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ORAL DISEASE AND NUTRITION (F NISHIMURA, SECTION EDITOR)

Periodontal Disease and Chronic Kidney Disease: the Impact of Oral Health on Inflammation and Nutrition in Patients Undergoing Hemodialysis

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Abstract

Purpose of Review Many clinical studies have reported an association between periodontal disease and chronic kidney disease (CKD). This review aims to update the underlying mechanism and the findings of clinical studies.

Recent Findings Basic research supports that inflammation might mediate the association between CKD and periodontal disease. Clinical evidence suggests that periodontal treatment improves renal function. Poor oral health has also been reported as a predictor of mortality in patients undergoing hemodialysis.

Summary Although clinical data have demonstrated a significant association between inflammation in the periodontal tissue and CKD, well-designed studies are needed for a consensus to be widely adopted. Malnutrition and systemic chronic inflammation are often interrelated in patients undergoing hemodialysis. Periodontal disease may contribute to chronic inflammation, and it is possible that a low number of teeth may be involved in impaired nutritional intake in patients undergoing hemodialysis. A novel perspective on malnutrition might be needed to manage oral health in patients with CKD, especially those undergoing dialysis, in addition to conventional factors such as bacterial infection and inflammation.

Keywords Chronic kidney disease · Dialysis · Periodontitis · Malnutrition inflammation atherosclerosis syndrome

Introduction

Periodontal disease is characterized by chronic inflammation caused by oral biofilms. Periodontal pathogens in the gingiva may be transferred throughout the systemic blood circulation, leading to elevation of inflammatory cytokines by bacterial lipopolysaccharides (LPS) [1, 2••]. Consequently, increased serum interleukin 17 (IL-17) [3], IL-1 tumor necrosis factor (TNF)-α, and activated nuclear factor kappa beta (NF-κB) [3, 4, 5, 6] cause inflammatory immune response. Oxidative stress has been suggested as a mechanism of enhanced inflammation. Periodontal disease has been reported to increase oxidative stress markers, 8-hydroxy-2′-deoxyguanosine, and isoprostanes in saliva and periodontal tissues [7, 8]. Moreover, periodontal disease also increases systemic oxidative stress by decreasing total antioxidant capacity levels and increasing malondialdehyde (MDA) and nitric oxide levels in the peripheral blood [9].

Conversely, various medical conditions also increase systemic oxidative stress. Hyperlipidemia, induced by obesity, metabolic syndrome, and hyperglycemia in diabetes mellitus, is a major cause of increased oxidative stress. Diabetes mellitus is a chronic hyperglycemic condition caused by insulin deficiency or resistance. This hyperglycemic state directly injures vascular endothelial cells owing to oxidative stress, resulting in complications associated with macro- and micro-blood vessels [10]. The suggested mechanisms include increased superoxide levels due to mitochondrial dysfunction [11] and activation of nicotinamide adenine dinucleotide phosphate oxidase in endothelial cells [12].

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In addition, under diabetic conditions, oxidative stress scavenging capacity is reduced due to the denaturation of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase. Periodontal tissues are also subjected to this systemic oxidative stress [13], resulting in delayed wound healing [14, 15], tissue regeneration in periodontal tissues [16], and impaired implant osseointegration [17], Much evidence has been accumulated for this bidirectional association between periodontal tissues and medical conditions, especially in diabetes mellitus [18]. Inflammation in periodontal tissue is associated with glycemic control independent of plaque control [19].

The inflammatory response to periodontal disease has been correlated with insulin resistance [20, 21], suggesting that severe periodontal disease may influence the development and progression of cardiovascular disease or nephropathy in diabetic patients [22, 23]. Recently, an association between periodontal disease and renal disease has been suggested. Diabetic nephropathy is one of the most common complications of diabetes, and it is possible that periodontal disease affects renal function. Furthermore, it has been speculated that periodontal disease may affect renal function independently of diabetes [23–25].

Chronic kidney disease (CKD) is defined as any renal impairment or a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for more than 3 months [26]. Progression of CKD leads to renal failure, which requires alternative renal therapies, such as renal transplantation or dialysis therapy. Patients undergoing dialysis for end-stage renal disease (ESRD) have a very high crude mortality rate of more than 20% [27]. Cardiovascular problems and infections are the most common causes of death in dialysis patients. Recently, nutritional status was shown to play a significant role in the prognosis of these patients [28, 29].

In this article, we review the relationship between periodontal disease and CKD, focusing on data from basic and clinical studies, including new perspectives, such as inflammation and nutritional intake, in addition to the conventional viewpoint of bacterial infection.

Association Between Periodontitis and Chronic Kidney Disease

In Vitro and In Vivo Studies

Periodontal disease may affect renal function through the following pathways: bacteria and their bacterial components may affect the kidneys and increase the concentration of circulating cytokines [30, 31].

In in vitro studies using vascular endothelial cells derived from mouse kidneys, stimulation with LPS of *Porphyromonas gingivalis* (*P. gingivalis*), even at low concentrations, increased the expression of serum amyloid a3 protein (Saa3) and toll-like receptor adaptor molecule 1 (TICAM1), which indicates chronic inflammation and may increase the risk of kidney disease [32].

In in vivo studies on the association between periodontal disease and CKD, two experimental designs, intravascular injection of LPS from periodontal pathogenic bacteria and ligation of molars, have been conducted to expose periodontal inflammation in the kidney. In an experiment involving intravascular injection with LPS of *P. gingivalis*, Harada et al. showed histological changes in the kidney and increased expression of Saa3 and TICAM1 following the 30-day LPS injection. These results indicate that LPS from periodontal pathogenic bacteria causes chronic inflammation in the kidney [32]. Furthermore, Sawa et al. demonstrated that LPS injection increased the accumulation of type I collagen in glomerular and urinary proteins and upregulated the expression of IL-6, TNF-α, and transforming growth factor (TGF)-β in the renal cortex of the glomeruli of streptozotocin-induced diabetic mice. This finding suggests that the circulating LPS of *P. gingivalis* causes the progression of diabetic nephropathy [33].

In the molar-ligation model, Fellipe et al. reported that acute periodontitis induced by ligature placement was associated with histological changes in the renal corpuscles; however, renal function evaluated by blood biomarkers (albumin, creatinine, glucose, and urea) was unaffected. In addition, a significant decrease in glutathione and an increase in MDA concentration in the kidney suggest that periodontal disease elevates renal oxidative stress [34].

Based on these studies, it is understood that periodontal disease affects the cellular function of the kidney, resulting in a decreased filtration rate due to glomerular fibrosis and cell damage.

Clinical Studies

Recent findings have suggested a pathological association between periodontal disease and renal dysfunction, with many clinical studies conducted in patients with periodontal disease and CKD [24, 35, 36]. A large cross-sectional study reported that periodontal disease was a potential risk factor for the development of CKD based on the assessment of estimated GFR (eGFR) [35]. A retrospective cohort study of 75-year olds showed that a higher periodontal inflammatory surface area (PISA) score was associated with an increased risk of decline in renal function (odds ratio 2.24, 95% confidence interval [CI], 1.05–4.79) [24]. Recently, a systematic review reported substantial evidence on the association between periodontitis and CKD; however, there are limited studies on the directional association [37]. Currently, the details of the mechanisms underlying this association are controversial. Periodontal disease may impair vascular

endothelial function and induce atherosclerosis and hypertension, resulting in renal dysfunction. Indirect interactions between CKD and periodontitis have also been presumed to occur due to diabetes and atherosclerosis associated with periodontitis.

Intervention studies have reported improvements in CKD disease status with periodontal therapy. In a cohort study of pre-dialysis patients with CKD, non-surgical periodontal treatment significantly reduced eGFR at 6 months after treatment [38]. In addition, endogenous inhibitors of nitric oxide synthase, asymmetric dimethylarginine (ADMA), were also significantly decreased [38]. This study highlights the comprehensive association between CKD, endothelial dysfunction, and periodontitis. A recent systematic review of 18 studies also showed that periodontal therapy improved the disease state of CKD [39••]. The findings of this review included significant improvements in serum C-reactive protein (CRP) levels [40]. as well as a significant reduction in inflammatory cytokines. Several studies have reported improvements in IL-6 levels. These findings suggest that periodontal treatment improves CKD marker levels by reducing systemic inflammation. Recent systematic reviews of intervention studies are summarized in Table 1, with two GFR analyses showing significant improvements [37] and one showing no statistically significant differences [41••]. In addition, one systematic review and meta-analysis reported a significant reduction in high-sensitivity CRP [42••].

There is much evidence that periodontal inflammation affects renal function (Fig. 1). However, more high-quality evidence is needed for consensus [43].

Clinical Studies of Oral Health in Patients Undergoing Hemodialysis

Patients undergoing hemodialysis are known to have a high incidence of oral diseases, including periodontal disease, because they are likely to have xerostomia [44] due to atrophy of salivary gland tissue, decreased body water content, and medications, as well as poor access to dental care [45]. A meta-analysis by Ruospo et al. reported a periodontal disease morbidity rate of 56.8% (95% CI 39.3–72.8) in ESRD patients who required dialysis treatment [46]. Furthermore, it has been reported that among patients undergoing hemodialysis, those with severe periodontitis had significantly higher levels of serum inflammatory markers [47], and that periodontal treatment significantly lowered the inflammatory markers [48]. These studies suggest that periodontitis may add to the inflammatory burden in patients undergoing hemodialysis who are often in a chronic inflammatory state.

We conducted a cohort study of patients undergoing hemodialysis and reported an association between oral and systemic conditions. Oral examinations, including salivary tests, were performed on 121 patients with ESRD undergoing hemodialysis and linked to their systemic condition data to explore the association between periodontal disease and systemic inflammation. The results showed that the number of *P. gingivalis* in saliva was positively and significantly associated with the levels of serum TNF receptors (TNFRs; TNFR1 and TNFR2) (TNFR1, coefficient 0.76, 95% CI 0.14–1.37, $p=0.02$; TNFR2, coefficient 0.95, 95% CI 0.09–1.80, $p=0.03$) even after adjusting for confounding factors such as age, sex, and diabetes [49•]. TNF1 and TNFR2 are markers of chronic inflammation and are known prognostic markers of mortality in patients undergoing hemodialysis [50]. Our study suggests that periodontal pathogenic bacteria may be involved in chronic inflammation in patients undergoing hemodialysis. Furthermore, a 3-year prospective cohort study in the same population showed that poor oral hygiene and dental caries predicted a high mortality rate in hemodialysis [51•]. We followed 266 patients undergoing hemodialysis for 3 years and showed that those with a debris index-simplified (DI-S) in the top tertile at baseline, namely those with poor oral hygiene, had a higher mortality rate with a hazard ratio of 3.04 (95% CI 1.50–6.17, $p=0.002$) at 3 years than those in the middle and lowest tertiles of DI-S after adjustment for confounding factors. Similarly, a higher number of decayed teeth at baseline were associated with significantly higher mortality at 3 years (hazard ratio 1.21, 95% CI 1.06–1.37, $p=0.003$). Further studies are required to determine the mechanism by which oral hygiene status affects mortality in patients undergoing hemodialysis. Previous epidemiological studies have shown that patients undergoing hemodialysis are more likely to suffer from xerostomia [52] and have poorer access to dental care [45], resulting in poor oral health compared to the healthy population [53]. As our study showed, poor oral health in patients undergoing hemodialysis may be related to their systemic condition and even to their life prognosis. Therefore, dental professionals are required to elucidate the details of these mechanisms and to take concrete actions to improve the oral health care environment for patients undergoing hemodialysis.

Relationship Between Malnutrition and Oral Diseases in Patients Undergoing Hemodialysis

Patients undergoing hemodialysis are known to have a high crude mortality rate of > 20% per year [27]. Cardiovascular disease (CVD) is the leading direct cause of death; however, nutritional status is known to play a significant role in life expectancy. Unlike simple undernutrition, such as starvation with low nutritional intake, malnutrition in patients undergoing hemodialysis is characterized by inflammation. Malnutrient patients undergoing hemodialysis are prone to

Table 1 Systematic reviews on the effect of periodontal treatment on renal function and systemic condition in patients with CKD. This is an original table prepared for this article

Author	Participants	Number of patients	Intervention	Outcome for renal function and systemic condition	Main findings
Zhao et al. [37]	Dialysis patients/patients with diagnosis of CKD with periodontitis	206 (from 5 studies)	Non-surgical periodontal therapy	eGFR, blood urea nitrogen, creatinine	The pooled mean of eGFR was not significantly different pre- and post-periodontal therapy using random and fixed effect models. The change in creatinine level was not significant using the random effect model but was significant when the fixed effect model was used ($p < 0.001$)
Yue et al. [42••]	Patients with end-stage renal disease and periodontitis undergoing dialysis	353 (from 5 studies)	Non-surgical periodontal therapy	hsCRP, albumin, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, IL-6, TNF-α	Periodontal therapy can moderately reduce serum hs-CRP levels in dialysis patients but did not significantly change IL-6 or albumin levels. For TNF-a and lipid metabolism markers, there is no sufficient evidence to support the fact that these levels are changed after periodontal therapy
da Silva et al. [41••]	Patients with CKD and periodontitis	77 (from 3 studies)	Non-surgical periodontal therapy	GFR	The GFR of individuals with CKD improved significantly after periodontal treatment

CKD chronic kidney disease; *eGFR* estimated glomerular filtration rate; *hsCRP* high-sensitivity C-reactive protein; *IL* interleukin; *TNF* tumor necrosis factor; *GFR* glomerular filtration rate

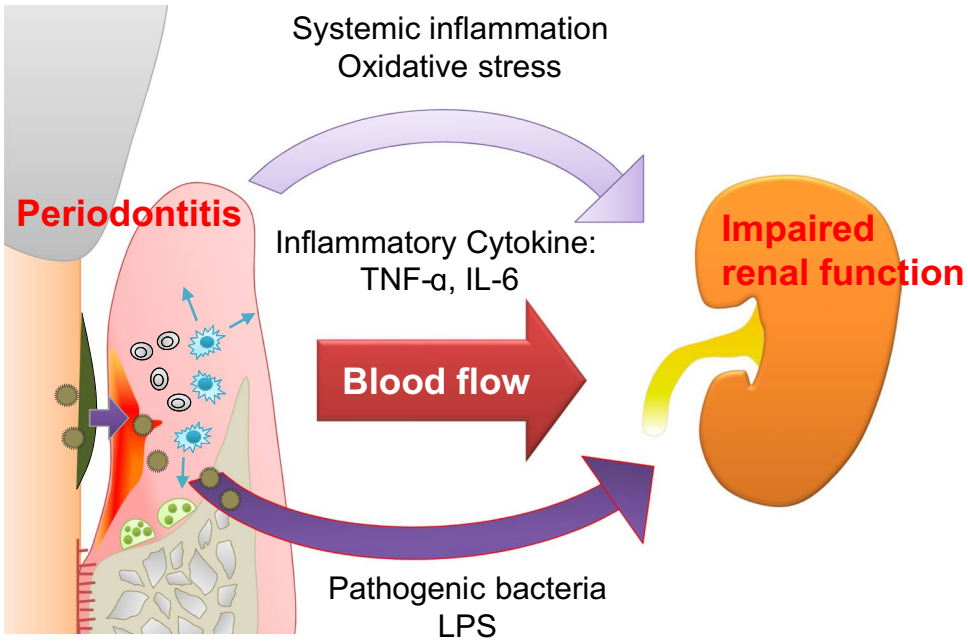

Fig. 1 Biologically plausible mechanisms linking periodontitis and chronic kidney disease. Periodontal pathogens in the dental plaque invade gingival connective tissue, causing an inflammatory response. This inflammatory response produces various cytokines that are released into the bloodstream and have the potential to reach the kidneys. Fragments of periodontal pathogens, such as *P. gingivalis* and lipopolysaccharides (LPS), released into the bloodstream may also reach the kidneys. In addition, chronic systemic inflammation and oxidative stress due to periodontitis may affect renal function. This is an original figure prepared for this article

chronic inflammation and atherosclerotic complications due to increased catabolism caused by inflammatory cytokines, such as IL-6, 8, 1b, 18, and TNF-α. This condition is called malnutrition inflammation atherosclerosis (MIA) syndrome [54], which is known to be prone to CVD and death. In the general population, overnutrition is a risk for CVD development, while in patients undergoing hemodialysis, malnutrition, such as low BMI and low cholesterol levels, is a risk for CVD development and mortality, known as "reverse epidemiology" [55, 56].

Various factors such as aging, smoking, decreased energy and protein intake, inflammatory cytokines, uremic substances, fluid overload, decreased muscle mass and physical function, dialysis-related factors, and complications (such as CVD, diabetes, and depression) are associated with nutritional disorders in patients undergoing hemodialysis. Patients undergoing hemodialysis experience gastrointestinal symptoms, such as decreased appetite, flatulence, early satiety, nausea, and gastroesophageal reflux due to decreased gastrointestinal motility [57, 58]. Inflammatory cytokines such as IL-6 and TNF-α are also associated with a decreased appetite, and chronic inflammation leads to decreased albumin production. Dialysis-related factors, such as general malaise, loss of amino acids to the dialysate solution, and uremia due to lack of dialysis, also have an impact on nutrient metabolism.

Chronic inflammation is often the cause of nutritional disorders in patients undergoing hemodialysis. Chronic inflammation is often caused by amyloidosis or atherosclerotic lesions, which renders the causative disease difficult to treat. In contrast, inflammation caused by periodontal disease is one of the candidates of a treatable inflammatory factor. Thus, we hypothesized that oral diseases, including periodontitis, may affect the mortality of patients undergoing hemodialysis via MIA syndrome (Fig. 2). MIA syndrome and periodontitis share common risk factors such as diabetes, smoking, and aging. Moreover, periodontitis increases systematic inflammatory responses due to the spread of inflammatory cytokines through the bloodstream and bacteremia caused by periodontal pathogenic bacteria [59, 60]. Our previous study showed that patients undergoing hemodialysis with high *P. gingivalis* levels in saliva

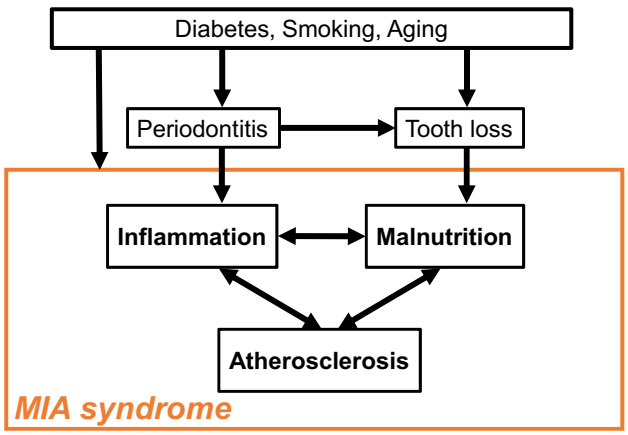

Fig. 2 A hypothesis between oral condition and malnutrition inflammation atherosclerosis (MIA) syndrome. It is commonly believed that various factors such as diabetes, smoking, and aging are involved in MIA syndrome in end-stage renal disease patients. Periodontitis might be associated with atherosclerosis via an increase in inflammation, and tooth loss was associated with malnutrition. This is an original figure prepared for this article

have significantly higher serum TNFRs, which are markers of chronic inflammation [49•]. Previous studies have also shown elevated inflammatory markers in patients undergoing hemodialysis with periodontitis compared to those without periodontitis [47, 61, 62]. Therefore, periodontitis may be an inflammatory burden in patients undergoing hemodialysis who are in a state of chronic mild inflammation. Periodontal disease is the leading cause of tooth loss in adults, while a low number of teeth increase the risk of malnutrition [63, 64]. In particular, dialysis patients with type 2 diabetes tend to experience a vicious cycle. Our recent cross-sectional study demonstrated that type 2 diabetes was significantly associated with periodontitis and the number of missing teeth in patients undergoing hemodialysis [65]. Based on these considerations, we hypothesized that poor oral health in patients undergoing hemodialysis is closely related to both inflammation and nutrient intake and may contribute to MIA syndrome. Further research will be conducted to verify this hypothesis.

Summary and Conclusion

Many clinical investigations have demonstrated an association between periodontal disease and CKD. These studies suggest that inflammation may mediate the association between CKD and periodontal disease. Interestingly, clinical evidence has demonstrated that periodontal treatment can improve renal function. However, large-scale and/or well-designed studies are needed for a consensus to be widely accepted. Chronic systemic inflammation is often the cause of nutritional impairment in patients undergoing dialysis. Periodontal disease may cause chronic inflammation, and it is also possible that a low number of teeth in dialysis patients may be involved. A novel perspective of nutritional intake might be needed to manage oral health in patients with CKD, especially those undergoing dialysis, and conventional factors, such as bacterial infection and inflammation.

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Declarations

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Conflict of Interest The authors declare no competing interests.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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