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**Title: Periodontitis:** Tip of The Iceberg in Chronic Kidney Disease

**Running title:** Periodontitis and CKD

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**Abstract:**

Prevalence of chronic kidney disease (CKD) population is constantly escalating not only in the industrialised countries but throughout the world. Its significance is tremendous owing to the consequences it brings about, leading to high morbidity and mortality. Strategies to tackle such a world health problem include identifying associated risk factors, co-morbidities, and complications as well as proper management to handle all the addressed 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 bi-directional fashion and has been massively studied. This paper, therefore, aims to review the recent evidences pertaining to the association between periodontal disease and a variety of renal maladies. Most of the current evidences collected were performed as cross-sectional studies and clinical trials. Substantial results revealed that periodontal disease contributes remarkably to the chronic systemic inflammatory burden, leading to cardiovascular and cerebrovascular complications, the principal causes of death among the chronic renal disease patients. Furthermore, several studies demonstrated that proper periodontal intervention could help improve the systemic inflammation and even nutritional status among the CKD patients, resulting in better quality of life. Suggestions have been made that periodontal disease be early detected, managed and controlled to, at least, eradicate a source of inflammation in this population. Awareness of such importance should have been drawn from the concerned parties.

**Key Words**: Periodontitis, Chronic kidney disease, Dialysis, Kidney Transplantation, Inflammation

**Core Tips:**

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 bi-directional fashion and has been massively studied. Designed as review article, vigilant selection of involved literatures was attempted. This paper, thus, illustrates both the supporting and conflicting results of current publications pertaining to the association of the periodontal disease and a variety of renal maladies including glomerular diseases, dialysis and kidney transplant population.

**INTRODUCTION**

To date, chronic kidney disease is globally recognised as a significant public health issue (1, 2).It leads to high morbidity and mortality (3), resulting from cardiovascular events (4). Apparently, the number of chronic kidney disease (CKD) population is progressively rising (5) across the world (6, 7), posing extensive burdens not only to the inflicted individuals, importantly in terms of quality of life. They also affect the society as a whole, especially, in terms of medical care and subsequent costs. As a result, it is important that all modifiable risk factors for CKD be identified and controlled such as blood pressure, blood sugar level, and calcium or phosphorus level (3). Moreover, there is a significantly non-traditional risk factor, chronic systemic inflammation, in which its source should be identified and treated.

Periodontal disease, a treatable infection of the oral cavity, is gaining more attention nowadays. This condition per se serves as a “source of social inequality, reduced quality of life, reduced chewing function, aesthetic impairment, tooth loss and disability” (8). 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 (8), CKD (5, 9, 10), and end-stage renal disease (ESRD) (11), glomerulonephritis (GN) (12), diabetes mellitus (DM) (13), rheumatoid arthritis (10, 14), chronic obstructive pulmonary disease (COPD), cognitive impairment, obesity and cancer (10).

Principally, the rationale is that periodontal disease contributes to chronic systemic inflammatory burden by disseminating periodontal pathogenic bacteria and inducing inflammatory cascade. This is clearly seen in an elevation of inflammatory mediators, particularly the C-reactive protein (CRP) and interleukin-6 (IL-6) (5, 13, 15). This brings about the endothelial dysfunction and atheroma formation (9), which in turn, ensues atherosclerotic complications. That is, myocardial infarction and cerebrovascular disease, the primary cause of high morbidity and mortality among the CKD population (5, 16).

Because of the mentioned significance, this paper aims to review the recent evidences pertaining to the close association between periodontal diseases and the chronic kidney disease.

**Definitions**

**Chronic kidney disease** is defined as a condition where there is persistent kidney damage, progressive and irreversible renal function loss, determined by albuminuria and a decreased glomerular filtration rate (GFR) for at least three months (17, 18, 19) (**Table 1**). Identified mechanisms taking part to the unremitting loss of renal function considerably involve “renal hyperfiltration, increased intra-glomerular pressure, arterial hypertension, renin-angiotensin system activation, proteinuria and renal ischaemia” (18). CKD is generally characterised by abnormal blood tests such as higher blood urea nitrogen (BUN) or serum creatinine (Cr) level that usually underestimate this condition (20).

Currently, the National Kidney Foundation’s Kidney Disease Outcome Quality Initiative’s (KDOQI) classified CKD into five stages according to the severity of condition. In this sense, microalbuminuria represents the degree of renal damage and measured GFR signifies reduced renal function (15) (**Table 2 and 3**). Simply put, CKD is classified based on **C**ause, **G**FR category, and **A**lbuminuria category (referred to as CGA) (20).

**Periodontal disease** is a group of infectious diseases affecting the dental supporting tissues (15, 21, 22), characterised by the progressive destruction of the tooth supporting apparatus (8, 10, 23). Commonly noted signs of periodontal disease comprise of “gum tenderness, gum bleeding, gum recession, alveolar bone loss, tooth mobility, and tooth loss” (16).

Periodontal diseases 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 (gingival) to the deeper structure (bone and ligament) (11, 21, 22), disseminating into the bloodstream and causing both local infection and bacteraemia (8, 15). As well as adhering to and proliferating in the coronary endothelial cells, resulting in formation, maturation and exacerbation of atheroma, platelet aggregation and vasculature relaxation impairment (8, 9, 24).

Classification of periodontal disease encompasses plaque-induced gingival disease, early-onset, chronic adult, and aggressive periodontitis. Plaque-induced gingival diseases (briefly called gingivitis) involve only tissue of the gingivae, characterised by gingival erythema, oedema, haemorrhage and tissue enlargement. It is treatable and reversible, in contrast to the other three conditions. Pathogenesis of periodontitis includes reduced salivary production. As well as increased salivary pH and salivary urea concentration, shift of normal oral flora from Gram–positives to Gram–negatives and secondary hyperparathyroidism of which role is yet proved (11).

**ASSOCIATION BETWEEN PERIODONTITIS AND KIDNEY DISEASES**

**Chronic Kidney Disease and Periodontitis**

Several studies have established the relationship between systemic diseases, including CKD, and the oral disease as an association rather than causal relationship (9, 11, 16, 25). Many described that linkage between the two entities is in a bidirectional (15, 21) or a reciprocal fashion (5, 19). Craig RG pointed out that CKD and periodontitis are mutually related and affecting each other. That is, CKD and renal replacement therapy (RRT), in any form, can exert an effect on oral tissues as well as dental management among these individuals. Periodontitis, likewise, puts in greatly to the overall systemic inflammatory burden and the management of the end stage renal disease patients (5).

* **Effects 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, access and utilise less of dental resources and procedures; hence, present with poor oral hygiene. This was attributed largely by immense physical and psychological burden and time–consuming RRT sessions. Furthermore, confounding factors, for instance, DM, smoking, dialysis vintage, age, degree of medical management of renal failure complications, demographic variables, may potentially impact the dental care search (5). Impact of CKD and RRT was identified on oral tissues such as xerostomia, delayed tooth eruption, enamel hypoplasia and altered salivary pH (5, 16, 21, 24). The tongue and salivary glands are as well affected (25) (**Table 4**).

Frequent oral problem is cyclosporine-induced gingival hyperplasia among the RRT patients particularly transplantation (5, 21, 24). In ESRD on haemodialysis (HD) patients, there were elevated level of plaque and calculus, gingival inflammation, and increased tendency and severity of periodontal disease. Uremic state was considered an important underlying cause of the mentioned state, along with immune system alteration and disturbances, and hence, reducing the host response (2, 5, 21).

Nevertheless, not all studies came across with similar findings with regards to extent and severity of periodontitis among the CKD population. In recent literatures, conflicting study results were reported. Many studies published in some of Asian, North and South American countries -Taiwan, Canada, U.S. and Brazil- demonstrated a higher prevalence of periodontitis in CKD and higher frequency of chronic severe periodontitis among HD patients. On the contrary, both cross–sectional and clinical trial studies from some the European countries such as Spain and the Netherland found no statistically significant association between periodontitis and HD patients, as compared to the healthy control group (25).

In the same way, investigation of the association of CKD and periodontal diseases did not show uniform findings even though performed in the same various ethnic groups. Grubbs *et al*. conducted a cross-sectional study among non-Hispanic blacks and whites, those with low income and lower educational level. At the end of study, the authors observed a noteworthy association between periodontal disease and CKD. The association is strongest among the non-Hispanic whites and the low income population after adjustment of such variables as age, race or ethnicity, diabetes and dental care use (9). In contrast, studies done in the same ethnicity as above reported disparities in the relationship between CKD and periodontitis. The outcomes suggested a higher prevalence of moderate periodontitis and missing teeth in the CKD subjects compared with the non-CKD participants, in all three ethnic groups, although degree of likelihood differed. Mexican–Americans CKD patients ranked the first with three-fold likelihood (37.3%), followed by non–Hispanic blacks, with a two-fold probability (38.9%) of having moderate periodontitis. However, findings in non-Hispanic whites (12.9%) were unremarkable. The same findings held true in terms of linkage between moderate periodontitis prevalence and the dose–response effect. Thus, the authors wrapped up the study as disparities existed across these ethnic groups in the association between periodontitis and prevalence of CKD (2).

* **Effects of periodontal diseases on chronic kidney disease**

The appreciable influence of periodontal disease on CKD was amplified by systemic inflammatory burden (5, 16, 21, 24, 25). Periodontal pathogens were able to not only cause the local inflammatory reaction but also invade into the bloodstream and cause bacteraemia (16, 24). Vastly mentioned, a greater number of pathogens were found in HD patients. *Porphyromonas gingivalis* is one of those species playing vital roles in bringing about such serious outcomes in these populations. Inflammatory process involves induction of several acute–phase mediators, such as elevated CRP, blood sugar and low–density lipoprotein (LDL) level as well as declining high-density lipoprotein (HDL) level and peripheral neutrophil counts and function. This, afterwards, activates the inflammatory cascade. Frequently reported, the higher CRP level correlates to the severity of periodontal disease (5, 21) (**Figure 1**).

A larger survey study was the third National Health and Nutrition Examination Survey. It included 11,200 adults and demonstrated the bidirectional relationship between periodontal disease and CKD. Multivariable logistic regression models were used to evaluate the direct effect of periodontal disease on the CKD while simultaneously controlling for direct effect of many other factors such as diabetes, hypertension, and socioeconomic status. Adults with periodontal disease and edentulous adults were approximately twice as likely to have CKD (odd ratio = 1.62 and 1.83, respectively) after adjusting for 14 other potential risk factors. Moreover, periodontal disease score was statistically important, such that for every one unit increase in the continuous periodontal disease score, the odds of having CKD increased by one percent when adjusting for the other factors (24).

A further study regarding major periodontal pathogens and their severity among CKD patients as compared to systemically healthy controls was done in Brazil. Sixty-six eligible chronic periodontitis patients comprised of 19 healthy, 25 pre-dialysis CKD, and 22 ESRD patients receiving RRT treatment were included. 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, analysed by the polymerase chain reaction method. The findings suggested higher severity of periodontitis in CKD patients as compared to their counterparts. *Eikenella corrodens* was the most prevalent periodontal pathogen found in parallel between the control and pre-dialysis groups. Conversely, the RRT group observed the outnumbered *P. gingivalis*. *Candida albicans* was of no less importance in the CKD population as it often predispose these individuals to opportunistic infections, signifying that administration of anti–fungal agent when chronic periodontitis occurred is crucial (18).

Aside from being the source of inflammation and infection, poor oral health state may act as a contributor to protein–energy wasting in 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 in CKD patients produces xerostomia which, sequentially, causes deglutition problem. Metallic taste is also reported in one-third of advanced CKD individuals, affecting the perception of food and leading to diminished nutrient intake. Poor oral hygiene, likewise, acts as a contributor to cardiovascular complications in CKD as a by-product of the inflammatory cascade (25). 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 (8, 9, 25). Subsequently, this leads to the final events of myocardial infarction and cerebrovascular accident, the primary causes of death in CKD patients (5, 16).

In pre-dialysis population, a study in Sweden was performed in 51 subjects presented with a variety of CKD, close to dialysis commencement. These participants were given comprehensive dental inspection, covering teeth, gums and soft tissue evaluation, periodontal pocket depth (PPD) measurement, hygiene assessment and bleeding on probing (BOP), aside from panoramic radiographs. The results undoubtedly revealed poor oral health in these ESRD individuals (27). Additionally, a clinical trial was conducted in 16 pre-dialysis CKD and 14 healthy subjects, aiming to inspect the outcome of non-surgical periodontal treatment on the sub-gingival microbiota in the CKD. These subjects underwent a full-mouth periodontal clinical examination, whereby microbial analyses were done at baseline and 3 months after therapy. The authors summarised that both groups shared similar microbial composition. In comparison with the healthy controls, the CKD participants exhibited more sites of therapy non-responsive species than its counterpart, and periodontal treatment affected fewer species (1).

Moreover, a cross-sectional study, in Finland, investigated the oral health in, specifically, pre-dialysis CKD patients. Eligible 148 subjects comprised 53 diabetic nephropathy (29 with type 1 and 24 with type 2 diabetes), and the remaining 95 with other renal diseases (29 with chronic GN, 32 with polycystic kidney disease (PKD), 19 with other specified kidney disease, and 15 with unspecified renal failure). Clinical oral examination encompassed number of teeth with dental erosion, number of periodontal pockets after probing, panoramic radiographs and mucosal health. The authors concluded as the followings. The poorer the HbA1C presented among diabetic patients, as compared to other types of CKD, the higher 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 the oral candidiasis (6).

Recently, a systematic review evaluating the association between periodontitis and chronic kidney disease as well as the effect of periodontal treatment on the estimated GFR was published. Four cross-sectional studies, one retrospective and three interventional studies were included. From four observational studies, the correlation between periodontitis and CKD was demonstrated along with an odd ratio of 1.95 (1.35-2.01) by pooled estimates. Interestingly, all interventional studies reported a positive effect of periodontal therapy on estimated GFR (28). Unfortunately, the reviewer critiqued on the report that this was not a well conducted systematic review. The main results were buried in abundant and mostly superfluous verbiage. To sum up, periodontitis may be associated with CKD, but current evidence is insufficient (29).

**Glomerular diseases and Periodontitis**

In contrast to frequent studies on the association between periodontitis and CKD, limited studies in GN haves been mentioned. Ardalan *et al*. reported the preliminary study of the association, recruiting 10 subjects with unknown primary GN (7 mesangioproliferative GN, 2 membranoproliferative GN and 1 of unknown origin). Severity of the periodontal disease 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/day (p=0.008), and 40 percent of the patients was found to have decreased CRP level. The study reported a high rate of periodontal disease through such mechanisms as direct glomerular invasion by periodontal pathogens and indirect systemic inflammatory burden of CRP. The authors, therefore, concluded that the association between periodontitis and primary GN was plausible (12). In addition, another comprehensive study analysed tonsil flora in immunoglobulin A nephropathy (IgAN) patients, the most common of primary glomerular disease. Sixty-eight IgAN patients against 28 controls were enrolled, by employing denaturing gradient gel electrophoresis methods. *Treponema* spp. or *Campylobacter rectus*, anaerobic bacteria reported to be causative agents of periodontal diseases, played a remarkable role in the remission of proteinuria (hazard ratio 2.35, p = 0.019), by which the IgAN subjects were found to have a higher incidence than those without these organisms (30).

By far, a common secondary glomerular disease is diabetic nephropathy, a complication of longstanding diabetes. DM is an unequivocally major risk factor of periodontitis. Commonly, the risk of periodontitis is increased about three times in diabetic as compared with non-diabetic populations. Level of glycaemic control was determined as a key risk indicator. Those with HbA1C level above 9% are likely to have severe periodontitis, compared with normal population after adjustment for age, sex, ethnicity, education and smoking (31).

A study in the Gila River Indian community with type 2 DM investigated the effect of periodontitis on development of macroalbuminuria or ESRD. Sixty percent of the subjects had moderate to severe periodontitis and 20 percent were edentulous at baseline and during follow-up period. Thirty-six percent developed macroalbuminuria and about 13 percent progressed to ESRD. Interestingly, the incidence of macroalbuminuria and ESRD was elevated as the degree of periodontitis progressed; thus, predicted the development of overt diabetic nephropathy and ESRD in a “dose-dependent” manner (13). A similar study in Pima Indians with type 2 DM was performed. The relationship between number of deaths per 1,000 person and years of follow-up was increasing along the continuum from none/mild, moderate to severe periodontitis, respectively. After adjustment for age, sex, duration of DM, HbA1C, macroabuminuria, body mass index, serum cholesterol, hypertension, electrocardiographic abnormalities and current smoking status, patients with severe periodontitis had 3.2 times the risk of cardio-renal mortality (ischemic heart disease and diabetic nephropathy combined) compared with the other two counterparts (32).

**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 of the oral manifestations. Oral features include uremic odour, dry mouth, taste disturbance, tongue coating, mucosal petechiae and ecchymosis, reduced salivary flow, mucosal inflammation and oral ulceration (5, 11, 25). Progression of periodontal disease has been reported as severity increases along the continuum from pre-dialysis, peritoneal dialysis (PD) to HD. Yet, study about prevalence of these symptoms between PD and HD patients is still sparse (25).

* **Peritoneal dialysis**

A study in Poland compared the periodontal status between three adult CKD groups, those on maintenance HD, continuous ambulatory peritoneal dialysis (CAPD), and pre-dialysis treatment group. 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 periodontal disease was clinically measured by the GI, papillary bleeding index (PBI), PI, CAL and community periodontal index of treatment needs (CPITN). HD patients revealed the most concerning values in all parameters of periodontal disease severity (33). Another study performed in Turkey evaluated periodontal parameters in PD, HD and healthy controls. The outcome revealed that GI, PI and calculus surface index (CSI) were significantly higher in PD and HD groups than the healthy controls (34).In the following years, the same authors further investigated the oral health in PD, HD and healthy controls. Salivary flow rate (SFR), salivary pH (SpH), salivary buffering capacity (SBC), decayed, missing, and filled teeth (DMFT) index and PI were analysed and compared among these populations. Interestingly, PD patients presented higher SFR, SpH, SBC, DMFT index and numbers of filled teeth than HD patients (35).

Next, a study of the relationship between periodontitis and risk of atherosclerosis was published in Turkey. The authors evaluated periodontal status of 110 eligible PD patients by using PI, GI and periodontal disease index (PDI). Besides, the atherosclerotic risk, nutritional and inflammatory markers were assessed. There found an association between poor periodontal status and parameters of malnutrition, inflammation and atherosclerotic risk factors. 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 (36). Additionally, a cross-sectional study in Brazil examined the extent and severity of periodontal diseases among the three CKD treatment regimens: pre-dialysis, CAPD and HD, as compared with the healthy controls. A total of 198 subjects were included (40 CAPD, 40 HD, 51 pre-dialysis and 67 healthy participants) and were provided with periodontal examination, covering the PI, BOP, PPD and CAL. In sum, the pre-dialysis, as compared to the CAPD and HD, subjects showed a higher BOP and frequency of generalised chronic periodontitis, which was enhanced by smoking. Furthermore, pre-dialysis and HD groups paralleled in such findings as having higher frequency of severe chronic periodontitis and percentage of sites with CAL> 6 mm. Due to the heterogeneity of data, PD seems to have a higher prevalence of periodontal disease than the general healthy population, but lower than the HD population. Conversely, CAPD patients and systemically healthy individuals appeared to share similarity in the periodontal conditions (37).

Recently, 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 BUN, from 47.33 to 51.8 mg/dl, reflected nutritional status improvement. Erythropoietin dosage requirement decreased from 8000 to 6000 units/week while 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 (38).

* **Haemodialysis**

Among the three modalities of renal replacement therapy - HD, PD and kidney transplantation (KT); haemodialysis is the most common form deployed among ESRD adult patients (39). ESRD patients, particularly those on maintenance HD, are at great risk of cardiovascular complications, resulting in high morbidity and mortality (5, 39). In the U.S., atherosclerotic events were reported as the leading cause, accounting for 44 percent of all deaths among the ESRD individuals, followed by infection. Clearly, this population group was loaded with elevated inflammatory burden as the centre of atherosclerotic pathogenesis. In this sense, an acute-phase inflammatory mediator, notably the CRP plays an essential role in activating the complement system and atheroma formation. CRP is found to increase alongside with other mediators of acute–phase response, namely, blood glucose and LDL in contrast to reduction of HDL, neutrophil count, iron, haemoglobin, and albumin. Effective management of periodontitis could result in CRP reduction although decreased cardiovascular complications remained to be further explored (5).

In this sense, 253 Taiwanese haemodialysis subjects were included in a study to investigate the adverse effect of periodontitis on inflammation and malnutrition status of these patients. 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 haematology were collected for analysis. The results conclusively revealed significant prevalence of periodontitis among the studied patients. Not only that these individuals were facing an elevated risk of cardiovascular impediment, they also encountered a state of protein–energy malnutrition. Increased degree of inflammation was observed from elevated levels of serum ferritin and CRP. The authors strongly believed that association between clinical periodontal status and systemic inflammation exists (23). Accordingly, an interventional uncontrolled clinical study in Iran was carried out to assess the impact of non–surgical periodontal treatment on CRP levels in CKD patients who were put on maintenance HD. Seventy-seven CKD patients on haemodialysis were recruited, they received a full-month periodontal examination on the number of teeth, PPD, gingival recession, CAL, PI and bleeding index (BI). All participants were then rendered non–surgical periodontal treatment after the baseline examination. The CRP level was measured at two intervals: before and eight weeks after the treatment. The results disclosed a significant reduction of serum CRP concentration from 9.369 to 5.628 (p < 0.001). The authors concluded that effective periodontal management might imply a lower level of risk in developing systemic complications in this population (19).

As well, almost studies about the effect of periodontal treatment in HD population showed positive effect on inflammation (19, 40, 41-43). What’s more, the effect of periodontal therapy in 30 stable HD patients demonstrated the significant improvement of clinical periodontal status (both PI and PDI), nutritional markers (pre-dialysis BUN and serum albumin) and erythropoietin responsiveness after completion of treatment (40). 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 dialysis patients. The study illustrated insignificant difference between the treated and control groups for serum albumin or IL-6 level at any time when adjusted for body mass index, diabetes and PI. The limitation of the study involved small sample size, only 53 randomly assigned patients, the relatively healthy subjects, and imbalance in diabetes (44).

**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-versus-host rejection, hypertension, and the tendency of reduce renal function with age advancement, (5, 45).

Gingival hyperplasia is a notable condition observed among the renal transplant patients, secondary to post-transplantation immunosuppressive agents such as cyclosporine and prednisolone. Primarily, dose-dependent cyclosporine was said to be the focal cause of this incidence. Additional use of calcium channel blockers like nifedipine may enhance the incidence and accelerate the severity of gum overgrowth. This can be successfully reduced by substitution with tacrolimus and surgical intenvention (5). An attempt to evaluate the linkage between the KT and oral lesions was carried out, including 33 renal transplant patients, 46 dialysed patients and 37 control populations. All subjects were intra-orally examined and oral findings were identified and treated. Similarly, gingival overgrowth was the most prevalent finding among the KT patients, resulting from cyclosporine administration either alone or in combination with the calcium channel blockers. Other frequent findings comprised of xerostomia, geographic tongue, and oral candidiasis. Metallic taste was observed more in dialysis patients. In sum, the prevalence of oral lesions was superior in the renal disease patients (45).

Investigation about the association between periodontal status and renal allograft function, estimated by GFR, was carried out in the United States. KT patients were categorised into two groups: deterioration or stable/improvement of renal function between two points of time, at least six months apart. Chronic periodontitis, defined by ≥ 6 probing depth > 5 mm, or clinical attachment level > 4 mm in at least six proximal sites, was significantly more prevalent in patients with deteriorated renal function (p=0.04). It acted as a statistically significant predictor of improved renal function overtime (p=0.04) (46). Interestingly, 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-sensivity CRP (p<0.05), serum cholesterol (p<0.05) and Cr levels (p<0.05). The authors summarized that chronic periodontitis and concomitant systemic inflammatory reaction in KT patients may be associated with LVH (47).

Finally, inflammation is recognised as playing a pivotal role in transplant rejection. CRP, IL-6, significant inflammatory markers, are documented as surrogate markers to identify patients who are at greater risk for rejection. In this light, a hypothesis was proposed that periodontitis may increase the risk of organ rejection by contributing to the systemic inflammation 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 significantly higher level of serum IL-6 and increased mean probing depth in transplant patients. Multivariable linear regression analysis, after adjusted for gender, diabetes, smoking and immunosuppressant dosage, 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 level (48). 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 to the control group (49).

**CONCLUSION**

Current literatures strongly supported the association between the periodontal disease and the chronic kidney diseases. They affect each other reciprocally. Periodontal disease, a treatable infective dental condition, potentially posed devastating chronic systemic inflammatory burdens to the CKD population, resulting in significant atherosclerotic complications and death. In the same way, chronic renal disease impacted the oral health in this population with gingival overgrowth as the most prevalent finding. Several studies believed that proper periodontal intervention rendered a promising outcome of the systemic improvement in CKD subjects. Thus, its diagnosis and management deserve better awareness. Further investigation especially the randomised-control trial should be conducted to allow more accurate evaluation. Also, a larger number of participants and ethnic subgroups recruited in the research are required to allow a bigger picture of comparison and conclusion.

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**Table 1**: **Criteria for chronic kidney disease (either of the following present for > 3 months)**

|  |  |
| --- | --- |
| **Markers of kidney damage (one or more)** | Albuminuria (AER > 30 mg/24 hours; ACR > 30 mg/g)  Urine sediment abnormalities  Electrolyte and other abnormalities due to tubular disorders  Abnormalities detected by histology  Structural abnormalities detected by imaging  History of kidney transplantation |
| **Decreased GFR** | GFR < 60 ml/min/1.73m2 (GFR categories G3a-G5) |

GFR: glomerular filtration rate, AER: albumin excretion rate, ACR: albumin-to-creatinine ratio

**Table 2: GFR categories in chronic kidney disease**

|  |  |  |
| --- | --- | --- |
| **GFR category** | **GFR (ml/min/1.73m2)** | **Terms** |
| G1  G2  G3a  G3b  G4  G5 | > 90  60-89  45-59  30-44  15-29  < 15 | Normal or high\*  Mildly decreased\*  Mildly to moderately decreased  Moderately to severely decreased  Severely decreased  Kidney failure |

GFR: glomerular filtration rate

\*In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfil the criteria for chronic kidney disease

**Table 3: Albuminuria categories in chronic kidney disease**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **AER**  **(mg/24 hours)** | **ACR (approximate equivalent)** | | **Terms** |
| **(mg/mmol)** | **(mg/g)** |
| A1  A2  A3 | <30  30-300  >300 | <3  3-30  >30 | <30  30-300  >300 | Normal to mildly increased  Moderately increased\*  Severely increased\*\* |

AER: albumin excretion rate, ACR: albumin-to-creatinine ratio

\*Relatively to young adult level

\*\*Including nephritic syndrome (albumin excretion usually > 2200 mg/24 hours, ACR>2200mg/g)

**Table 4: Common oro-facial problems associated with chronic kidney disease itself or caused by therapy** (25)

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

**Figure 1**: Impact of periodontal disease in the chronic kidney disease

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