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REVIEW

Periodontitis: Tip of the iceberg in chronic kidney disease

Monchai Siribamrungwong, Pawadee Chinudomwong

Monchai Siribamrungwong, Pawadee Chinudomwong, Department of Internal Medicine, Lerdsin General Hospital, College of Medicine, Rangsit University, Bangkok 10500, Thailand
Author contributions: Siribamrungwong M and Chinudomwong P contributed to this review.
Correspondence to: Monchai Siribamrungwong, MD, MSc, Department of Internal Medicine, Lerdsin General Hospital, College of Medicine, Rangsit University, Bangkok 10500, Thailand. monsiri_dr@hotmail.com
Telephone: +66-2-3539800 Fax: +66-2-3539756
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Abstract

The prevalence of chronic kidney disease (CKD) is constantly escalating not only in industrialized countries but throughout the world. It is of major significance because of to its high morbidity and mortality. Strategies to tackle this worldwide health problem include identification of its associated risk factors, comorbidities, and complications as well as proper management to handle all the pertinent issues. Periodontal disease, a treatable infectious state of the dental supporting tissues, is common in CKD patients. Its association with CKD is believed to be in a reciprocal or bidirectional fashion and has been massively studied. This paper, therefore, aims to review the recent evidence pertaining to the association between periodontal disease and a variety of renal illnesses. Most of the current evidence was collected from cross-sectional studies and clinical trials. There is substantial evidence indicating that periodontal disease contributes markedly to the chronic systemic inflammatory burden, leading to cardiovascular and cerebrovascular complications, the principal causes of death among chronic renal disease patients. Furthermore, several studies demonstrated that proper periodontal intervention could help improve systemic inflammation and even nutritional status among CKD patients, resulting in a better quality of life. Suggestions have been made that periodontal disease should be diagnosed early, and managed and controlled to, at least, eradicate a source of inflammation in this population. Awareness of such an important issue should be increased in the relevant medical personnel.

Key words: Periodontitis; Chronic kidney disease; Dialysis; Kidney transplantation; Inflammation

Core tip: Periodontitis is gaining extensive public recognition due to its devastating impact on systemic diseases. Its association with chronic kidney disease is believed to be in a reciprocal or bidirectional fashion and has been extensively studied. In this review article, careful selection of involved studies was performed. This paper, thus, illustrates both the supporting and conflicting results of current publications pertaining to the association of periodontal disease and a variety of renal illnesses including glomerular diseases, and dialysis and kidney transplant populations.

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INTRODUCTION

Chronic kidney disease (CKD) is recognized as a significant global public health issue[1,2] because it leads to high morbidity and mortality[3,4]. The prevalence of CKD is progressively increasing[5] across the world[6,7]. Globally, CKD affects more than 50 million people[8] and more than 1 million of these undergo renal replacement therapy (RRT)[9]. CKD poses extensive burdens not only on the inflicted individuals particularly in terms of quality of life, but also on society as a whole in terms of medical care and subsequent costs. Many developed nations spend more than 2%-3% of their annual health-care budget to

provide treatment for end-stage renal disease (ESRD)[10]. For instance, a study in the United States revealed that the total management cost of CKD alone was $8000 per patient. In addition, if CKD-related comorbidities existed, the cost of care increased to $14000[11]. In 2007, the United States Medicare expenditures on CKD patients exceeded $60 billion, representing 27% of the total Medicare budget[10]. Likewise, in England, the National Health Service (NHS) disclosed that the annual cost of medical care for kidney disease was about the same as those for American patients. The estimated cost of English CKD patients was about one-third of all NHS expenditure and more than a half of the sum was spent on RRT[12].

As a result, it is important that all modifiable risk factors for CKD be identified and controlled such as blood pressure, blood glucose level, and calcium or phosphorus level[3]. Moreover, there is a significant non-traditional risk factor, chronic systemic inflammation, and its source should be identified and treated.

Periodontal disease (PD), a treatable infection of the oral cavity, is gaining more attention nowadays. PD *per se* serves as a "source of social inequality, reduced quality of life, reduced chewing function, esthetic impairment, tooth loss and disability"[13]. In relation to other diseases, a large number of studies have been carried out to demonstrate its association with numerous systemic diseases such as cardiovascular disease[13], CKD[5,14,15], ESRD[16], glomerulonephritis (GN)[17], diabetes mellitus (DM)[18], rheumatoid arthritis[15,19], chronic obstructive pulmonary disease, cognitive impairment, obesity and cancer[15].

In relation to CKD, studies have shown an increased rate of PD in this population[20], which probably results from the state of inflammation and malnutrition. The observed prevalence of PD in CKD is globally elevated and is noted as the fourth most costly disease to manage in developed countries[21]. Several studies demonstrated that CKD patients suffered more from PD than healthy subjects. For instance, one study revealed a 100% prevalence of mild to moderate gingivitis in CKD subjects compared with 85% in the general population[22]. Similarly, an investigation in the United States by the Third National Health and Nutrition Survey Ⅲ disclosed an increased prevalence of moderate periodontitis (14.6%) among CKD individuals in comparison with the control group (8.7%)[22,23].

A number of retrospective and prospective studies have also shown a marked association between periodontitis and mortality in CKD subjects, even after adjustment for various confounders such as age and smoking. The studies revealed a notable increase in mortality rate of CKD patients with periodontitis of particularly moderate-to-severe degree[20,24]. Because of the above-mentioned significance of PD, this paper aims to review the recent evidences pertaining to the close association between PD and CKD.

Definitions

CKD is defined as a condition where there is persistent kidney damage along with progressive and irreversible renal function loss[25-27] through such mechanisms as "renal hyperfiltration, increased intra-glomerular pressure, arterial hypertension, renin-angiotensin system activation, proteinuria and renal ischemia"[26]. Diagnostic criteria for CKD involve either the presence of reduced glomerular filtration rate (GFR) or markers of renal damage such as albuminuria, abnormal urine sediment, electrolytes or structure and histology for 3 or more months, and a history of kidney transplantation (KT)[28].

The National Kidney Foundation's Kidney Disease Outcome Quality Initiative classified CKD into 5 stages according to the severity of the condition. Thus, microalbuminuria represents the degree of renal damage and the measured GFR signifies the reduced renal function[29]. Simply put, CKD is classified based on Cause, GFR category, and Albuminuria category (referred to as CGA)[28].

PD is a group of infectious diseases affecting the dental supporting tissues[29-31], and is characterized by progressive destruction of the tooth supporting apparatus[13,15,32]. Commonly noted signs of PD comprise "gum tenderness, gum bleeding, gum recession, alveolar bone loss, tooth mobility, and tooth loss"[33].

PDs are derived from the microflora formed in the biofilm or dental plaque, adhering to the teeth. Significantly, periodontal pathogens are capable of invading the dental superficial tissue (gingiva) to the deeper structures (bone and ligaments)[16,30,31]. They contribute to the chronic systemic inflammatory burden by causing both local infection and disseminating into the bloodstream, leading to bacteremia[13,29]. An inflammatory cascade is then activated, as clearly seen by an elevation of inflammatory mediators, particularly C-reactive protein (CRP) and interleukin-6 (IL-6)[5,18,29], which adhere to and proliferate in the coronary endothelial cells, resulting in formation, maturation and exacerbation of atheroma, platelet aggregation and impairment of vascular relaxation[13,14,34]. These mechanisms eventually result in atherosclerotic complications, the primary cause of high morbidity and mortality among the CKD population[5,33].

Classification of PD encompasses plaque-induced gingivitis, and chronic and aggressive periodontitis. Plaque-induced gingivitis involves only tissue of the gingivae, characterized by gingival erythema, edema, hemorrhage and tissue enlargement. It is treatable and reversible, in contrast to the other 2 conditions. The pathogenesis of periodontitis includes reduced salivary production, as well as increased salivary pH and salivary urea concentration, a shift of normal oral flora from Gram-positive to Gram-negative, and secondary hyperparathyroidism, the role of which remains to be elucidated[11].

ASSOCIATION BETWEEN PERIODONTITIS AND KIDNEY DISEASES

CKD and periodontitis

Several studies have established the relationship between

Table 1 Common orofacial problems associated with chronic kidney disease itself or caused by therapy[35]

Organs	Manifestations	Organs	Manifestations
Oral mucosal lesions	Ulceration	Mouth	Poor oral hygiene
	Uremic stomatitis		Uremic odor, bad odor/halitosis
	Mucosal petechia/ecchymosis		Uremic frost
	Metastatic soft tissue calcifications		
	Macules, nodules		
	Papillomas		
	Pyogenic granuloma	Salivary glands	Acute suppurative sialadenitis
	Fibro-epithelial polyps		
	White patch, erythematous patch		
	Angular cheilitis/candidiasis	Tongue	Tongue coating
	Oral hairy leukoplakia		Geographic tongue
	Lichen planus-like disease		Black hairy tongue
	Epstein-Barr virus like lesions		
	Non-Hodgkin's lymphoma		
	Kaposi's sarcoma		
Bone	Decreased thickness of cortical bone	Periodontium	Gingival overgrowth
	Radiolucent lesions		Increased deposits of calculus
	Abnormal bone healing after extraction		Severe periodontal destruction
	Osteolytic areas		Increased tooth mobility
	Premature bone loss in the jaw		
	Decreased trabeculation	Teeth	Premature tooth loss
	Bone demineralisation		Malocclusion
	Brown tumour of the maxilla		Erosion of lingual tooth surface
	Pulp calcification		
	Pulp narrowing		
	Delayed eruption		
	Necrotic teeth		

systemic diseases, including CKD, and oral disease as an association rather than causal relationship[14,16,33,35,36]. Many described that the link between the 2 entities was bidirectional[29,30] or reciprocal[5,27]. That is, CKD and RRT, in any form, can exert an effect on oral tissues as well as dental management among these individuals. Periodontitis, likewise, adds greatly to the overall systemic inflammatory burden and the management of ESRD patients[5].

A large survey of 11200 adults demonstrated the bidirectional relationship between PD and CKD. Multivariable logistic regression models were used to evaluate the direct effect of PD on CKD, while simultaneously controlling for a direct effect of many other factors such as DM, hypertension, and socioeconomic status. Adults with PD and edentulous adults were approximately twice as likely to have CKD (OR = 1.62 and 1.83, respectively) after adjusting for 14 other potential risk factors. Moreover, the PD score was statistically important, such that for every one unit increase in the continuous PD score, the risk of having CKD increased by 1% when adjusting for other factors[34].

Impact of chronic renal disease on periodontal tissues

Numerous studies have agreed on the fact that ESRD patients neglect or pay less attention to dental care, and access and utilize dental resources and procedures less often, hence, are more likely to present with poor oral hygiene. This was attributed largely to the immense physical and psychological burden and time-consuming RRT sessions. Furthermore, confounding factors, for instance, DM, smoking, dialysis period, age, degree of medical management of renal failure complications, and demographic variables, may potentially impact on the seeking of dental care[5]. The impact of CKD and RRT was identified in oral tissues, such as xerostomia, delayed tooth eruption, enamel hypoplasia and altered salivary pH[5,30,33,34]. The tongue and salivary glands are also affected (Table 1)[35].

A frequent oral problem is cyclosporine-induced gingival hyperplasia among RRT patients particularly those with a renal transplant[5,31,34]. In ESRD patients on hemodialysis (HD), there were elevated levels of plaque and calculus, gingival inflammation, and increased rates and severity of PD. The uremic state was considered an important underlying cause, along with immune system alteration and disturbances, and hence, a reduction in the host response[2,5,31]. In the pre-dialysis population, a study in Sweden was performed in 51 subjects presenting with a variety of CKDs, and close to dialysis commencement. These participants were given a comprehensive dental inspection and the results undoubtedly revealed poor oral health in these ESRD individuals[37].

Nevertheless, not all studies reported similar findings with regard to the extent and severity of periodontitis among the CKD population. In recent literature, conflicting study results were reported. Many studies published in some Asian, and North and South American countries (Taiwan, Canada, United States and Brazil) demonstrated a higher prevalence of periodontitis in CKD and a higher frequency of chronic severe periodontitis among HD patients. In contrast, both cross-sectional and clinical trial studies from some European countries such as Spain and

the Netherlands found no statistically significant association between periodontitis and HD patients, compared with healthy control group[35].

In the same way, investigation of the association of CKD and PDs did not show uniform findings even though performed in various ethnic groups. In a cross-sectional study among non-Hispanic blacks and whites, non-Hispanic whites and those with a low income and lower educational level showed the strongest association between PD and CKD after adjustment of such variables as age, race or ethnicity, diabetes and dental care use[14]. In contrast, other studies done in the same ethnic groups reported that such an association in non-Hispanic whites was unremarkable compared with Mexican-American and non-Hispanic black CKD patients[2].

Impact of periodontal diseases on CKD

The appreciable influence of PD on CKD is amplified by the systemic inflammatory burden[5,31,33-35]. Periodontal pathogens are able to not only cause a local inflammatory reaction but also invade into the bloodstream and cause bacteremia[33,34]. The inflammatory process involves induction of several acute-phase mediators, such as elevated CRP, blood sugar and low-density lipoprotein level as well as a reduction in high-density lipoprotein level and peripheral neutrophil counts and function. This then activates the inflammatory cascade. Activation of the complement system, accumulation of pathogens in the vascular endothelium, atheroma formation and impaired vascular relaxation are all involved in the pathogenesis of atherosclerosis[13,14,35]. Subsequently, this leads to the final events of myocardial infarction and a cerebrovascular accident, the primary causes of death in CKD patients[5,33].

It is often mentioned that a greater number of pathogens are present in HD patients. *Porphyromonas gingivalis* (*P. Gingivalis*) is one of those species playing vital roles in bringing about serious outcomes in these populations. A further study regarding major periodontal pathogens and their severity among CKD patients as compared to systemically healthy controls was performed in Brazil. Sixty-six eligible chronic periodontitis patients comprised 19 healthy subjects, 25 pre-dialysis CKD patients, and 22 ESRD patients receiving RRT treatment. These patients underwent periodontal assessment in terms of periodontal pocket depth (PPD), gingival recession, and clinical attachment loss (CAL). Subgingival plaque was collected and then analyzed by polymerase chain reaction. The findings suggested a higher severity of periodontitis in CKD patients compared with their counterparts. *Eikenella corrodens* was the most prevalent periodontal pathogen found in parallel between the control and pre-dialysis groups. Conversely, the RRT group had greater numbers of *P. Gingivalis* and *Candida albicans* which are of importance in the CKD population as they often predispose these patients to opportunistic infections, signifying that administration of an antifungal agent is crucial when chronic periodontitis occurs[26].

Aside from being the source of inflammation and infection, poor oral health may act as a contributor to protein-energy wasting in the CKD population. It presents as anorexia, muscle atrophy, low anabolic hormones, insulin resistance and raised energy expenditure through a number of pathways. A variety of medications taken by CKD patients produce xerostomia which, in turn, causes deglutition problems. A metallic taste is also reported in one-third of advanced CKD individuals, affecting the flavor of food and leading to diminished nutrient intake. Poor oral hygiene, likewise, acts as a contributor to cardiovascular complications in CKD as a byproduct of the inflammatory cascade[35].

Recently, a systematic review evaluating the association between periodontitis and CKD as well as the effect of periodontal treatment on the estimated GFR was published. Four cross-sectional studies, one retrospective and 3 interventional, were included. The correlation between periodontitis and CKD was demonstrated, with an odds ratio of 1.95 (95%CI: 1.35-2.01) by pooled estimates. Interestingly, all interventional studies reported a positive effect of periodontal therapy on estimated GFR[38]. Unfortunately, the reviewer considered that the report was not a well conducted systematic review[39].

Glomerular diseases and periodontitis

In contrast to frequent studies on the association between periodontitis and CKD, limited studies in GN have been mentioned. Ardalan *et al*[17] reported a preliminary study of the association, recruiting 10 subjects with unknown primary GN (7 mesangioproliferative GN, 2 membranoproliferative GN and 1 of unknown origin). The severity of PD was determined by plaque index (PI), gingival index (GI) and PPD. All received appropriate dental treatment after initial examination. After therapy, median urine protein excretion was reduced significantly from 3100 to 900 mg/d ($P = 0.008$), and 40% of the patients were found to have decreased CRP levels. The study reported a high rate of PD through such mechanisms as direct glomerular invasion by periodontal pathogens and an indirect systemic inflammatory burden of CRP. The authors, therefore, concluded that the association between periodontitis and primary GN was plausible[17]. In addition, another comprehensive study analyzed tonsil flora in immunoglobulin A nephropathy (IgAN) patients, the most common primary glomerular disease. Sixty-eight IgAN patients and 28 controls were enrolled. *Treponema* spp. or *Campylobacter rectus*, anaerobic bacteria reported to be causative agents of PDs, played a marked role in the remission of proteinuria (HR = 2.35, $P = 0.019$), by which the IgAN subjects were found to have a higher incidence than those without these organisms[40].

The most common secondary glomerular disease is diabetic nephropathy, a complication of longstanding DM. DM is an unequivocally major risk factor of periodontitis. Commonly, the risk of periodontitis is increased about 3-fold in diabetic compared with non-diabetic populations. The level of glycemic control was determined as a key risk indicator[41]. The poorer the HbA_{1C} level among diabetic patients, the greater the risk of developing periodontitis. This, in turn, may predict the

development and progression of ESRD itself. Diabetic nephropathy patients possessed worse dental health, in terms of more dental caries and deep periodontal pockets, as well as lower salivary secretion. These patients also tended to have higher observed yeast counts, predisposing to oral candidiasis[6].

A study in the Gila River Indian community of type 2 DM patients investigated the effect of periodontitis on development of macroalbuminuria or ESRD. Sixty percent of the subjects had moderate to severe periodontitis and 20% were edentulous at baseline and during follow-up. Thirty-six percent developed macroalbuminuria and about 13% progressed to ESRD. Interestingly, the incidence of macroalbuminuria and ESRD was increased as the degree of periodontitis progressed; thus, it predicted the development of overt diabetic nephropathy and ESRD in a "dose-dependent" manner[18]. A similar study in Pima Indians with type 2 DM was performed. The relationship between number of deaths per 1000 persons and years of follow-up increased with the continuum from none/mild, moderate to severe periodontitis. After adjustment for age, sex, duration of DM, HbA1c, macroalbuminuria, magnetic resonance imaging (BMI), serum cholesterol, hypertension, electrocardiographic abnormalities and current smoking status, patients with severe periodontitis a 3.2-fold risk of cardio-renal mortality (ischemic heart disease and diabetic nephropathy combined) compared with the controls[42].

Dialysis and periodontitis

Major changes in the oral condition usually accompany the initiation of dialysis. Studies have illustrated higher rates of oral pathology in dialysis patients, presenting with one or more oral manifestations. Oral features include uremic odor, dry mouth, taste disturbance, tongue coating, mucosal petechiae and ecchymosis, reduced salivary flow, mucosal inflammation and oral ulceration[5,16,35]. Progression of PD has been reported as severity increases along the continuum from pre-dialysis, peritoneal dialysis to HD. However, studies on the prevalence of these symptoms in peritoneal dialysis and HD patients are still sparse[35].

Peritoneal dialysis

A study in Poland compared the periodontal status between 3 adult CKD groups, those on maintenance HD, continuous ambulatory peritoneal dialysis (CAPD), and pre-dialysis treatment. The study involved 202 dialysis patients (141 on HD and 61 on CAPD), and 160 CKD patients (35 on HD, 33 on CAPD and 38 pre-dialysis). Two control groups were allocated: a group of 26 healthy individuals with advanced periodontitis and 30 individuals from the general population. The severity of PD was clinically measured by the GI, papillary bleeding index, PI, CAL and community periodontal index of treatment needs (CPITN). HD patients showed the most concerning values in all parameters of PD severity[43]. A study in Brazil in 3 similar groups as above revealed that pre-dialysis patients, compared with CAPD and HD subjects, showed greater bleeding on probing, and frequency of generalized chronic periodontitis, which was enhanced by smoking. Pre-dialysis and HD groups paralleled such findings in having higher frequency of severe chronic periodontitis and percentage of sites with CAL > 6 mm. Due to the heterogeneity of the data, PD seems to have a higher prevalence of PD than the general healthy population, but lower than in the HD population. Conversely, CAPD patients and systemically healthy individuals appeared to share similarities in the periodontal conditions[44].

In Turkey, many studies were performed. One study revealed that GI, PI and calculus surface index were significantly higher in PD and HD groups than the healthy controls[45]. In addition, PD patients presented with higher salivary flow rate, salivary pH, salivary buffering capacity, decayed, missing, and filled teeth index and numbers of filled teeth than the HD counterparts[46]. Another study on the relationship between periodontitis and risk of atherosclerosis was published. The authors evaluated periodontal status of 110 eligible PD patients by using PI, GI and PD index (PDI). Atherosclerotic risk and nutritional and inflammatory markers were also assessed. There was an association between poor periodontal status and parameters of malnutrition, inflammation and atherosclerotic risk. Multiple regression analysis demonstrated that age, albumin level and duration of dialysis were independently associated with the severity of periodontitis. This study consequently confirmed the relationship between both periodontitis and non-surgical periodontal treatment and chronic systemic inflammation[47].

Recently, in a study conducted in Thailand, clinical periodontal status was evaluated in 32 stable PD patients by PI and PDI. At baseline, high sensitivity CRP positively correlated with clinical periodontal status (PI; $r = 0.57$, $P < 0.01$ and PDI; $r = 0.56$, $P < 0.01$). After completion of periodontal therapy, clinical periodontal indexes were significantly lower and CRP significantly decreased from 2.93 to 2.21 mg/dL. In addition, increased blood urea nitrogen (BUN) from 47.33 to 51.8 mg/dL, reflected nutritional status improvement. Erythropoietin dosage requirement decreased from 8000 to 6000 units/wk while the hemoglobin level remained stable. The authors, hence, concluded that periodontitis is a potential treatable source of systemic inflammation in PD patients and periodontal treatment can improve systemic inflammation, nutritional status and erythropoietin responsiveness among these patients[48].

Hemodialysis

Among the 3 modalities of RRT, HD, peritoneal dialysis and KT, HD is the most common among ESRD adult patients[49]. ESRD patients, particularly those on maintenance HD, are at great risk of cardiovascular complications, resulting in high morbidity and mortality[5,49]. In the United States, atherosclerotic events were reported as the

leading cause of death, accounting for 44% of all deaths among ESRD individuals, followed by infection.

To support this, a prospective observational study was performed in Taiwan, aiming to investigate the relationship between periodontitis and cardiovascular disease (CVD) mortality in HD patients. The dental health status of 253 included HD patients was indicated by 3 methods of examination, namely, PI, GI and PDI. After a 6-year follow-up period, the subjects with moderate-to-severe periodontitis were found at greater risk of having increased CVD-related mortality (1.83-fold), even after adjustment for various confounders such as age, smoking and educational level[24]. Similarly, with the same objective as above, a retrospective analysis was carried out in the United States One hundred and sixty-eight adults were recruited and given a dental examination to determine PD. After 18 mo of follow-up, the study concluded that HD subjects with moderate-to-severe periodontitis had a 5-fold increase in CVD mortality. Adjustment for other covariables did not significantly affect such a strong association between the 2 conditions[20].

In another study, the 253 Taiwanese HD subjects were included in a study to investigate the adverse effect of periodontitis on inflammation and malnutrition status. Three methods of assessment included PI, GI and PDI. Data on demography such as age and sex, biochemistry such as BUN, Cr, CRP, albumin and ferritin, and hematology were collected for analysis. The results conclusively revealed a significant prevalence of periodontitis among the studied patients. Not only did these individuals face an increased risk of CVD, they were also more likely to have protein-energy malnutrition. An increased degree of inflammation was observed from elevated levels of serum ferritin and CRP. The authors strongly believed that an association between clinical periodontal status and systemic inflammation existed[32]. Accordingly, effective periodontal management could result in CRP reduction and might imply a lower level of risk in developing systemic complications in this population[27], although a reduction in cardiovascular complications remain to be explored[5].

Most studies on the effect of periodontal treatment in the HD population showed a positive effect on inflammation[27,50-53]. In addition, the effect of periodontal therapy in 30 stable HD patients demonstrated a significant improvement in clinical periodontal status (both PI and PDI), nutritional markers (pre-dialysis BUN and serum albumin) and erythropoietin responsiveness after completion of treatment[50]. Nevertheless, some studies failed to show this effect. An example was a randomized controlled trial investigating an effect of intensive periodontal therapy on metabolic and inflammatory markers in 342 HD patients. The study reported an insignificant difference between the treated and control groups for serum albumin or IL-6 level at any time when adjusted for BMI, diabetes and PI. The limitation of the study was the small sample size, only 53 randomly assigned patients, the relatively healthy subjects, and the imbalance in numbers with diabetes[54].

Kidney transplantation and periodontitis

Kidney transplantation (KT) is the most efficient and preferred choice of long-term RRT despite disadvantages such as risk of opportunistic infection, graft-*vs*-host rejection, hypertension, and the tendency for reduced renal function with increased age[5,55].

Gingival hyperplasia is a notable condition observed among renal transplant patients, secondary to post-transplantation immunosuppressive agents such as cyclosporine and prednisolone. Primarily, cyclosporine was said to be the focal cause of gingival hyperplasia in a dose-dependent manner. Additional use of calcium channel blockers such as nifedipine may enhance the incidence and accelerate the severity of gum overgrowth. This can be successfully reduced by substituting cyclosporine with tacrolimus and by surgical intervention[5]. An attempt to evaluate the link between KT and oral lesions was carried out in a study including 33 renal transplant patients, 46 dialyzed patients and 37 controls. All subjects were intra-orally examined and oral disorders were identified and treated. Gingival overgrowth was the most prevalent finding among KT patients, resulting from cyclosporine administration either alone or in combination with calcium channel blockers. Other frequent findings comprised of xerostomia, geographic tongue, and oral candidiasis. A metallic taste was observed more in dialysis patients. In summary, the prevalence of oral lesions was higher in renal disease patients[55].

Investigation of the association between periodontal status and renal allograft function, estimated by GFR, was carried out in the United States. KT patients were categorized into 2 groups: deterioration or stable/improvement of renal function between 2 time points at least 6 mo apart. Chronic periodontitis, defined by $\geqslant 6$ sites with probing depth $\geqslant 5$ mm, or clinical attachment level $\geqslant 4$ mm in at least 6 proximal sites, was significantly more prevalent in patients with reduced renal function ($P = 0.04$). It acted as a statistically significant predictor of improved renal function over time ($P = 0.04$)[56]. Interestingly, the impact of chronic periodontitis on other cardiovascular conditions among these individuals was further studied. A study from Poland illustrated this when it aimed to assess whether periodontitis may contribute to left ventricular hypertrophy (LVH) in KT patients. Ninety-nine patients were classified according to CPITN score into patients with advanced disease (CPITN 3-4) and none/moderate lesions (CPITN 0-2). The advanced lesion group had higher plasma high-sensitivity CRP concentration ($P < 0.05$) and left ventricular mass index (LVMI) ($P < 0.001$), compared with the other group. Besides, LVMI was dependent on CPITN ($P < 0.001$), high-sensitivity CRP ($P < 0.05$), serum cholesterol ($P < 0.05$) and Cr levels ($P < 0.05$). The authors concluded that chronic periodontitis and a concomitant systemic inflammatory reaction in KT patients may be associated with LVH[57].

Finally, inflammation is recognized as playing a pivotal role in transplant rejection. CRP and IL-6, significant

inflammatory markers, are documented as surrogate markers to identify patients who are at greater risk of rejection. In light of this, a hypothesis was proposed that periodontitis may increase the risk of organ rejection by contributing to the systemic inflammatory load in organ transplant patients. A study about the link between periodontitis and serum IL-6 was performed in 47 transplant patients and 18 healthy age-matched controls. The result demonstrated a significantly higher level of serum IL-6 and increased mean probing depth in transplant patients. Multivariable linear regression analysis, after adjustment for sex, diabetes, smoking and immunosuppressant dose, showed that the mean probing depth, number of missing teeth and mean percentage of sites with at least 4 mm of attachment loss were independent predictors for elevated serum IL-6 levels[58]. Besides, a study with a larger group of subjects (90 transplant patients compared with 72 age-matched controls) reported a higher level of IL-6 and CRP in transplant individuals, compared with the control group[59].

CONCLUSION

The current literature strongly supports an association between PD and CKD. They affect each other reciprocally. PD, a treatable infective dental condition, potentially places a devastating chronic systemic inflammatory burden on the CKD population, resulting in significant atherosclerotic complications and death. In the same way, chronic renal disease impacts on oral health in this population with gingival overgrowth as the most prevalent finding due to a cyclosporine-mediated mechanism. Several studies concluded that proper periodontal intervention rendered a promising outcome in the systemic improvement of CKD subjects although its impact on cardiovascular complications remained to be further explored. Thus, PD diagnosis and management deserve better awareness. Further investigation, especially prospective randomized controlled trials, with intervention should be conducted to allow more accurate evaluation. Also, a larger number of participants and ethnic subgroups are required to be recruited in the research to provide more data to make firmer conclusions.

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