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EDITORIAL

Periodontitis and chronic kidney disease: A bidirectional relationship based on inflammation and oxidative stress

Melissa Martínez Nieto, Martha Leticia De Leon Rodríguez, Rocio del Carmen Anaya Macias, Sarah Monserrat Lomelí Martínez

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Abstract

Chronic kidney disease (CKD) and chronic periodontitis (CP) are prevalent conditions which significantly impact public health worldwide. Both diseases share inflammatory and oxidative stress mechanisms, an indication of a likely bidirectional relationship. This editorial explored the association between CKD and CP by highlighting common inflammatory mechanisms and recent research findings that address this interrelationship. Through reviews of recent studies, we discussed how periodontal bacteria may activate systemic immune responses that affect both periodontal and renal tissues. Additionally, meta-analysis data indicated an increased risk of CKD development in patients with CP, and vice versa. The results suggest the need for more rigorous research in the future in order to address the confounding factors and evaluate specific periodontal health interventions and their direct effects on kidney function. We emphasized the importance of comprehensive and multidisciplinary care for the improvement of the overall health of patients affected by CP and CKD.

Key Words: Periodontitis; Chronic kidney disease; Periodontal disease; Oxidative stress; Inflammation

Core Tip: In this editorial, we reviewed the recent meta-analysis by Yang *et al*, which investigated the association between chronic periodontitis (CP) and chronic kidney disease (CKD). The analysis showed that CP patients have increased risk of CKD, and vice versa. This review also incorporated findings from other significant studies that support this link. We highlighted the need for more consistent definitions, rigorous adjustment for confounding factors, and well-designed prospective studies to ascertain the causal relationship between CP and CKD. This ongoing investigation is crucial for enhancing the management of periodontal health of CKD patients and for improving overall patient outcomes.

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INTRODUCTION

Chronic kidney disease (CKD) presents a global public health problem. The Clinical Practice Guideline for the evaluation and management of chronic kidney disease (KDIGO) has estimated that currently, approximately 9.1% of the global population has this condition in one clinical stage or the other[1,2]. The World Health Organization (WHO) has stated that CKD is the fourteenth leading cause of death worldwide[3,4]. Moreover, WHO has projected that CKD may become the fifth leading cause of death by 2040[3,5]. This is due to the high morbidity and mortality associated with cardiovascular diseases, severe infections, diabetes mellitus, among others, which generate high treatment costs[4,6,7]. In the United States, it has been estimated that approximately 64 million dollars are spent each year as treatment costs. However, not much is known on he related expenditure costs in Latin American countries[2,7]. Therefore, the identification of patients at high risk of developing CKD, as well as implementation of timely diagnosis and treatment, are of high health priority[1,8]. CKD is defined as kidney function failure or structural failure for a minimum of 3 months, with health implications accompanied by a decrease in the glomerular filtration rate (GFR) below 90 mL/min/L/1.73 m². It is classified into 5 stages based on GFR and albuminuria category of the KDIGO 2024[7]. There are multiple causes of CKD. These causes are diabetes mellitus, obesity, dyslipidemia, hypertension, chronic inflammatory states, autoimmune diseases, and smoking, in addition to other factors[3,5,8,9]. However, regardless of the cause, CKD affects multiple processes which under normal conditions, maintain systemic homeostasis. As the GFR decreases, there are more imbalances in other organs and systems[3]. Most of the imbalances involve elevation of nitrogenous wastes, hematological and immunological disorders; changes in acid-base balance and body water distribution; electrolyte disorders affecting potassium, calcium and magnesium, and failure of the renin-angiotensin-aldosterone system[10]. Moreover, the elevation of inflammatory markers such as IL1 and C-reactive protein in CKD patients are potent predictors of development of atherosclerotic vascular disease and infectious processes, which significantly increase mortality in these patients[3].

Periodontitis is a highly prevalent disease which affects approximately 50% of the general population[1,9], and it is the sixth most prevalent dental disease worldwide[5,11,12]. A previous estimate indicated that at least 743 million people worldwide were affected by periodontitis. However, over the last 30 years, up to 99% increase in prevalence of periodontitis has been observed, especially in developing countries[1]. This makes it an epidemiologically relevant condition [13]. Chronic periodontitis (CP) is an inflammatory infection that affects the supporting tissues of the teeth, *i.e.*, the gums, cementum, alveolar bone, and periodontal ligament. The development and maturation of dental biofilm consisting of bacterial colonies on the teeth, is the primary etiological factor that contributes to the pathogenesis of periodontal disease [1,14]. Some biomarkers associated with the inflammatory processes observed in CP are C-reactive protein, tumor necrosis factor-alpha, interleukin-6, and interleukin-1 beta[3,15].

Multiple studies have demonstrated the relationship amongst periodontitis, various systemic conditions such as diabetes mellitus, pregnancy and CKD[7]. In all cases, it was determined that the association is governed by systemic immunoinflammatory reactions in patients with periodontitis[3,11,14], especially in those with severe stages of the disease. This suggests a direct relationship between the severity of CP and the progression of CKD, with the worsening of one disease potentially exacerbating the other[7,10,16].

The objective of this editorial was to study the association between CP and CKD, thereby highlighting common inflammatory mechanisms and recent research findings that address this interrelationship. In doing so, we hoped to emphasize the importance of comprehensive and multidisciplinary care in improving the overall health of patients affected by the two diseases.

ASSOCIATION BETWEEN CHRONIC KIDNEY DISEASE AND PERIODONTAL DISEASE

Although CP and CKD have various causes, recent studies have demonstrated a bidirectional association between the two conditions[2,5,11,17]. Clinical trials suggest higher incidence and severity of periodontal problems in CKD patients, with figures ranging from 75% to 90% in different studies[3]. Cross-sectional studies have shown that advanced CP increases the risk of CKD in stages 4 and 5 up to 3.9 folds[7,9]. A cohort study on a large number of CKD patients demonstrated that the risk of mortality was increased by 32%-41% when the patients also had periodontitis[10,18]. In a meta-analysis on 17 studies, a relationship between CKD and periodontitis was observed with an odds ratio (OR) of 1.49 to 2.39, which tended to increase in cases of severe periodontitis[5,8].

In another comparative study on 66 periodontal disease patients, 33 of whom had pre-dialysis CKD, while 33 had no renal disease, all subjects received non-surgical periodontal treatment. Serum inflammatory markers were measured before and after periodontal treatment. It was found that patients with periodontitis and CKD had significantly higher levels of these parameters than patients without CKD before receiving non-surgical treatment ($P < 0.05$). However, six weeks after non-surgical management, there were significant reductions in levels of inflammatory markers ($P < 0.05$), thereby demonstrating the importance of maintaining adequate periodontal health in these patients[3,19].

Various mechanisms have been described in the association of these conditions. These mechanisms include the migration of bacteria from periodontal pockets along with cytokines and pro-inflammatory factors and lipopolysaccharides that cause endothelial damage, resulting in a persistent systemic inflammatory state. This favors the development of hypertension and cardiovascular diseases which are significant risk factors for CKD and renal endothelial damage[5,20]. Additionally, the systemic inflammatory state promotes insulin resistance which leads to the onset or worsening of diabetes mellitus[9,21], another disease that may cause CKD. Changes in CKD, such as increased serum urea and changes in salivary pH, modify the oral microbiota and increase the risk of pathogenic bacterial colonization[5,10,17].

The exacerbated inflammatory state caused by both diseases leads to a significant imbalance in oxidative stress response at the systemic level, with increased generation of reactive oxygen species (ROS)[15,21], and a decrease in glutathione peroxidase, a key antioxidant and a potent enzyme involved in regulating oxidative stress. This enzyme is produced mainly in the kidney, but it is also found in other structures, including periodontal tissues. A comparative study amongst four groups (healthy, periodontitis, CKD without periodontitis, and CKD with periodontitis) measured serum glutathione peroxidase levels, and it was observed that patients with CP had the highest levels of this enzyme, while those with CKD and CP had reduced levels, which may be associated with multiple causes[22] (Figure 1). However, the study is inconclusive.

Several studies on the connection between PD and CKD have been carried out by focusing on inflammation and oxidative stress as key mechanisms. These connections are particularly relevant in patients with underlying conditions like diabetes and hypertension.

Shinjo *et al*[23] reported that hyperglycemia, hyperlipidemia, chronic inflammation, and impaired insulin function are crucial factors in the progression of periodontitis in individuals with diabetes. The relationship between hyperglycemia and oxidative stress is particularly significant, as elevated glucose levels in people with diabetes may damage pancreatic β-cells, leading to insulin deficiency and chronic hyperglycemia, which in turn, trigger oxidative stress through inflammation, leading to diabetes-related complications. Additionally, hyperglycemia-related oxidative stress may cause macrophages to adopt an M1 polarization, leading to excessive production of inflammatory cytokines. Furthermore, hyperlipidemia, often linked to obesity-induced insulin resistance, contributes to chronic inflammation which further exacerbates periodontitis in diabetic patients[23].

The link between periodontitis and hypertension is driven mainly by systemic inflammation and immune system activation. The inflammation leads to endothelial dysfunction, a critical factor in the etiology of hypertension. Immune cells such as T cells, and cytokines, *e.g.*, interferon-gamma, which are involved in periodontitis and hypertension, damage blood vessels and increase sodium retention in the kidneys, thereby raising blood pressure. Additionally, chronic oral bacterial infections, particularly infections with *Porphyromonas gingivalis* which often occur in periodontitis, intensify systemic inflammation, thereby further contributing to hypertension and increasing the cardiovascular burden[24] (Figure 2).

Yang *et al*[25] published an intriguing paper, which was focused on the correlation between CP and CKD. Data from 22 studies on the clinical attachment level (CAL) and pocket probing depth (PPD) of CKD and non-CKD individuals were integrated. The results demonstrated that patients with CP were 1.54 times more likely to develop CKD than non-CP subjects (relative risk, RR: 1.54, 95%CI: 1.40-1.70). The incidence of CP in CKD patients was 1.98 times higher than that in healthy individuals (OR: 1.98, 95%CI: 1.53-2.57). Patients with CKD presented higher levels of CAL [standardized mean difference (SMD): 0.65, 95%CI: 0.29-1.01] and PPD (SMD: 0.33, 95%CI: 0.02-0.63), when compared to healthy controls. The study established a bidirectional association between CP and CKD through a meta-analysis of observational studies. Additionally, the risk of CKD was higher in patients with CP[25]. These findings are similar to those reported by Deschamps-Lenhardt *et al*[5]. In the latter study, a total of 37 articles from observational investigations were subjected to systematic review, out of which only 17 were used for the meta-analysis. The primary objective was to investigate the association between CP and CKD through analyses of related studies and studies on the effect of CP on renal health. The meta-analysis showed a positive association between CKD and PD, and the strength of the association increased when severe PD was considered [OR = 2.39 (1.70-3.36)]. This association was identified even after adjusting for major CKD risk factors or after using precise diagnostic criteria [OR = 2.26 for severe PD (1.69-3.01)][5]. In each of these studies[5,25], it was concluded that there was a strong correlation between CP and CKD. However, Yang *et al*[25] provided a more detailed analysis of how specific clinical parameters, *e.g.*, CAL and PPD are affected in patients with CKD, thereby highlighting the importance of oral health in managing systemic diseases. However, in contrast, Nanayakkara *et al*[26]

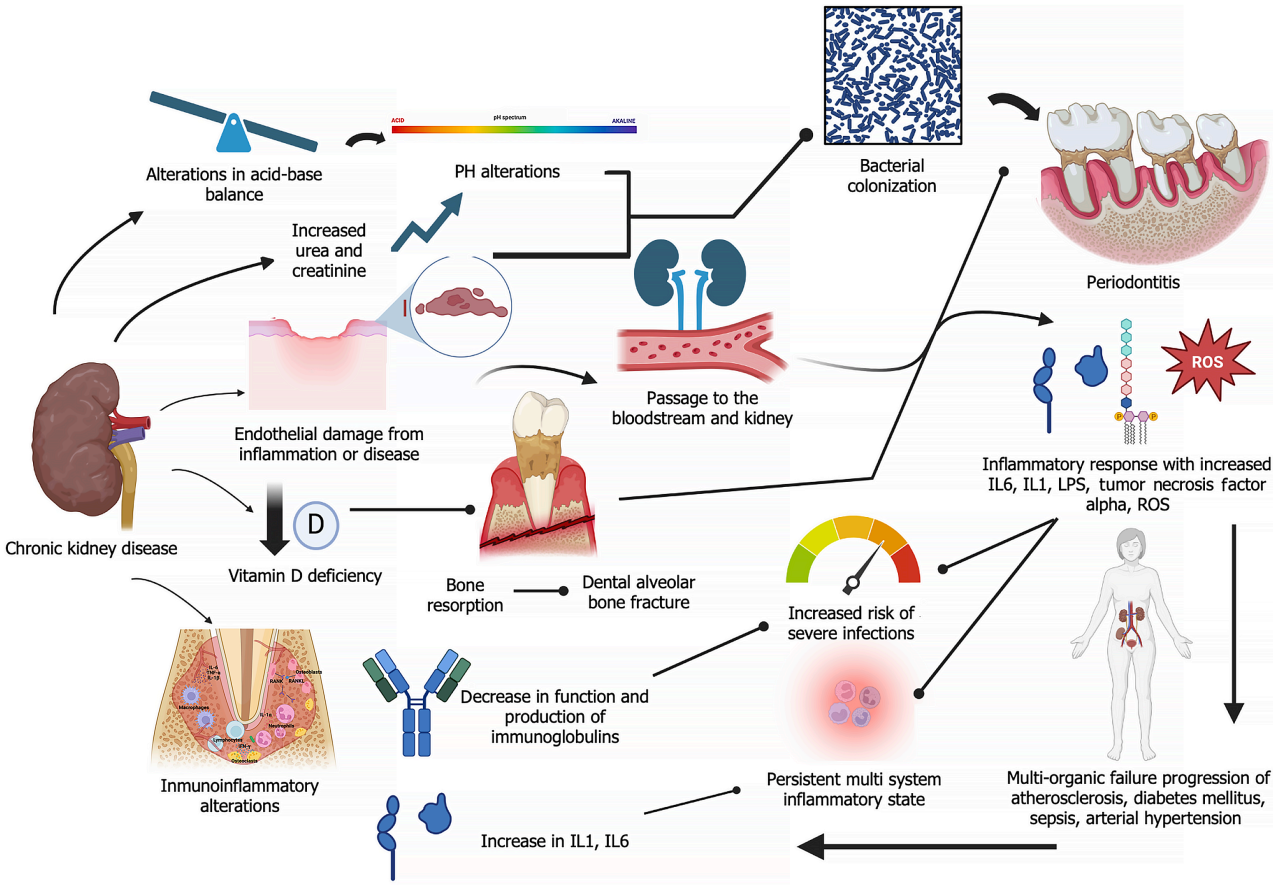

Figure 1 Image showing the main pathophysiological alterations in chronic kidney disease and periodontitis. The green arrows illustrate the alterations in periodontal disease and how the association of both conditions predisposes the patient to a persistent inflammatory state and multi-organ damage (Created with BioRender.com). IL1: Interleukin-1; IL6: Interleukin-6; LPS: lipopolysaccharide; ROS: Reactive oxygen species.

analyzed the possible association between CP and CKD through a systematic review and meta-analysis of observational studies reported in 47 articles. They concluded that participants with CP were 3.54 times more likely to have CKD than subjects without periodontitis, although significant heterogeneity was observed amongst the studies (I^2 = 88.3%, P < 0.001). However, the findings were inconclusive on directional association: The random effects model showed an incidence rate ratio (IRR) of 2.10, while the fixed effects model resulted in an IRR of 1.76, with significant heterogeneity (I^2 = 78.3%, P = 0.031)[26]. Therefore, the results indicated that there was a non-directional association between CP and CKD, although evidence for a causal association was limited. Thus, there is need for adequately designed prospective studies and longer follow-up periods in order to establish the causal relationship more clearly.

Although comparative studies provide valuable insights into the association between CP and CKD, it is essential to consider methodological limitations and potential biases in order to accurately interpret the results. The heterogeneities in the measurement methods, definitions and diagnostic criteria for CKD and CP, as well as the variabilities in the study populations presented in the study by Yang *et al*[25], may affect the validity of the findings. The research by Deschamps-Lenhardt *et al*[5] highlighted variabilities in the inclusion and exclusion criteria used in the integrated studies, which may compromise the representativeness of the results. Additionally, the absence of uniform adjustments for critical risk factors such as diabetes, smoking, and hypertension, may have introduced bias in the results, since these factors are associated with both CP and CKD. Furthermore, Nanayakkara *et al*[26] reported high heterogeneity (I^2 = 88.3%) amongst the integrated studies, indicating significant variabilities in study design, population, and outcome measures. These variabilities made it difficult for the researchers to conclusively establish the association between CP and CKD. Future studies should consider standardizing methods and definitions, rigorous adjustments for confounding factors, and employment of more robust designs, so as to enhance the quality and reliability of the findings.

CLINICAL IMPLICATIONS

Given the bidirectional relationship between CP and CKD, it is crucial for periodontists and nephrologists to collaborate closely in developing and implementing treatment strategies aimed at improving the management and outcomes of patients affected by the two concurrent diseases. Systemic inflammation and oxidative stress are underlying mechanisms that link both diseases. Thus, it is very likely that comprehensive management will significantly benefit patients' overall health.

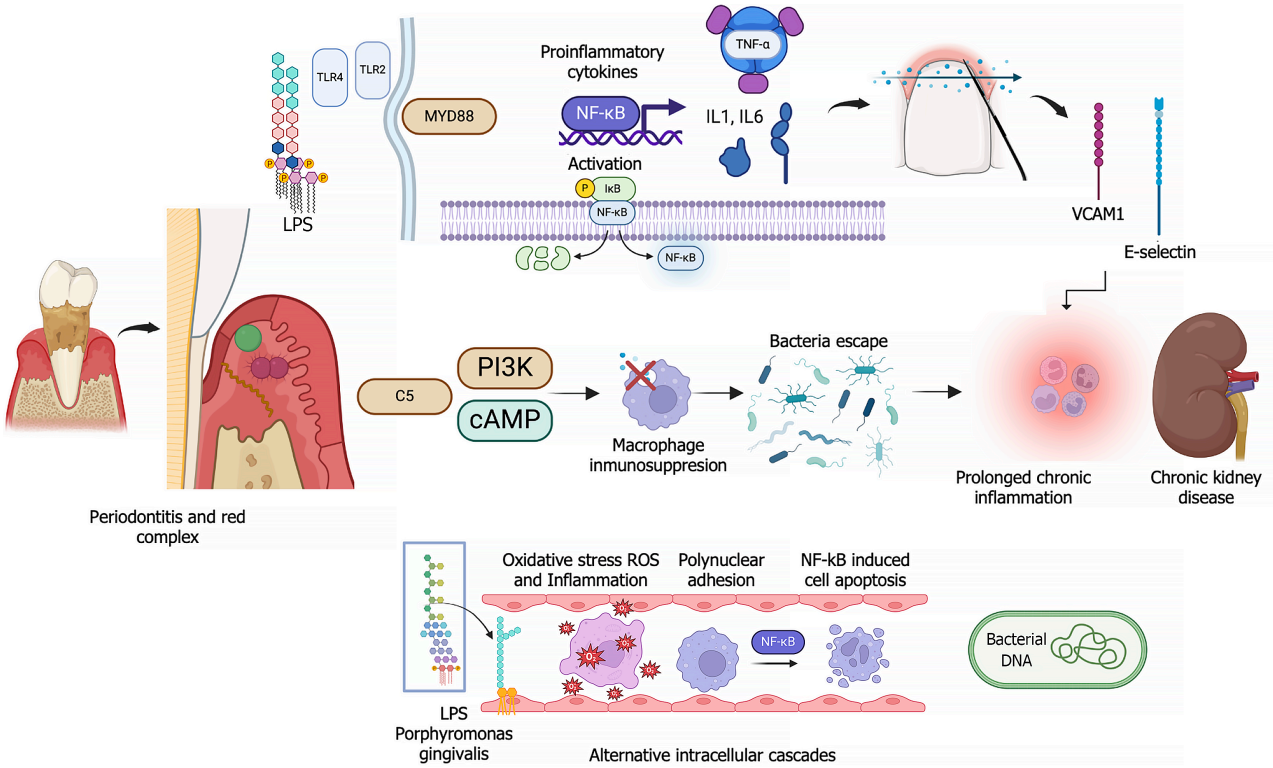

Figure 2 Bacteria from the "red complex" of periodontal disease, such as *Porphyromonas gingivalis*, activate toll-like receptors-2 and toll-like receptors-4 on immune cells *via* lipopolysaccharide. This activation triggers an inflammatory cascade mediated by MyD88 and nuclear transcription factor-kappa B (NF-kB), leading to the production of cytokines [interleukin (IL)-1, IL-6 and tumour necrosis factor alpha (TNF-α)] and adhesion molecules (VCAM1 and E-selectins). Intracellular pathways such as PI3K and cAMP induced by complement factor C5 suppress macrophage immune responses, thereby allowing pathogen survival and causing persistent inflammation. Oxidative stress driven by the presence of lipopolysaccharide from *P. gingivalis* and the production of reactive oxygen species leads to inflammation, polymorphonuclear adhesion and cellular apoptosis induced by NF-kB, which directly target bacterial DNA. This cycle of inflammation and oxidative stress exacerbates periodontal disease and chronic kidney disease, thereby negatively impacting renal and periodontal health (Created with BioRender.com). LPS: Lipopolysaccharide; TLR2: Toll-like receptors-2; TLR4: Toll-like receptors-4; MyD88: Myeloid differentiation primary response 88; NF-kB: Nuclear transcription factor-kappa B; TNF-α: Tumor necrosis factor alpha; IL1: Interleukin-1; IL6: Interleukin-6; IkB: Inhibitory protein; VCAM1: Vascular cell adhesion molecule 1; C5: Complement component 5; PI3K: Phosphoinositide 3-kinase; cAMP: Cyclic adenosine monophosphate; ROS: Reactive oxygen species.

It is essential for periodontists and nephrologists to work together to design, develop, and implement comprehensive treatment plans that address both periodontal and renal health. Effective communication and teamwork between these professionals are vital for early detection and timely intervention. In dental and nephrology clinics, it would be highly beneficial to design early detection programs for identifying patients at risk of developing CP and CKD. Early detection allows for preventive interventions that may slow down the progression of these conditions, while periodic evaluations of periodontal and renal health enable the early identification of changes and relevant treatment adjustments.

Specific periodontal therapeutic interventions and systemic inflammation control should be successfully implemented. Non-surgical and surgical periodontal therapies should be tailored in order to control the inflammatory process and reduce the bacterial load in CKD patients. Treatments should be personalized to meet each patient's specific needs. Regarding systemic inflammation control, interventions aimed at managing inflammation and oxidative stress such as the use of anti-inflammatory and antioxidant drugs, should be considered in order to improve both periodontal and renal health. It is crucial for healthcare professionals to be trained to recognize the signs and symptoms of CP and CKD, and it is vital to understand the importance of simultaneous management for the two conditions. Continuing education may enhance knowledge and cooperation among specialists.

In clinical practice, integrating these recommendations will significantly improve the management of patients with CP and CKD, thereby enhancing their quality of life and reducing the progression of the conditions. A multidisciplinary and comprehensive approach is essential for effectively addressing this bidirectional relationship and its implications for overall health.

FUTURE PERSPECTIVES

The findings presented in the meta-analysis by Yang *et al*[25] on the association between CP and CKD open several important directions for future research for enhancement of the understanding of this relationship.

Although the current study has established an association between CP and CKD, future research must ensure uniformity in the definition and classification of CP in order to guarantee more accurate comparisons and dose-response

analyses. It would be valuable to conduct randomized controlled trials to assess whether immune suppression induced by CKD increases susceptibility to CP. Additionally, it would be beneficial to investigate whether the systemic inflammatory response caused by CP leads to chronic pathological changes in renal function. Furthermore, more rigorous and consistent adjustment for confounding factors is required to reduce bias and obtain more reliable results. Research on the bidirectional relationship between CP and CKD would provide insights into how each condition may influence the other, and help develop comprehensive, multidisciplinary treatment strategies.

There is need for studies on the efficacy of specific periodontal health intervention such as non-surgical periodontal therapy, in improving renal outcomes. Randomized clinical trials aimed at investigating how periodontal treatment may influence CKD progression would be particularly valuable. Additionally, well-designed longitudinal cohort studies would be beneficial in assessing the long-term impact of periodontal interventions on renal health.

In summary, prioritizing these future research directions will not only deepen the understanding of the association between CP and CKD but also unravel the underlying mechanisms and yield more robust and precise conclusions on their relationship.

CONCLUSION

Although several studies have established an association between CP and CKD, the causal relationship between these two conditions remains uncertain due to the presence of multiple uncontrolled confounding factors in the analyzed studies. Additionally, the significant heterogeneity amongst studies suggests that the evidence is not yet conclusive enough to allow for proposal of a definitive association. Therefore, prospective research with adequate control and design are needed for the identification of the specific impact of CP on the progression of CKD, as well as studies on the specific interventions in periodontal health, in order to determine their direct effect on renal function. Until then, managing periodontal health in patients with CKD should be considered a general preventive measure without attributing a decisive influence on the progression of chronic kidney disease. Fostering interdisciplinary collaboration between periodontists and nephrologists is essential for the design, development, and implementation of treatment plans that address both periodontal and renal health. Public health policies should also prioritize the early detection and preventive management of CP and CKD by developing comprehensive health programs that integrate oral and renal care. These programs should ensure that all patients have access to quality care and promote preventive interventions to reduce the progression of both conditions. Additionally, awareness campaigns should be designed to educate the public on the importance of maintaining good oral health to prevent renal complications.

FOOTNOTES

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