Kidney failure; Periodontitis; Systematic review; Periodontal diseases; Umbrella review.

RESUMEN: La periodontitis y la enfermedad renal crónica (ERC) comparten mecanismos fisiopatológicos comunes, siendo la periodontitis una comorbilidad inflamatoria crónica que exacerba la inflamación sistémica en pacientes con ERC. Este estudio tuvo como objetivo analizar el efecto de la terapia periodontal quirúrgica y no quirúrgica sobre la función renal, los biomarcadores inflamatorios y la mortalidad en pacientes con ERC según la evidencia disponible. Se realizó una revisión en paraguas que incluyó revisiones sistemáticas y metaanálisis provenientes de bases de datos como PubMed, Clinical Key, Scopus, Cochrane, Scielo y Google Scholar. La calidad metodológica se evaluó mediante AMSTAR-2 y la calidad del reporte con PRISMA. Se analizaron cinco revisiones sistemáticas y metaanálisis que abarcaron 21 estudios primarios. La evidencia indica que la terapia periodontal reduce significativamente los biomarcadores inflamatorios sistémicos, como la interleucina-6 (IL-6) y la proteína C reactiva, además de mejorar los marcadores de función renal, incluyendo un aumento en la tasa de filtración glomerular. La terapia periodontal no quirúrgica se asoció con una reducción estadísticamente significativa de la mortalidad y la morbilidad cardiovascular, especialmente cuando se aplicó de forma intensiva y con seguimiento. Estos hallazgos sugieren que el tratamiento periodontal podría beneficiar la salud renal al disminuir la inflamación sistémica y reducir el riesgo de mortalidad relacionada con complicaciones cardiovasculares. Sin embargo, la heterogeneidad de los diseños de estudio y de las variables analizadas limita la posibilidad de establecer conclusiones definitivas. Se requiere investigación futura de alta calidad para clarificar estas asociaciones.

PALABRAS CLAVE: Biomarcadores; Insuficiencia renal; Periodontitis; Revisión sistemática; Enfermedades periodontales; Revisión en paraguas.

INTRODUCTION

Periodontitis is a chronic infectious and inflammatory disease that causes the progressive destruction of tooth-supporting tissues. It is clinically recognized by attachment loss and radiographically recognized by alveolar bone loss. It varies in degrees of progression and severity according to intrinsic and extrinsic factors (1). This multifactorial condition responds to the interaction among specific microorganisms in a dysbiotic biofilm, environmental factors such as smoking, genetic and epigenetic factors (1). In terms of prevalence, periodontitis is the most common chronic inflammatory condition in humans. In its severe form, it is the sixth most common human disease, occurring in 11.2% of the world's population (2).

Another non-communicable chronic disease with very similar prevalence is chronic kidney disease (CKD). This disease is characterized by a reduction in renal function or by the presence of kidney damage markers for at least 3 months, an estimated glomerular filtration rate (eGFR) of less than 60 ml/min per 1.73 m2, or kidney damage markers, such as albuminuria, hematuria, or abnormalities detected through laboratory tests. This medical condition is progressive and entails an irreversible change in kidney function, which progresses in five stages. In the early stages —1 to 3—, the kidneys are still able to remove waste from the blood. In later stages —4 and 5—, the kidneys struggle to purify the blood and might stop working completely (3). Nearly 10% of the world's population suffers from CKD, a figure that reaches

50% in geriatric population. CKD causes a significant increase in mortality: stage 5 patients have a 50% higher mortality rate than controls, which has been associated with comorbidities that appear throughout the process (4).

According to the latest evidence-based clinical guidelines, periodontitis therapeutic management is divided into several stages. The initial anti-inflammatory stage is when behavior management should be performed to control parafunctions and oral hygiene habits, smoking, and healthy lifestyles that include control of diet and carbohydrate intake, physical activity, weight management, interconsultations and follow-up of the patient's systemic condition. In this stage, the aim is to encourage patients to become empowered not only in the control of the biofilm but also in the care of their health at a comprehensive level. In the second stage, an individualized non-surgical therapy is performed based on the specific needs of the patient. Also, other local factors, and other oral, endodontic and occlusal pathologies are controlled. In the third phase a specific surgical periodontal therapy is performed for areas with residual bone defects and where inflammatory processes persist, with resective or regenerative approaches. The fourth phase is supportive and maintenance periodontal therapy. All these stages are intersected by a permanent re-assessment of the patient. More advanced stages of periodontitis may require multidisciplinary management where orthodontic; rehabilitation and other interventions are required (5).

To better illustrate the parallel progression and management strategies of periodontitis and chronic kidney disease, Figure 1 provides a comparative flowchart. This visual representation underlines how both conditions require a staged, multidisciplinary approach, emphasizing the importance of early intervention, tailored treatment, and ongoing patient monitoring.

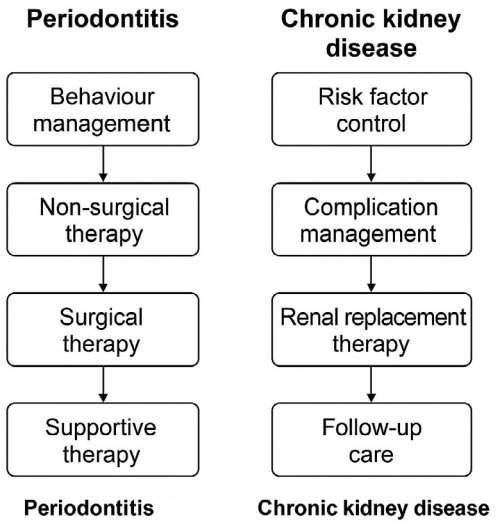

Figure 1. Comparative flowchart of therapeutic stages in periodontitis and chronic kidney disease. The figure illustrates the stepwise therapeutic approach to periodontitis and chronic kidney disease (CKD), highlighting behavioral, non-surgical, surgical, and supportive care in periodontitis, alongside risk factor management, complication control, renal replacement, and follow-up care in CKD.

On the other hand, the management of CKD is staggered according to its stages. In early stages (1 and 2), the goal is to identify and control risk factors, such as hypertension and diabetes, to prevent or slow disease progression (6). In intermediate stages (3 and 4), in addition to controlling risk factors, complications related to CKD, such as anemia and bone disease, are managed (7). In stage 5, also known as end-stage renal disease (ESRD), renal replacement therapies —such as dialysis or kidney transplant— are required (8). There are mainly two types of dialysis: hemodialysis and peritoneal dialysis. During hemodialysis, a machine (artificial kidney) is used to clean the blood. It is usually performed in a dialysis center three times a week (9). Peritoneal dialysis, by contrast, uses the lining of the patient's abdomen to filter the blood. It can be done at home and is often a more flexible option (7).

Periodontitis and chronic kidney disease share pathophysiological mechanisms and may

have a bidirectional relationship. Both pathologies may be affected by renal replacement therapy, hyperphosphatemia, phosphate retention, and hypocalcemia (10). Renal function is important in regulating bone metabolism, tubular calcium filtration, and vitamin D activation. Chronic kidney failure may lead to oral manifestations primarily due to secondary hyperparathyroidism (11). These conditions, without proper medical management, lead to bone changes called renal osteodystrophy, which includes fibrous dysplasia, hyperosteoidosis, osteosclerosis, growth retardation, and osteoporosis, which can affect tooth-supporting tissues (10) Likewise, renal replacement therapy, including hemodialysis, peritoneal dialysis or renal transplant, may affect periodontal tissues, producing gingival hyperplasia in immunocompromised renal transplant patients, higher levels of dental biofilm, calculus and gingival inflammation. In addition, hyperphosphatemia, phosphate retention, and hypocalcemia occur in CKD. Hyperphosphatemia decreases renal activation of vitamin D, which further decreases the calcium level and, in turn, stimulates the release of parathyroid hormone, leading to secondary hyperparathyroidism (11).

The association between periodontitis and chronic kidney disease has already been established by scientific evidence (12). Periodontitis can function as a comorbid chronic inflammatory disease in patients with chronic kidney disease, contributing to the increase in systemic inflammation (10-12). This risk factor may be amenable to treatment. Additionally, significant reductions in systemic inflammatory markers (IL-6, C-reactive protein) have been reported after periodontal therapy in hospitalized patients (9-11). Recently, there has been an increase in interventional studies seeking to establish the effect of periodontal therapy on renal function. However, there are gaps in terms of the effect of different modalities of periodontal therapy on renal function and on markers of systemic inflammation and their involvement in reducing mortality associated with CKD (11,12). Therefore, the aim of this review is to analyze the effect of surgical and non-surgical periodontal therapy on renal function and inflammatory biomarkers, and mortality in patients with chronic kidney disease using the best available scientific evidence.

MATERIALS AND METHODS

METHODOLOGICAL DESIGN

Using the umbrella review strategy, a systematic review was conducted to identify systematic reviews and meta-analyses that according to the general objective (13). This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14). Likewise, the protocol of this systematic review was registered (PROSPERO CRD42021282293).

PICOS QUESTION

Question posed according to the PICOs (population, intervention, comparison, outcome and study design) format: Patient/Population: Patients with chronic kidney disease and periodontitis; Intervention: surgical and non-surgical periodontal treatment; Comparison: Patients with chronic kidney disease and periodontitis without surgical and non-surgical periodontal treatment; Outcomes: Changes in renal function biomarkers, inflammatory biomarkers, and mortality; Study design: Systematic reviews and meta-analyses based on studies conducted in humans, with designs of randomized and non-randomized controlled clinical trials, interventional studies and observational studies. Inclusion criteria were selected to assess the eligibility of studies based on the following research question:

What is the effect of surgical and non-surgical periodontal therapy on renal function biomarkers, inflammatory biomarkers, and mortality in patients with chronic kidney disease compared to patients without periodontal treatment?

Inclusion criteria: Systematic reviews and meta-analyses, conducted in human, elaborated from randomized and non-randomized controlled clinical trials, observational and interventional or experimental studies in English, Spanish or Portuguese.

Exclusion criteria: narrative or systematic reviews not conducted in humans, animal studies, in vitro, review articles, case reports or series, expert opinions.

SEARCH STRATEGY

For the selection of eligible studies, the researchers first searched for free terms and MeSH terms, developed the equations for the search strategy initially for PubMed, and then adapted it according to the syntax rules of the other databases, using MeSH terms and free text words combined with Boolean operators. Two researchers (MP and AV) independently performed the searches in different databases.

Searches were updated in September 2025, in the following electronic databases: PubMed, Clinical Key, Scopus, Cochrane, Scielo and manual searches (Google Scholar). Combinations of free text words and MeSH terms were used: chronic renal disease and periodontal disease, chronic kidney disease, renal function, dialysis; as well as thesaurus terms that included: (periodontitis) MeSH term OR (gingivitis) MeSH term OR (periodontal disease) MeSH term AND (chronic renal disease) OR (chronic kidney disease) OR (renal function) OR (dialysis) (therapy) MeSH term AND (chronic renal disease) MeSH term OR (chronic kidney disease) MeSH term OR (renal function) MeSH term.

Search equations were created to apply to each database: (periodontitis) (MeSH term) OR (periodontal disease) (MeSH term) AND (chronic renal disease) (MeSH term) AND (chronic kidney disease) (MeSH term), (periodontal therapy) (MeSH term) AND (chronic renal disease) (MeSH term) OR (chronic kidney disease) (MeSH term) OR (renal function) (MeSH term).

RESULT VARIABLES

Renal function biomarkers assessed as glomerular filtration rate (GFR); serum creatinine; blood urea nitrogen (BUN]; other biomarkers of kidney damage (if available], such as cystatin C; changes in biomarkers of kidney function after periodontal treatment; biomarkers of systemic inflammation assessed as CRP, IL-6, TNF-α, among other possible options; changes in biomarkers of systemic inflammation after periodontal treatment; mortality outcomes with and without periodontal therapy. Type of periodontal therapy applied: surgical or non-surgical.

EVALUATION AND SELECTION PROCESS

Two researchers (AV and MP) reviewed titles and abstracts and selected systematic reviews and meta-analyses to assess the likelihood of full-text appropriateness. Disagreements between them were discussed with a third and fourth author. The Kappa test was used to measure the value of inter-observer agreement (K=0.95).

DATA COLLECTION

For study selection and data collection, studies identified from the literature search were selected sequentially by title, abstract, and full text by one of the researchers, with subsequent independent double-checking against the eligibility criteria of another author. For data extraction, a Microsoft® Excel® tool was developed to extract the most relevant information from the selected

reviews. This activity was conducted individually by the researchers and the records were later cross-checked. The verified information included authors names, publication date, study objective, number of studies included, methodological design of the studies included, biomarkers evaluated, periodontal intervention in terms of surgical or non-surgical therapy, follow-up in months after therapy, and other primary outcome variables.

CRITICAL ASSESSMENT AND RISK OF BIAS ASSESSMENT

The evaluation of the methodological quality of the systematic reviews and meta-analyses included was conducted using the PRISMA 2020 guidelines for systematic reviews (14). AMSTAR-2 was used to establish the degree of confidence in the review and the risks of bias (15). These assessments were independently performed by two authors (AV and MP) and were analyzed and reviewed by the third and fourth author.

RESULTS

Five systematic reviews and meta-analyses were included (12-19) (Figure 2), comprising a total of 21 primary studies (20-40) of the following type: controlled and uncontrolled clinical trials, case-control, cohort, and experimental studies.

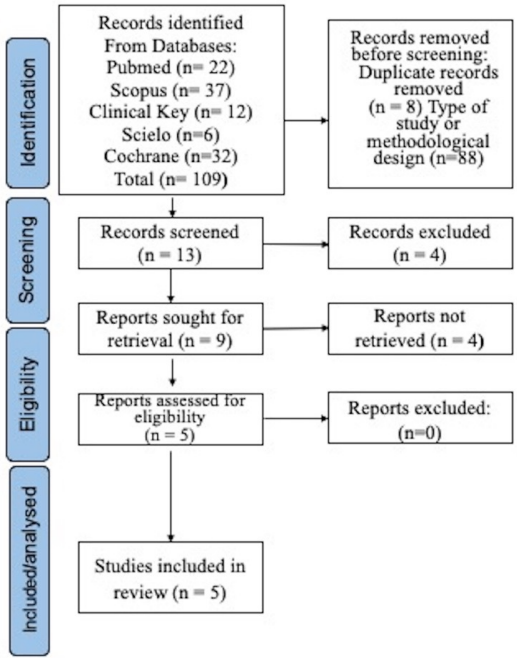

Figure 2. PRISMA flow diagram.

Extracted results analyze the relationship between surgical and non-surgical periodontal therapy and changes in biomarkers of systemic inflammation and renal function, as well as mortality in some cases (Table 1).

The quality assessment of the report indicated that the studies had adequate quality according to the PRISMA 2020 criteria, with low to medium risk of general bias. Likewise, after the evaluation of the critical and non-critical domains

and a global analysis based on the AMSTAR-2 guidelines, the confidence level was high for two studies (17,18) and low for the remaining ones (12,16,19) (Table 2).

Regarding biomarkers of systemic inflammation, it was evidenced that non-surgical periodontal therapy showed a significant decrease in C-reactive protein (CRP) in several primary studies (20,22-24,25,27, 31-34,39). In some studies, a significant decrease in IL-6 levels was also observed (20,31). No significant changes in TNF-α levels were observed in the Fang *et al*. (20) and Guo and Lin (32) studies (Table 3).

Table 1. Features of included reviews.

Author and year	Objective	Number of articles included for analysis	Number of articles included for meta-analysis	Included studies type	Review type	Periodontal intervention	Evaluated biomarkers
Hui Yue *et al*. 2020 (17)	To investigate whether non-surgical periodontal therapy (NSPT) can reduce systemic inflammatory levels and improve metabolism in patients undergoing hemodialysis (HD) and/or peritoneal dialysis (PD).	5	5	RCT	Systematic review and meta-analysis	Non-surgical therapy	Systemic inflammation and renal function biomarkers
Dan Zhao *et al*. 2019 (18)	To evaluate the impacts of non-surgical periodontal therapy (NSPT) in patients with chronic kidney disease (CKD) and periodontitis to explore causality and assess the potential benefits of co-management.	5	3	Case-control study	Systematic review and meta-analysis	Non-surgical therapy	Systemic inflammation and renal function biomarkers
Da Silva *et al*. 2021 (19)	To assess the impact of periodontal treatment on the glomerular filtration rate (GFR) of individuals with chronic kidney disease (CKD).	3	3	CT	Systematic review and meta-analysis	Non-surgical therapy	Renal function biomarkers
Delvobe *et al*. 2021 (16)	To assess the effect of periodontal treatment (PT) on glomerular filtration rate (GFR), systemic inflammation, or mortality in patients with chronic kidney disease (CKD).	13	N/A	Cohort study, RCT, experimental study, CT, observational prospective study, observational cohort study	Systematic review	Non-surgical and surgical therapy and indicated extractions	Systemic inflammation and renal function biomarkers, mortality
Chambrone *et al*. 2013 (12)	To evaluate the association between periodontitis and chronic kidney disease (CKD) and the effect of periodontal treatment (PT) on the estimated glomerular filtration rate (eGFR).	3	N/A	Intervention	Systematic review	Non-surgical therapy	Renal function biomarkers

Table 2. Evaluation of the methodological quality of the systematic reviews and meta-analyses.

Author and year	PRISMA	AMSTAR (# critical domains)	AMSTAR (overall confidence)	Risk of bias	Scales for assessing risk of bias and/or quality of primary study reporting
Hui Yue *et al.* 2020 (17)	26/27	7	High	Low	Cochrane Collaboration's tools
Dan Zhao *et al.* 2019 (18)	26/27	7	High	Low	ROBINS-I for CT and Cochrane Collaboration's tools for RCT
Da Silva *et al.* 2021 (19)	23/27	6	Low	Medium	MINORS
Delvobe *et al.* 2021 (16)	21/27	6	Low	Medium	Newcastle-Ottawa Scale and Cochrane Collaboration's tools for RCT
Chambrone *et al.* 2013 (12)	26/27	6	Low	Low	Newcastle-Ottawa Scale and Cochrane Collaboration's tools for RCT

Table 3. Main results.

Primary article	Systematic review where it was included					Total number of patients	Follow-up months	Periodontal intervention	Systemic inflammation biomarker	Renal function biomarker	Periodontal therapy outcome and systemic inflammation biomarker	Periodontal therapy outcome and renal function biomarker	Periodontal therapy outcome and mortality
	Hui Yue *et al.* (17)	Dan Zhao *et al.* (18)	Da Silva *et al.* (19)	Delvobe *et al.* (16)	Chambrone *et al.* 2013 (12)								
Fang *et al.* 2015 (20)	X	X		X		94	3 and 6	Non-surgical therapy	CRP, IL-6, TNF-α	Creatinine, BUN	Significant decrease of CRP, IL-6, not significant TNF-α	eGFR increase, statistically significant BUN	No report
Wehmeyer *et al.* 2014 (21)	X			X		25	3 and 6	Non-surgical therapy	IL-6,	Albumin	No difference	No difference	No report
Li *et al.* 2019 (22)	X					72	2	Non-surgical therapy	CRP	No report	Significant decrease of CRP	No report	No report
Zhang *et al.* 2017 (23)	X					61	1	Non-surgical therapy	CRP	No report	Significant decrease of CRP	No report	No report
Ma *et al.* 2018 (24)	X					98	1.5	Non-surgical therapy	CRP	No report	Significant decrease of CRP	No report	No report
Almeida *et al.* 2017 (25)		X	X	X		26	3 and 6	Non-surgical therapy	No report	eGFR	No report	statistically significant eGFR increase	No report
Siribamrungwong 2014 (26)		X		X		32	4	Non-surgical therapy	CRP	BUN	Significant decrease of CRP	Statistically significant BUN increase	No report
Siribamrungwong 2012 (27)		X		X		30	2	Non-surgical therapy	CRP	BUN	Significant decrease of CRP	Statistically significant BUN increase	No report
Artese *et al.* 2010 (28)		X	X	X	X	21	3	Non-surgical therapy	No report	GFR, creatinine	No report	Statistically significant eGFR increase	No report
Ebong 2018 (29)			X			30	3	Non-surgical therapy	No report	GFR	No report	Statistically significant GFR increase	No report
Rapone *et al.* 2019 (30)				X		66	3 and 6 months	Non-surgical therapy	CRP	Creatinine, albumin	Significant decrease of CRP	No difference	No report
Tasdemir *et al.* 2018 (31)				X		60	3	Non-surgical therapy	CRP, IL-6, TNF-α	Albumin, BUN	Significant decrease of CRP, IL-6, TNF-α	No difference	No report
Guo and lin *et al.* 2017 (32)				X		83	1.5	Non-surgical therapy	CRP, IL-6, TNF-α	No report	Significant decrease of CRP, not significant IL-6, TNF-α	No report	No report
Kocyigit *et al.* 2014 (33)				X		43	3	Non-surgical therapy	CRP	Albumin	Significant decrease of CRP	No difference	No report
Kiany *et al.* 2013 (34)				X		77	2	Non-surgical therapy	CRP	No report	Significant decrease of CRP	No report	No report

Primary article	Systematic review where it was included					Total number of patients	Follow-up months	Periodontal intervention	Systemic inflammation biomarker	Renal function biomarker	Periodontal therapy outcome and systemic inflammation biomarker	Periodontal therapy outcome and renal function biomarker	Periodontal therapy outcome and mortality
	Hui Yue *et al.* (17)	Dan Zhao *et al.* (18)	Da Silva *et al.* (19)	Delvobe *et al.* (16)	Chambrone *et al.* 2013 (12)								
De Souza 2014 (36)				X		79	64	Non-surgical therapy	No report	No report	No report	No report	34 fatal events, in multivariate model, no significant differences were found between groups with therapy and follow-up appointments.
Santos-Paul *et al.* 2019 (37)]				X		409	24	Non-surgical therapy, extractions and required endodontic therapy	No report	No report	No report	No report	Periodontal therapy had a significant statistical association with reduced mortality (and other cardiovascular morbidity events].
Huang *et al.* 2018 (38)				X		7226	Followed up until a new outcome diagnosis was obtained based on the hospitalization	Non-surgical and surgical therapy					After adjusting for other variables and when compared to patients not treated with hemodialysis, the cohort with intensive surgical and non-surgical periodontal treatment and follow-up, as needed, showed a statistically significant reduction in the risk of mortality associated with cardiovascular disease.
Kadiroglu *et al.* 2006 (39)				X		21	1	Non-surgical therapy	CRP, erythrocyte sedimentation rate	No report	Significant decrease of CRP, erythrocyte sedimentation rate	No report	No report
Graziani *et al.* 2010 (40)					X	32	6	Non-surgical therapy	No report	GFR	No report	Statistically significant GFR increase	No report

In general, non-surgical periodontal therapy is found to have positive effects on decreasing biomarkers of systemic inflammation, such as CRP and interleukin-6 (IL-6). However, results for tumor necrosis factor alpha (TNF-α) are conflicting (Table 3).

When discussing renal function biomarkers, it is observed that in several studies non-surgical periodontal therapy displayed a statistically significant increase in eGFR (20,25-29,35,40). Significant increases in blood urea nitrogen (BUN) were observed in some studies (26,27). No significant differences in creatinine levels (30,31,35) and no differences in albumin levels were reported in other studies (21,30,33).

Regarding renal function biomarkers, some studies describe an improvement in eGFR and BUN. No significant differences in creatinine and albumin are observed in most studies (Table 3).

Concerning the relationship between periodontal therapy and mortality, only the systematic review by Delvobe *et al*. 2021 (16) reported this variable in three of their primary studies. In comparison with the groups that did not receive intensive non-surgical periodontal therapy, non-surgical periodontal therapy had a statistically significant relationship with reducing mortality and other morbidity events caused by cardiovascular complications (37). Likewise, hemodialysis patients who underwent surgical therapy as indicated and had adequate follow-up and periodontal control showed a reduction in the mortality risk associated with cardiovascular diseases. There were statistically significant differences even after adjusting for other related variables. However, in this same review, a primary study failed to find significant differences between groups with non-surgical periodontal therapy (Table 3).

To better visualize the therapeutic effects of periodontal interventions on systemic inflammation, renal biomarkers, and mortality in CKD patients, a summary figure was developed (Figure 3). This figure synthesizes the evidence extracted from included systematic reviews and highlights domains where outcomes are consistent, partial, or inconclusive.

To provide a clearer interpretation of findings across different CKD stages, we stratified the evidence regarding periodontal therapy outcomes by disease stage (Table 4). This breakdown underscores stage-specific differences in inflammatory response and renal function, and clarifies where mortality-related data were available.

Table 4. Reported Effects of Periodontal Therapy Stratified by Chronic Kidney Disease Stage. This table summarizes the therapeutic outcomes of periodontal interventions stratified by CKD stage (2-5), detailing inflammatory and renal biomarkers affected and whether mortality outcomes were evaluated.

CKD Stage	Periodontal Therapy Type	Inflammatory Biomarker Effect	Renal Biomarker Effect	Mortality Outcome Reported	Systematic Review Source(s)
Stage 2-3	Non-surgical	↓ CRP, ↓ IL-6	↑ eGFR	Not reported	Yue *et al*. (17), Zhao *et al*. (18)
Stage 4	Non-surgical	↓ CRP, mixed IL-6, TNF-α	↑ eGFR, ↑ BUN	Not reported	Da Silva *et al*. (19), Yue *et al*. (17)
Stage 5	Surgical + non-surgical	↓ CRP, ↓ ESR	No change in creatinine	↓ Mortality (significant)	Delvobe *et al*. (16)
ESRD	Non-surgical	↓ CRP	No improvement	Mixed results	De Souza (19), Delvobe *et al*. (16)

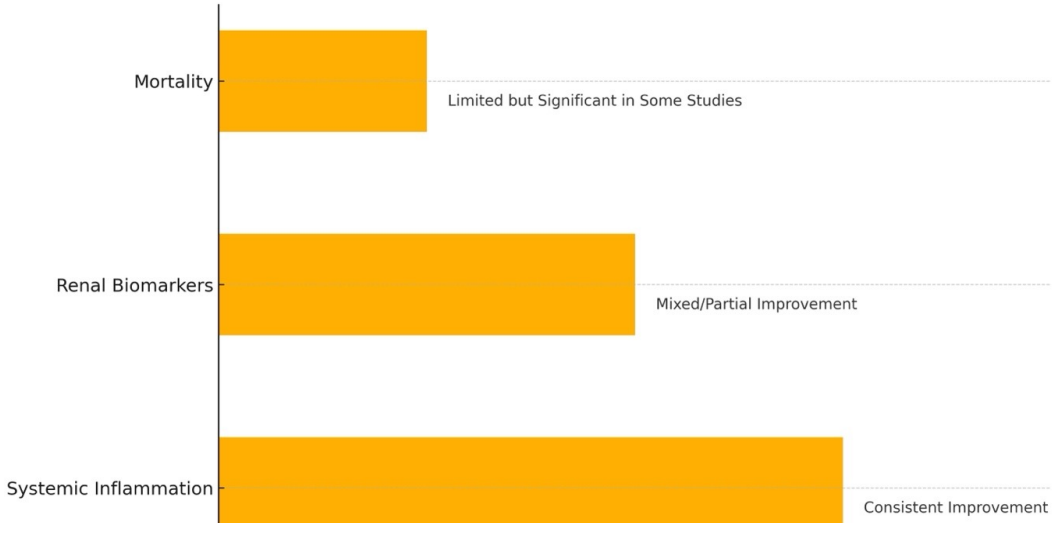

Figure 3. Summary of the impact of periodontal therapy on systemic inflammation, renal biomarkers, and mortality in CKD patients. This figure illustrates the summarized outcomes of periodontal therapy across three domains—systemic inflammation, renal biomarkers, and mortality—based on evidence extracted from the umbrella review.

DISCUSSION

CKD is a condition with high mortality and morbidity rates. Chronic inflammation in individuals with CKD is a concern. Therefore, it is essential to identify the factors linked to this serious disease and to establish measures to reduce systemic inflammation. In patients with chronic kidney disease —at different stages and even in patients on hemodialysis treatment—, non-surgical and surgical periodontal therapy appear to have a positive effect on reducing biomarkers of systemic inflammation, in improving renal function and reducing cardiovascular mortality. However, studies evaluating the effects of surgical therapy and maintenance, or supportive periodontal therapy are very limited.

The association between periodontitis and systemic conditions has been extensively evaluated, systemic dissemination of proinflammatory mediators —such as IL-1β, IL-6 and TNF-α— from periodontal tissues into the bloodstream has been reported. These cytokines can stimulate the immune system and contribute to inflammatory processes, which aggravates or contributes to pre-existing conditions, such as endothelial dysfunction, atherosclerosis, coronary artery disease and glomerulonephritis. Likewise, this relationship has been suggested to be a risk factor contributing to diabetes, cardiovascular diseases, neurodegenerative diseases, and adverse effects of pregnancy. This further supports the association between periodontitis and chronic kidney disease (12,37,38).

Risk factors associated with CKD, such as diabetes and smoking, are also associated with a higher periodontitis prevalence and progression degree. Therefore, risk factors shared by CKD and periodontitis should be considered. Synergism with other risk factors has also been hypothesized. However, in many studies these risk factors were not reported, analyzed and controlled in the analyses to determine the most reliable statistical weight of association between biomarkers and mortality in CKD patients undergoing periodontal therapy. However, literature has shown that periodontitis is associated with CKD, regardless of diabetes as a confounding variable (37,38).

Periodontitis has been associated with cardiovascular alterations (37,38); however, the weight of these alterations is more established and much higher in kidney disease. This is explained by the fact that as kidney disease progresses, the kidneys lose their ability to adequately filter waste and maintain balance in the body. This can lead to fluid and salt accumulation, increasing blood pressure and the risk of hypertension. In addition, imbalances in cholesterol and lipid levels due to kidney disease can cause plaque to build up in the arteries, narrowing them and hindering normal blood flow to the heart and other vital organs (26-28).

When patients start renal replacement therapy, such as hemodialysis or peritoneal dialysis, they also face additional risks to their cardiovascular health. During dialysis therapy, complications such as hypotension may occur due to the rapid elimination of fluids and waste. On the other hand, fluid and sodium retention in the body can lead to high blood pressure, which further increases cardiovascular risk. Moreover, renal replacement therapy may contribute to cardiac fibrosis, which is the stiffness and scarring of heart tissue (16-21).

This can be the result of chronic inflammation and stress associated with dialysis therapy. Cardiac fibrosis can affect heart function and increase the risk of cardiovascular disease. Dialysis therapy may also increase the risk of infection since vascular access is needed to perform the

procedure. Infections can have serious consequences on the cardiovascular system, such as infectious endocarditis (12,39,40).

In the management of periodontitis, surgical and non-surgical periodontal therapy, as well as supportive therapy, are associated with decreased biomarkers of systemic inflammation, as indicated by the findings of this study. The explanation for this may be the decrease in oxidative stress, markers such as CRP and IL-6, which may contribute to lower the burden on renal function and thus decrease all possible cardiovascular complications. Additionally, intensive periodontal treatment was found to be associated with reduced risks of general infectious diseases, which may contribute to favorable survivorship outcomes. Survivorship benefits also increased with frequency of treatment, although study designs are heterogeneous in this regard and randomized clinical trials are needed (12,16-19).

Regarding kidney disease biomarkers and their relationship with periodontal therapy, it is of particular interest that some studies have shown an association between kidney damage and periodontitis. Although there are multiple primary studies with different methodological designs that also include randomized controlled clinical trials, some variables —such as renal dysfunction severity and periodontitis degree of progression and severity— require further studies that evaluate periodontal support and surgical or intensive therapies in different modalities. Although the results are promising in terms of improvement of systemic inflammation and GFR, further evidence is required to draw solid conclusions about the relationship between other kidney disease biomarkers and periodontal therapy (16,17). It is important to emphasize that the included studies used eGFR as the main outcome for assessing renal function. However, there are limitations regarding the methods used for quantification since most studies reported their use without specifying the methods of calculation (12). Furthermore, studies that evaluated the eGFR in CKD and periodontitis patients reported non-surgical periodontal therapy having a beneficial effect on renal function in stages 2 to 4. Dialysis patients had elevated levels of BUN and serum creatinine that decreased very little after periodontal therapy. This is possibly explained by the influence of dialysis itself, which should be widely analyzed (17,18).

CONCLUSIONS

Periodontitis has an already established influence on the overall health of patients with chronic kidney disease. For instance, chronic inflammation associated with periodontitis can exacerbate systemic inflammation and oxidative stress, which can worsen the state of chronic kidney disease and increase the risk of cardiovascular complications. Periodontal treatment — non-surgical treatment in particular, as it is included the most in the studies— has been shown to reduce systemic inflammation measured through markers such as C-reactive protein and interleukin-6. This suggests that controlling periodontal infections may have a beneficial impact on systemic inflammation and potentially on renal function. This in turn leads to a decrease in mortality, generally associated with complications arising from kidney disease in the cardiovascular system.

Generally speaking about renal function biomarkers, some studies suggest that in patients with early-stage chronic kidney disease, periodontal treatment may have beneficial effects on glomerular filtration rate. An improvement in GFR has been observed in individuals with CKD in stages 2 to 4 after periodontal treatment. However, it is important to highlight that although there are several primary studies with evidence in this aspect, there is still work to be done regarding the evaluation methods of renal function markers, as the aim is to find the ones that allow to analyze the data in a global way with more statistically solid

results. Additionally, designs with multidisciplinary approaches would allow for a greater understanding of all variables involved in the variation of biomarkers and mortality. This will in turn produce more conclusive results about the impact of periodontal treatment on renal function at different stages of kidney disease and will improve the weight of current scientific evidence.

Further research should be conducted to evaluate biomarkers specific to early renal dysfunction in order to assess the effect of periodontal treatment in individuals with different levels of CKD severity and different levels of periodontitis. The type of periodontal treatment can be beneficial for kidney health, which can lead to the establishment of interdisciplinary nephrologist-periodontist protocols to reduce clinical markers of inflammation and promote renal function in patients.

FUNDING: This research did not receive grants.

CONFLICT OF INTEREST: The authors declare that they have no conflicts of interest.

INFORMED CONSENT: Not required.

DATA AVAILABILITY STATEMENT: Records were obtained from the included investigations.

ETHICS COMMITTEE STATEMENT: Not required.

AUTHOR CONTRIBUTION STATEMENT: Conception, Design, Supervision, Fundings, Materials, Data collection and/or processing, Analysis and/or interpretation, Literature, Review: A.M.V.B., M.T.P.R., G.M.T., C.P.H.; A.A.A.S. and C.M.A.; Writing, Critical review: A.M.V.B., A.A.A.S. and C.M.A.

REFERENCES

1. Papapanou P.N., Sanz M., Buduneli N., Dietrich T., Feres M., Fine D.H., et al. (2018) Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the classification of periodontal and peri-implant diseases and conditions. J Periodontol 89 (Suppl 1): S173-S182. https://doi.org/10.1002/JPER.17-0721.
2. Nazir M., Al-Ansari A., Al-Khalifa K., Alhareky M., Gaffar B., Almas K. (2020) Global prevalence of periodontal disease and lack of its surveillance. ScientificWorldJournal 2020: 2146160. https://doi.org/10.1155/2020/2146160.
3. Ammirati A.L. (2020) Chronic kidney disease. Rev Assoc Med Bras (1992) 66 (Suppl 1):s03-s09.https://doi.org/10.1590/1806-9282.66.S1.3.
4. Bernuy J., Gonzales G.F. (2015) Bone mineral metabolism in patients with chronic kidney disease: Review of its pathophysiology and morbimortality. Rev Peru Med Exp Salud Publica 32 (2): 326-334. https://doi.org/10.17843/rpmesp.2015.322.1628.
5. Sanz M., Herrera D., Kebschull M., Chapple I., Jepsen S., Berglundh T., et al. (2020) Treatment of stage I–III periodontitis—the EFP S3 level clinical practice guideline. J Clin Periodontol 47 (Suppl 22): 4-60. https://doi.org/10.1111/jcpe.13290.
6. Centers for Disease Control and Prevention (2021) Chronic kidney disease in the United States, 2021. [Internet]. Available from: https://www.cdc.gov/kidneydisease/publications-resources/2021-national-facts.html.
7. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013)

KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 3 (1):1-150. https://doi.org/10.1038/kisup.2012.73.

8. Saran R., Robinson B., Abbott K.C., Bragg-Gresham J., Chen X., Gipson D., et al. (2020) US Renal Data System 2019 Annual Data Report: Epidemiology of kidney disease in the United States. Am J Kidney Dis 75 (1 Suppl 1): A6-A7. https://doi.org/10.1053/j.ajkd.2019.09.003.
9. National Institute of Diabetes and Digestive and Kidney Diseases (2017) Hemodialysis. [Internet]. Available from: https://www.niddk.nih.gov/health-information/kidney-disease/kidney-failure/hemodialysis.
10. Mandalunis PM, Steimetz T, Castiglione JL, Ubios AM (2003) Alveolar bone response in an experimental model of renal failure and periodontal disease: A histomorphometric and histochemical study. J Periodontol 74 (12): 1803-1807. https://doi.org/10.1902/jop.2003.74.12.1803.
11. Zhao D., Zhang S., Chen X., Liu W., Sun N., Guo Y., et al. (2014) Evaluation of periodontitis and bone loss in patients undergoing hemodialysis. J Periodontol 85 (11): 1515-1520. https://doi.org/10.1902/jop.2014.140119.
12. Chambrone L., Foz A.M., Guglielmetti MR, Pannuti CM, Artese HPC, Feres M, et al. (2013) Periodontitis and chronic kidney disease: A systematic review of the association and the effect of periodontal treatment on estimated glomerular filtration rate. J Clin Periodontol 40 (5): 443-456. https://doi.org/10.1111/jcpe.12067.
13. Joanna Briggs Institute (2014) Methodology for JBI umbrella reviews. In: JBI reviewers' manual. Adelaide: Joanna Briggs Institute.
14. Page M.J., McKenzie J.E., Bossuyt P.M., Boutron I., Hoffmann T.C., Mulrow C.D., et al. (2021) The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 372: n71. https://doi.org/10.1136/bmj.n71.
15. Shea B.J., Reeves B.C., Wells G., Thuku M., Hamel C., Moran J., et al. (2017) AMSTAR 2: A critical appraisal tool for systematic reviews. BMJ 358: j4008. https://doi.org/10.1136/bmj.j4008.
16. Delbove T., Gueyffier F., Juillard L., Kalbacher E., Maucort-Boulch D., Nony P., et al. (2021) Effect of periodontal treatment on glomerular filtration rate in chronic kidney disease: A systematic review. PLoS One 16 (1): e0245619. https://doi.org/10.1371/journal.pone.0245619.
17. Yue H., Xu X., Liu Q., Li X., Xiao Y., Hu B. (2020) Effects of non-surgical periodontal therapy on systemic inflammation and metabolic markers in dialysis patients: A systematic review. BMC Oral Health 20 (1): 18. https://doi.org/10.1186/s12903-020-1004-1.
18. Zhao D., Khawaja A.T., Jin L., Chan K.W., Tonetti M., Tang S.C.W., et al. (2020) Effect of non-surgical periodontal therapy on renal function in chronic kidney disease patients with periodontitis: A systematic review and meta-analysis of interventional studies. Clin Oral Investig 24 (4): 1607-1618. https://doi.org/10.1007/s00784-019-03066-w.
19. da Silva T.A., Abreu L.G., Esteves Lima R.P. (2021) A meta-analysis on the effect of periodontal treatment on the glomerular filtration rate of chronic kidney disease individuals. Spec Care Dentist 41 (6): 670-678. https://doi.org/10.1111/scd.12625.
20. Fang F., Wu B., Qu Q., Gao J., Yan W., Huang X., et al. (2015) The clinical response and systemic effects of non-surgical periodontal therapy in end-stage renal disease patients: A 6-month randomized controlled clinical trial. J Clin Periodontol 42 (6): 537-546. https://doi.org/10.1111/jcpe.12411.
21. Wehmeyer M.M.H., Kshirsagar A.V., Barros S.P., Beck J.D., Moss K.L., Preisser J.S., et

al. (2013) A randomized controlled trial of intensive periodontal therapy on metabolic and inflammatory markers in patients with ESRD: results of an exploratory study. Am J Kidney Dis 61 (3): 450-458. https://doi.org/10.1053/j.ajkd.2012.10.021

22. Li H., Li M.Y. (2018) Therapeutic effect of periodontal treatment in renal disease and periodontitis. J Beihua Univ 19: 374-377.
23. Zhang J., Liu J.S., Ma M., Hou X.Y., Guo L.L., Peng C. (2017) Effects of periodontal basic treatment on peritoneal dialysis in patients with periodontitis. Tianjin Med J 45 (3): 282-284. https://doi.org/10.11958/20161196
24. Ma X., Li H., Chou H.Y., Yan L. (2018) Effect of periodontal therapy on periodontal index, gingival crevicular fluid inflammatory factors and renal indices in patients with chronic kidney disease and periodontitis. J Chin Pract Diagn Ther 32: 255-257.
25. Almeida S., Figueredo C.M., Lemos C., Bregman R., Fischer R.G. (2017) Periodontal treatment in patients with chronic kidney disease: a pilot study. J Periodontal Res 52 (2): 262-267. https://doi.org/10.1111/jre.12390
26. Siribamrungwong M., Yothasamutr K., Puangpanngam K. (2014) Treatment of periodontal diseases can improve systemic inflammation, nutritional status and erythropoietin responsiveness in peritoneal dialysis patients. Ther Apher Dial 18 (3): 305-308. https://doi.org/10.1111/1744-9987.12105
27. Siribamrungwong M., Puangpanngam K. (2012) Treatment of periodontal diseases reduces chronic systemic inflammation in maintenance hemodialysis patients. Ren Fail 34 (2): 171-175. https://doi.org/10.3109/0886022X.2011.643351
28. Artese H.P.C., Sousa C.O., Luiz R.R., Sansone C., Torres M.C.M. (2010) Effect of non-surgical periodontal treatment on chronic kidney disease patients. Braz Oral Res 24 (4): 449-454. https://doi.org/10.1590/S1806-83242010000400013
29. Ebong E.A. (2018) Effects of periodontal treatment on CKD stages 3-5. J Med Health Sci 2018.
30. Rapone B., Converti I., Santacroce L., Cesarano F., Vecchiet F., Cacchio L., et al. (2019) Impact of periodontal inflammation on nutrition and inflammation markers in hemodialysis patients. Antibiotics (Basel) 8 (4): 209. https://doi.org/10.3390/antibiotics8040209
31. Tasdemir Z., Özsarı Tasdemir F., Gürgan C., Eroglu E., Gunturk I, Kocyigit I (2018) Effect of periodontal therapy in peritoneal dialysis. Int Urol Nephrol 50 (8): 1519-1528. https://doi.org/10.1007/s11255-018-1913-y
32. Guo N., Lin G. (2017) Nonsurgical periodontal therapy and inflammatory markers in CKD. Biomed Res 28 (9): 3899-3902.
33. Kocyigit I., Yucel H.E., Cakmak O., Dogruel F., Durukan D.B., Korkar H., et al. (2014) Periodontal problems as an inflammation source in peritoneal dialysis. Int Urol Nephrol 46 (10): 2021-2028. https://10.1007/s11255-014-0716-z
34. Kiany Yazdi F., Karimi N., Rasouli M., Roozbeh J. (2013) Periodontal treatment and C-reactive protein in hemodialysis. Ren Fail 35 (5): 711-717. https://doi:10.3109/0886022X.2013.777890
35. Vilela E.M., Bastos J.A., Fernandes N., Ferreira A.P., Chaoubah A., Bastos M.G. (2011) Chronic periodontitis treatment reduces serum prohepcidin in CKD. Clinics (Sao Paulo) 66 (4): 657-662. https://doi:10.1590/s1807-59322011000400022
36. de Souza C.M., Braosi A.P.R., Luczyszyn S.M., Olandoski M., Kotanko P., Craig R.G., et al. (2014) Oral health, periodontitis,

treatment, and mortality in hemodialysis. J Periodontol 85 (6): e169-e178. https://doi: 10.1902/jop.2013.130427
37. Santos-Paul M.A., Neves R.S., Gowdak L.H.W., de Paula F.J., David-Neto E., Bortolotto L.A., et al. (2019) Periodontal treatment and cardiovascular risk in transplant candidates. Clin Transplant 33 (8). https://doi: 10.1111/ctr.13658
38. Huang S.T., Yu T.M., Ke T.Y., Wu M.J., Chuang Y.W., Li C.Y., et al. (2018) Intensive periodontal treatment reduces cardiovascular disease and all-cause mortality in dialysis. J Clin Med 7 (10): 344. https://doi.org/10.3390/jcm7100344
39. Kadiroglu A.K., Kadiroglu E.T., Sit D., Dag A., Yilmaz M.E. (2006) Periodontitis: an occult source of inflammation in hemodialysis. Blood Purif 24 (4): 400-404. https://doi: 10.1159/000093683
40. Graziani F., Cei S., La Ferla F., Vano M., Gabriele M., Tonetti M. (2010) Non-surgical periodontal therapy and glomerular filtration: exploratory trial. J Clin Periodontol 37: 638-643. https://doi: 10.1111/j.1600-051X.2010.01578.x