

## Review Article

### Nexus between Periodontal Disease and Chronic Kidney Disease: A Narrative Review

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#### Abstract:

**Background:** Several decades of research have established the relationships between systemic diseases and periodontal diseases. Chronic kidney disease (CKD) is a chronic medical condition in which the homeostatic and excretory activity of the kidneys is progressively declines. Periodontitis is a complex, polymicrobial disease that involves both the host and the environment. Tissue destruction is primarily associated with the host's hyperresponsiveness, resulting in the release of inflammatory markers. **Aim:** This paper reviewed the evidence linking CKD, inflammatory markers, and periodontal disease and the effect of periodontal therapy on inflammatory markers and kidney function as well as dental parameters. **Setting and Design:** The sources of data were compiled and reviewed from MEDLINE, SCOPUS and Web of Sciences from 2010 to 2021. **Result and Discussion:** This review identifies biologically plausible bidirectional nexus between periodontitis and CKD. Periodontitis has emerged as non-traditional risk factor of CKD and vice versa. In addition, inflammatory markers are considered to play a role in the linkages between periodontitis and CKD. Recent study, has linked an increase in the production of inflammatory markers to a poorer renal outcome in patients with CKD. Periodontal therapy is effective in lowering the inflammatory markers levels and periodontal parameters as well as halting the progression of CKD. **Conclusion :** Understanding these links may help in identifying high-risk individuals and providing essential care at an early stage.

**Keywords:** chronic kidney disease; periodontitis; systemic inflammation; non-surgical periodontal therapy; risk factor; inflammatory markers

Bangladesh Journal of Medical Science Vol. 22 No. 02 April'23 Page : 260-271  
DOI: <https://doi.org/10.3329/bjms.v22i2.64983>

#### Introduction:

Mouth is one of a significant diagnostic tool in the clinical assessment of systemic health. The oral health of patients may be affected by various medical

conditions. Dentists are expected to see an increase in the number of patients with complicated medical conditions as a result of advances in medical research and increased survival rates for many disorders<sup>1</sup>. Unusual oral findings have been reported in variety

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of systemic diseases such as infection, coronary heart disease (CHD), diabetes mellitus, graft versus host disease, as well as chronic kidney disease (CKD)<sup>2</sup>.

According to epidemiological research, oral disease, notably periodontitis, has been linked to health consequences in non-oral tissues. On the other hand, systemic illnesses including diabetes and CKD have been linked to an increase in the prevalence, severity, and development of periodontitis in human<sup>3</sup>. Periodontitis and CKD are now known to be connected to systemic factors as well. Periodontitis and CKD share a number of risk factors, including uncontrolled diabetes, age, obesity and smoking<sup>4</sup>. Several investigations have discovered a connection between the two diseases based on biological hypothesis that on-going bacterial migration from periodontal pockets to organs including the kidney.

Periodontitis is thought to be a risk factor for CKD due to possible role of the inflammatory response to periodontal disease in the chronic systemic inflammatory load<sup>5</sup> and accumulation of periodontal inflammation. As a result, it has been related to the gradual decline in kidney function<sup>6</sup>.

Periodontitis promotes the inflammatory burden by producing cytokines including IL-1, IL-6, IL-8 and Transforming Growth Factor  $\beta$  (TGF-  $\beta$ )<sup>4</sup>. This is because bacterial and cytokine dispersal from the periodontal pocket through systemic circulation may have an effect on endothelial and kidney function. Because systemic effects such inflammation, infections, and protein-energy loss, the presence of this dual link would result in higher morbidity and mortality<sup>7</sup>.

NSPT is a commonly used treatment for eliminating dental plaque biofilm from the periodontium, as well as for reducing pain, halitosis, and periodontitis-related complications<sup>8</sup>. Its goal is to improve and protect the natural dentition. Periodontal therapy has been shown to lower morbidity and mortality, as well as glomerular filtration rate (GFR) and serum inflammatory markers<sup>9</sup>.

There has been limited research into the relationship between CKD and periodontitis as well as the impacts of NSPT on inflammatory markers. To address this shortcoming, this narrative review is conducted to enlighten and discuss the recent findings on the relationships between these two chronic diseases. This review also focuses on the pathophysiology of periodontitis and CKD in order to better understanding the bidirectional connection

between periodontitis and CKD as well as the effects of NSPT on the systemic inflammatory burden.

### Method and Material:

The sources of data are compiled from MEDLINE, SCOPUS and Web of Sciences using the keywords “chronic kidney disease”, periodontitis, “systemic inflammation”, “non-surgical periodontal therapy”, “risk factor” and “inflammatory markers” from 2010 until 2021.

### Periodontitis

Periodontitis is a chronic, non-communicable<sup>10</sup> and multifactorial disease with various etiologic and contributing factors<sup>11</sup>. It is usually characterized by the accumulation of inflammatory cells in the tissues that support the teeth<sup>12</sup>. It is caused by a pathogenic bacterium that resides in the biofilm or dental plaque that constantly surrounds the teeth<sup>15</sup>. When the inflammation penetrates deep into the tissues, it results in the destruction of supporting connective tissue and alveolar bone, ultimately leading to tooth loss known as periodontitis<sup>14</sup> as shown in Figure 1. Periodontitis may have deteriorating effects on the individual’s aesthetics and masticatory functions, leading to a decline in the quality of life<sup>10</sup> According to the National Health and Nutrition Examination Survey from 2009 to 2014, periodontitis affected 42 % of dentate United States of America (USA) people 30 years or older, with 7.8 % having severe periodontitis<sup>15</sup>.



**Figure 1:** A picture of a patient with generalized severe periodontitis.

(Informed consent was obtained from the patient)

### Chronic Kidney Disease

CKD is chronic condition in which the kidneys’

homeostatic and excretory gradual functions gradually and irreversibly deteriorate. The pathological appearance is characterised by a progressive loss of functional nephrons due to a decrease in the GFR. According to the National Kidney Foundation normal values ranged from 90 to 120 mL/min/1.73 m<sup>2</sup>. While GFR declines with age, elderly will have lower than normal GFR levels<sup>16</sup>. According to the Kidney Disease Outcomes Quality Initiative (K/DOQI), CKD is divided into the following progressive phases based on the degree of renal impairment<sup>17</sup>.

- Stage I with normal or high GFR (GFR > 90 mL/min)
- Stage II CKD (GFR = 60-89 mL/min)
- Stage III CKD (GFR = 30-59 mL/min)
- Stage IV CKD (GFR = 15-29 mL/min)
- Stage V CKD (GFR < 15 mL/min)

The progression of CKD is based on the measurement of estimated GFR in every routine clinical practice using Chronic Kidney Disease Epidemiology Collaboration Equation<sup>18</sup>. The deterioration of renal impairment is accelerated in diabetes, obesity, hypertension and primary renal disorders. CKD patients with pre-diabetic is known to have low level of Vitamin D. Hypovitaminosis D causes the NF- $\kappa$ B cascade to be upregulated and activated, resulting in the progression of renal disease and diabetic nephropathy through the production of cytokines, chemokines and other inflammatory factors<sup>8</sup>. Low vitamin D levels are also linked to inflammation, renin-angiotensin system activation, decreased expression of the insulin gene & calbindin and direct  $\beta$ -cell dysfunction.<sup>9</sup>

Cardiovascular disease (CVD) is the leading cause of death in CKD patients while CKD is recognized as a potential independent risk factor for CVD and its outcomes<sup>5</sup>. In addition, periodontitis is strongly related to elevated risk of all-cause mortality in persons with CKD<sup>15</sup>. The effects of renal impairment can lead to frequent hospitalization<sup>19</sup>, cognitive dysfunction<sup>20</sup> and poor quality of life<sup>21</sup>. An estimated 20 million people in the USA have been reported to suffer from CKD, the majority of whom are remain undiagnosed<sup>5</sup>. According to a 2016 survey, approximately 35% of the population over 70 years of age are affected by this disease and this number is increasing by the day<sup>22</sup>.

### CKD as a Risk Factor for Periodontitis

CKD has been shown to have an impact on periodontium, teeth, oral mucosa, salivary glands, and tongue<sup>14</sup> as well as bone, mouth cavity and mandibular joints<sup>7</sup>. This is associated with an inflammatory immune system and abnormal collagen production<sup>23</sup>. According to Hou et al., 2017 systemic inflammatory response, immunodeficiency, metabolic derangement, a weaker defence system against infections, and a lower ability to self-repair all play a part in the development of periodontal disease.

Xerostomia, gingivitis, tooth mobility, malocclusion, altered taste, dental erosion, mucosal lesions, parotitis, pallor mucosa, enamel hypoplasia, and delayed eruption are the oral manifestations seen in CKD and its associated therapies<sup>24</sup>. Furthermore, because of increased levels of salivary urea and phosphate in CKD patients, the formation of calculus accelerate<sup>25</sup>. In uremic CKD patients, saliva continuously produces infectious agents<sup>18</sup> and periodontopathic bacteria as well as in subgingival plaque<sup>27</sup>.

Oral disease is a preventable source of adverse health outcomes in patients with CKD. It is extremely common worldwide and is the fourth most costly disease to be handled in most developing countries<sup>28</sup>. Periodontitis and other indicators of poor oral health are common in individuals with CKD and may contribute to increased morbidity and mortality. This is due to systemic effect such as complication from atherosclerosis, infections, protein-energy loss, and inflammation<sup>7</sup>. Nyugen et al.<sup>21</sup> compared the periodontal health of CKD and non-CKD individuals in the Vietnamese population in order to determine the link between CKD and periodontitis. After controlling for relevant variables, the findings of a multivariate logistic regression analysis revealed that the CKD group had a statistically significant greater periodontitis ratio than the non-CKD population. In another study, Oyetola et al.<sup>2</sup> assessed the significant role of dental health care in the treatment of individuals with CKD. Oral lesions such as gum bleeding and periodontitis were shown to be statistically significant when CKD patients were compared to non-CKD patients in oral examination. Another established study found that CKD affects the periodontium, salivary glands, oral mucosa, tongue, and teeth. It has a detrimental impact on the patient's oral health status. Decreased oral hygiene and elevated plaque and inflammation levels are related to abandonment of dental care due to the existence of end-stage renal disease<sup>5</sup>.

Malnutrition, inflammation, and atherosclerosis were seen in greater percentages in the severe periodontitis group<sup>29</sup>. Cengiz et al<sup>20</sup> examined periodontal health in 110 patients undergoing continuous ambulatory peritoneal dialysis (CAPD), found that 85 percent of patients had poor periodontal health. Several studies have found that neglecting oral health care in CKD patients, increases plaque, calculus, and gingival irritation. A study from Sweden and the United States, found that CKD patients using haemodialysis (HD), had much higher attachment loss, poor oral hygiene, and severe gingival inflammation than controls<sup>30</sup>. On the other hand, several researchers discovered no significant association between the CKD and periodontitis and suggested that further longitudinal studies be conducted to evaluate the likelihood of a link. According to prospective research conducted in the United States, there was no significant difference in the connection between periodontitis and CKD among subgroups<sup>31</sup>.

### Severity and degree of Periodontitis in CKD Patients

There have been divergent perspectives among researchers worldwide regarding severity and degree of periodontitis in patients with CKD. According to a study, patients with more severe CKD had a higher prevalence of severe periodontitis<sup>32</sup>. According to Tawfig et al, the most advanced and symptomatic form of periodontitis in haemodialysis patients was followed by periodontitis in CAPD and pre-dialysis CKD patients<sup>33</sup>. Ibrahim HA et al, recently demonstrated a higher prevalence and severity of periodontitis among pre-dialysis CKD patients (stage 3 and 4) at Northeast Peninsular Malaysia tertiary hospital<sup>[28]</sup> Several studies, however, have discovered no statistically significant difference in the prevalence of periodontitis between stages of CKD and the severity<sup>35</sup>.

### Periodontitis as a Risk Factor for CKD

Periodontitis could be a risk factor for CKD in what ways? This is the question which has been investigated by number of researchers throughout the world. The majority of studies have identified periodontitis as a cause of inflammation, increasing the systemic inflammatory load via acute phase reactants and establishing it as a risk factor for CKD<sup>36</sup>. Chambrone et al. in 2013 conducted a systematic review and reported a consistent relationship with CKD and an important positive impact of periodontitis therapy on the estimated glomerular filtration rate

(eGFR) of subjects with CKD<sup>37</sup>. A study conducted in 2019 highlighted the potential negative impact of periodontitis on CKD<sup>4</sup>. The researcher further proclaimed of its utility in the early identification and reduction in the progress of the kidney disease<sup>38</sup>. Another Korean study analysed the data of 15,729 Korean individuals and found statistically significant impacts of severe periodontitis on CKD indicators such as reduced GFR, proteinuria, and haematuria, suggesting that periodontitis is a risk factor for CKD<sup>39</sup>. Similarly, the cross-sectional study identified edentulism and low serum titre to *Aggregatibactera ctinomycetemcomitans*(A.a) as risk factors for CKD. A.a is an exogenous bacterium that produces genuine infections and is transmissible among exposed humans<sup>40</sup>. In a cohort study conducted in 2014, Sharma et al. identified different risk factors for the CKD and found markedly high significance and prevalence of periodontitis in the patients of CKD<sup>41</sup>.

In a recent joint European and American Consensus Workshop on Periodontology, the mechanisms by which periodontitis might affect other systemic disorder were explored. Among the mechanisms are:

1. Both oxidative stress responses and acute are triggered by periodontal bacteria and their by-products.
2. The leakage of inflammation into the bloodstream by the outcomes of local inflammatory immune response<sup>42</sup>.
3. Increase in systemic inflammation burden caused by periodontitis locally induced inflammatory mediators such as interleukin (IL) -1, IL-6, Prostaglandin E2 (PGE 2) and Tumour Necrosis Factor -alpha (TNF - $\alpha$ )<sup>42</sup>
4. Link of periodontitis with the increase systemic inflammation and augmented production of pro inflammatory mediators like IL-1, IL-6, and TNF- $\alpha$ , which play a part in the activation of the hepatic acute phase response (increased C reactive protein synthesis) (CRP)<sup>23</sup> and endothelial destruction .

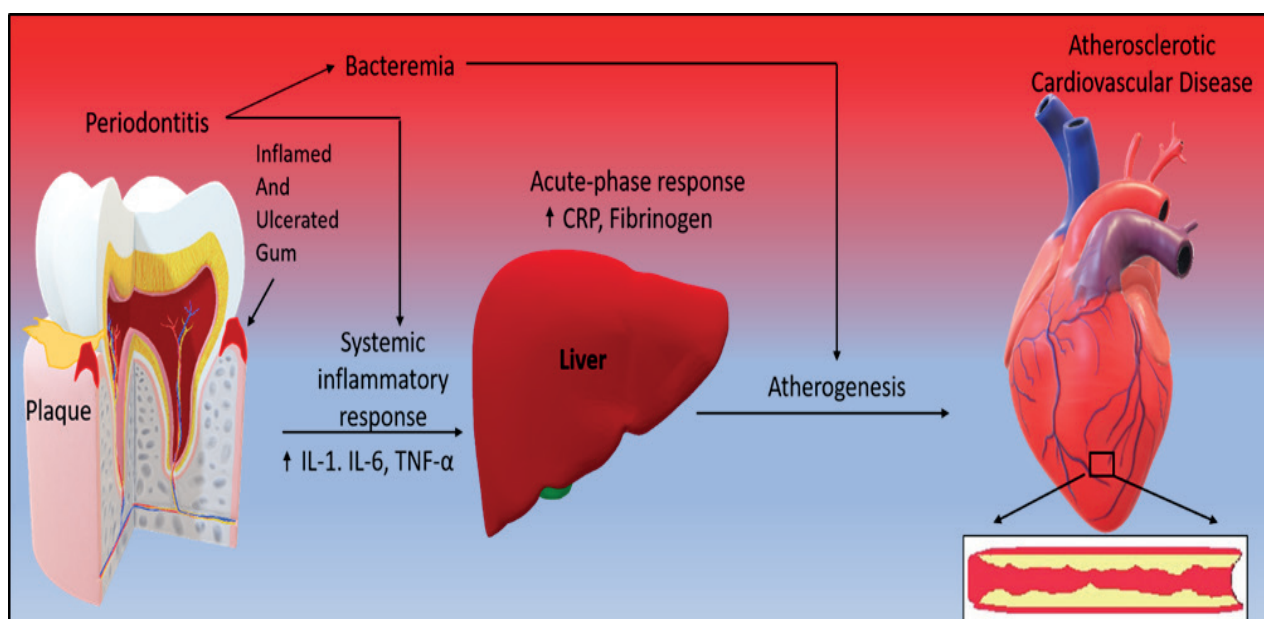
### Relationship between Periodontitis, Chronic Kidney Disease and Cardiovascular Disease (CVD)

One of the primary causes of mortality among CKD patients is the relation of periodontitis to CVD (and its other complications like atherosclerosis) is. High CRP levels and low plasma adiponectin levels are linked to an increased risk of atherosclerosis<sup>43</sup>. In CKD patients, infection as well as atherosclerotic

vascular are the leading causes of morbidity and death. According to the United States Renal Data System, atherosclerosis-related problems account for almost 38 percent of annual mortality in dialysis patients, accounting for nearly half of all deaths<sup>44</sup>. Atherosclerosis is an inflammatory process that is one of the main reasons of myocardial infarctions and thromboembolic events in CVD. It occurs in the first or second decade of life and takes years to manifest its signs and symptoms, which lead to adverse clinical consequences. The build-up of low-density lipoproteins (LDLs) in the tunica intima of the afflicted artery leads the accumulation of monocytes and lymphocytes in the intimal layer, resulting in lumen blockage and atherosclerosis<sup>45,46</sup>.

Periodontitis has recently been discovered as a risk factor for CVD in epidemiological research. The spread of infection after bacteraemia, microbial toxin damage and inflammation, endothelial dysfunction, and hemorheology have all been hypothesised as possible links between the two disease types<sup>23</sup>. Multiple studies have determined the association between periodontitis and indications of chronic inflammatory and atherosclerosis-related complications in patients<sup>47</sup>. As an on-going

source of inflammatory load, periodontitis boosts the synthesis of pro-inflammatory mediators and adhesion molecules, increasing leucocyte adherence to the vascular wall and, in turn, a pro-atherogenic response in the endothelium<sup>48</sup>. The periodontitis theory is based on mediators such as CRP, IL-6, and tumour necrosis factor-alpha (TNF-alpha) (Figure 2). The kind of reaction is either induced by a bacterial infection in the area causing severe inflammatory damage to periodontal tissue, or by the migration of bacteria, their toxins, and products throughout the body during the vicious cycle of periodontitis<sup>43</sup>. These inflammatory products such as interleukins (IL-1, IL-6), TNF- $\alpha$ , CRP, matrix metalloproteinases (MMP-8, MMP-9, MMP-1) etc., which are produced in response to bacterial outrage, then enter into systemic circulation where they boost the production of other inflammatory mediators such as monocyte chemotactic protein (MCP-1), vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM), macrophage colony-stimulating factor (MCSF), E-selectin and P-selectin. These mediators further recruit monocytes and transform them to macrophages which gets converted to foam cells upon taking LDL, thus promoting the production of pro-inflammatory cytokine<sup>49</sup>.



**Figure 2:** Illustration of proposed relationship between periodontal disease and cardiovascular disease. This above figure explains that inflammation caused by periodontitis give raise to CVD. Inflammation, often known as swelling, is the body's normal reaction to infection. When phagocytes (neutrophils and macrophages) move to the lesion site they initiate the inflammatory process. Gingival epithelium aided this process by releasing more chemical mediators such as IL-1, IL-6 and TNF- $\alpha$  to recruit neutrophils. Besides that, periodontal bacteria can colonize atherosclerotic plaques by incading artery walls directly. These oral bacteria have been discovered in the fatty deposits of patients suffering from atherosclerosis. These deposits can constrict arteries and completely block them, resulting in a heart attack or stroke.

By increasing the synthesis of a protein implicated in platelet aggregation, oral bacteria can contribute to platelet aggregation and thromboembolic events, which strengthens the link between vascular events and periodontitis. CRP has also been linked to the production of tissue factors by monocytes/macrophages, which activate the coagulation pathway and cause blood coagulation to increase. Thus, CRP levels in the gingival crevicular fluid (GCF) may represent a novel method to predict the risk of CVD in periodontitis patients<sup>43</sup>.

### **Serum Inflammatory Markers in CKD and Periodontitis.**

Inflammation is the physiological response of the tissue reaction to harmful stimuli such as infections or irritants<sup>50</sup>. Cytokines, chemokines, and acute-phase proteins enhance and coordinate the immune system's migration to the stimuli's target area, which is facilitated and coordinated by inflammation. Although it is commonly thought of as a maladaptive response, it is however helping in protecting the host by eliminating sources of damage and commencing repair<sup>51</sup>. However, the incident of tissue damage and fibrosis can be caused and triggered by chronic inflammation<sup>52</sup>. Therefore, an inflammatory response is initiated as the effect of systemic response. It increases in inflammatory biomarkers<sup>53</sup> as summarised in Table 1. The interaction of bacterial compounds' and antigens, as well as those several putative periodontal bacteria with inflammatory cells, resulting in the development and synthesis of essential mediator of several immunological inflammatory events such as cytokines (IL-1)<sup>54</sup>.

Macrophage plays a crucial function in the inflammatory response by secreting cytokines, chemokines, and matrix metalloproteinases<sup>55</sup>. Locally secreted cytokines and periodontal pathogens will potentially penetrate the blood stream and lead to damage elsewhere in the body, and some evidence of that phenomenon appears to be accessible<sup>56</sup>. Patients with periodontitis have enhanced development of systemic inflammatory cytokines (TNF-alpha, Interleukin-1 beta [IL-1 $\beta$ ], IL-6), that can induce plasma protein synthesis in the acute process, such as CRP and reduce serum albumin levels<sup>57</sup>. Additionally, higher serum levels of these cytokines, CRP and fibrinogen have been found in periodontitis patients than in regular periodontal patients<sup>56</sup>. Periodontitis can increase the inflammatory load by generating cytokines such as IL-1, IL-6, IL-8 and Transforming Growth Factor  $\beta$

(TGF-  $\beta$ ). This explains why bacterial and cytokine dispersion from the periodontal pocket via blood flow might impact endothelial and kidney function<sup>4</sup>. It is shown by rising levels periodontal infections such *Porphyromonas gingivalis*, *Treponema denticola*, and *Aggregatibacter actinomycetemcomitans* and decreased kidney function<sup>4</sup>. Inflammation has been described thoroughly in recent and previous study as one of the most powerful elements that contribute to the disastrous consequences of CKD<sup>58</sup>. Inflammatory and prothrombotic indicators predict renal function deterioration and the development of kidney disease<sup>14</sup>. A research substantiates the proof of an increased inflammatory burden, as indicated by increased levels of CRP, in 30-50% of dialysis patients<sup>35</sup>.

### **Periodontal Therapy and its effect on inflammatory markers**

Prior research has shown that periodontal therapy, including local cleaning and root planning, is particularly effective in decreasing inflammatory markers (Table 2). A meta-analysis of ten cross-sectional and four interventional studies discovered that NSPT significantly reduced CRP levels<sup>59</sup>. Similarly, periodontal therapy has been shown in various cross-sectional studies to reduce the levels of numerous biomarkers, including CRP<sup>43,60</sup>. Biyikoglu et al,<sup>61</sup> investigated haematological parameters, CRP levels, and periodontal parameters (gingival index plaque index, probing pocket depth, and periodontal disease index) in 41 HD patients receiving recombinant human erythropoietin therapy before and post periodontal therapy to explain the positive outcomes of periodontal therapy in CKD patients. The findings demonstrate a statistically significant reduction in mean CRP and erythrocyte sedimentation rate, as well as high haemoglobin value, indicating a reduction in overall inflammation. In a similar study published in 2013, Yazdi et al., evaluated the advantages of NSPT on CKD patients with periodontitis undergoing HD, and baseline data were compared to samples collected after 8 weeks. A statistically significant reduction in CRP levels was observed regardless of periodontal stage, showing a definite relationship between CRP and periodontitis. Sanjay Chaudhry<sup>22</sup> recruited 21 CKD patients and 13 healthy people to investigate there was a link between periodontal infections and inflammatory markers in CKD patients. CKD patients reported had significantly higher levels of CRP and a greater severity of periodontitis as compared to the control group.

Another study by Almeida et al.<sup>62</sup> looked at the effects

**Table 1: Summary of studies on inflammatory markers level in periodontitis patient**

No	Authors	Study design	Objectives	Outcome
1	Zhang et al 2016 <sup>60</sup>	Cross sectional study	To evaluate the levels of five biomarkers (IL-6, IL-10, CRP, TNF-a and alkaline phosphatase (ALP)) levels in gingival crevicular fluid of healthy group, aggressive and periodontitis patients:	The levels of IL-6, IL-10, CRP, TNF-a and ALP in GCF, were significantly higher in untreated sites of aggressive and periodontitis patients as compared to healthy group which proved significant correlation of clinical parameters with these five biomarkers.
2	Chandy et al, 2017 <sup>63</sup>	Cross-sectional descriptive study	To compare the levels of serum plasma fibrinogen, and CRP, in healthy people, chronic periodontitis patients, and aggressive periodontitis patients.	Serum CRP and plasma fibrinogen were increased in people with chronic and severe periodontitis in comparison to healthy controls,
3	Santosh Kumar et al. 2014 <sup>43</sup>	Meta-analysis study	To observe the effect of NSPT on CRP levels in chronic generalised periodontitis patients.	CRP level were reduced 90% after 14 days of NSPT demonstrating it as one of the underlying inflammatory causes of periodontitis.
4	Siribamrungwong et al, 2014 <sup>64</sup>	Perspective study	To examine the periodontal health in peritoneal dialysis patients after receiving periodontal therapy.	Treatment of periodontal diseases in peritoneal dialysis patients can improve nutritional status, erythropoietin responsiveness, and periodontal health.
5	Yoshihara et al, 2016 <sup>65</sup>	Logistic regression analysis	To investigate the relationship between CKD and periodontal disease	The results shown that CKD and periodontal disease have mutual consequences.
6	Yazdi et al. 2013 <sup>66</sup>	Interventional study (uncontrolled clinical trial)	The purpose of this study was to see how NSPT affected CRP levels in CKD patients on HD.	In CKD patients on HD, NSPT significantly lowers CRP levels. In CKD patients, periodontitis is a major source of systemic inflammation

of clinical periodontal treatment for patients with CKD who had severe periodontitis and found that after 3 months, all clinical parameters showed progression and improvement in each group compared to their baseline values. Thus, based on evidence presented, periodontitis may be a cause of an increase in various serum inflammatory markers, including CRP in CKD patients and effective periodontal treatment can counteract these detrimental changes. Table 1 summarises the studies on inflammatory markers in periodontitis patient

### Discussion:

The evidence provided suggest a bidirectional relationship between CKD and periodontitis, both of which are potential risk factors for each other (Table 3). However, the establishment of cause-effect association between periodontitis, CKD, systemic inflammatory markers and CVD has not been thoroughly established and further investigations are needed.

Some unanswered questions which may serve as potential subjects for future research may include

1) Lack of a vicious cycle that suggests the predisposition of periodontitis to systemic inflammation in CKD and vice versa.

2) Patients with periodontitis have been shown to be

at higher risk of developing systemic inflammation. But to what degree of severity and stage of periodontitis are we referring to?

3) Although positive impacts of periodontal therapy on systemic inflammatory indicators in CKD patients have been documented, however research on the extent of the of the aforementioned therapy on these markers is lacking.

Fisher et al investigated the nexus between these two diseases by analysing NHANES data of 11211 subjects. The study used two-step analytic method using multiple logistic regression models to independently links periodontitis and CKD. Given the possibility of a bidirectional link between these two diseases, more study on the direct and indirect consequences of periodontitis in CKD and vice versa was done. Three of the four structural equation models provided in the study, strongly supported the hypothesis of a two-way relationship between periodontitis and CKD mediated by hypertension and the duration of diabetes.

Some studies have reported that periodontal therapy has positive effects of on reducing inflammatory markers, but further exploratory research is needed in the future to confirm its effect in the CKD and other systemic diseases as summarised in Table 2. In the future, combined efforts by nephrologists and

**Table 2.: Summary of studies on the effects of periodontal therapy on systemic inflammatory conditions.**

1	Lang et al, 2019 <sup>72</sup>	Review article	To assess the effect of nonsurgical therapy on periodontitis patients	Nonsurgical therapy has gained clinical significance and has resulted in good therapeutic outcomes on periodontitis patient.
2	Zhao et al, 2020 <sup>73</sup>	Systemic review and meta-analysis	To study the effects of NSPT in patients CKD and periodontitis in order to investigate causality and evaluate the possible benefits of co-management.	The findings revealed that NSPT has the potential benefits to improve renal function in CKD patients with periodontitis.
3	Almeida et al, 2016 <sup>62</sup>	Pilot cohort study	To investigate the consequences of periodontal therapy on kidney function and metabolic markers in CKD patients with chronic periodontitis.	Periodontal treatment improves the periodontal status by showing an improvement in periodontal parameters including renal function and metabolic markers in CKD patients with chronic periodontitis.
4	Teles et al, 2011 <sup>56</sup>	Interventional study	To study the effect of the periodontal treatment and periodontal parameters level in periodontitis patients	There is relationship between the presences of clinical periodontal therapy on periodontitis patients. The results of every periodontal parameter shown a good improvement needed.
5	Grubbs et al, 2015 <sup>51</sup>	Longitudinal analysis	To evaluate the consequences of the periodontitis to the renal function progression on CKD patients	There is relationship between the periodontitis and CKD. Periodontitis affect the renal function progression on CKD patients.
6	Delbos et al, 2021 <sup>74</sup>	Retrospective study	To examine how NSPT affects GFR, systemic inflammation, and mortality in individuals with CKD.	Periodontal therapy positively affects CKD status, particularly by decreasing systemic inflammation and mortality in individuals with CKD.
7	Preshaw et al, 2020 <sup>10</sup>	Descriptive study	To assess how periodontal therapy affects systemic inflammation in CKD patients	The systemic inflammation in periodontitis and CKD patients was decreased after the periodontal therapy.
8	Orlandi et al, 2020 <sup>75</sup>	Review article	To study the effect of periodontitis treatment on cardiovascular outcomes	Periodontal treatment has a positive effect on cardiovascular events by lowering numerous cardiovascular risk variables.

dentists are needed to improve quality of life of CKD patients by early diagnosis, prevention and halting or reversing the severity of kidney impairment. Further long-term investigation on the link between periodontitis and all-cause CVD is also required. In addition to CRP, the role of additional inflammatory markers, in linking oral and systemic health should also be explored.

Despite the poorly understood relationship between CKD and periodontitis, timely evaluation and improvement of periodontal health appears to be important in overall reduction of the systemic inflammatory markers in the CKD patients, thus improving their condition. Because treating CKD patients is complex, and despite advances in expertise and early detection technologies, CKD continues to be a substantial cause of death and cardiovascular disease. Periodontitis is a new, treatable risk factor that may be identified and treated at a low cost. Consequently, it is important to identify new risk are modifiable or treatable., which should be offered by both the medical and dental health providers.

### Conclusion:

A bidirectional nexus between periodontitis and kidney disease is biologically plausible. Periodontitis has emerged as non-traditional risk factor of CKD and vice versa. A small number of studies demonstrate periodontal therapy may help in lowering the inflammatory markers levels and periodontal parameters as well as halting the progression of CKD. Understanding these links may help in identifying high-risk individuals and providing essential care at an early stage. Hence, more large-scale interventional studies are needed to evaluate whether NSPT reduces all-cause and cardiovascular mortality in patients. Therefore, in the multidisciplinary treatment of CKD or at-risk patients, a referral to a dentist should be included. Furthermore, due to chronic nature of periodontitis, long-term therapy at regular intervals would be required. Apart from that. there has been insufficient research on the molecular relationship of inflammatory biomarkers in periodontitis patient with CKD. More extensive research is needed to elucidate the modulation of inflammatory biomarkers



**Table 3: Summary of studies on the relationship between periodontitis and CKD**

No	Authors	Study Design	Objectives	Outcomes
1	Nguyen et al. 2016 <sup>12</sup>	Cross Sectional study	To compare the periodontal state of CKD patients and non-CKD patients in Vietnamese	CKD patients had worse periodontal condition as compared to non-CKD patients and there is significant relationship between periodontitis and CKD
2	Sharma et al. 2015 <sup>67</sup>	Cohort study	To determine the relationship between mortality rates in stage 3 to stage 5 CKD patients and periodontitis.	Periodontitis was found to have strong association to increased mortality rates in CKD patients.
3	Grubbs et al. 2011 <sup>31</sup>	Cross-sectional analysis of NHANES data	To investigate the link between CKD and periodontitis in different subpopulations.	The link between CKD and periodontitis varies substantially between different subpopulations.
4	Fisher et al. 2011 <sup>5</sup>	Cross-sectional study	To study the possible bidirectional relationship between CKD and periodontitis, diabetes and hypertension	A bidirectional relationship between periodontitis and CKD has been demonstrated, as has the regulation of the effect by diabetes duration and hypertension.
5	Wahid et al 2012	Review article	To review the possibility of two-way interaction between CKD and periodontitis.	There is bidirectional relationship of CKD and periodontitis.
6	Zhang et al 2017 <sup>68</sup>	Eight cohort study	To investigate the connection of the periodontitis with mortality of the CKD people	The cause of mortality in CKD populations was associated with the presence of periodontitis
7	Sharma et al, 2021 <sup>69</sup>	Cross-sectional study	To look into the relationship between periodontal inflammation and renal function.	In CKD patients, periodontal inflammation underlying source of oxidative stress.
8	Trzcionka et al, 2020 <sup>70</sup>	Cross-sectional study	To assess dental requirements of individuals with end-stage CKD using clinical examination of periodontal tissues	It shows that CKD groups have a higher number of periodontal pocket as well as bleeding index number than healthy groups.
9	Wahid et al, 2013 <sup>23</sup>	Longitudinal study	To investigate the correlation of oral health and the effectiveness of periodontal treatment on CKD patients	The systemic inflammatory response has been demonstrated to be reduced by non-surgical treatment.
10	Brody et al. 2021 <sup>71</sup>	Cross-sectional study	To study the connection between CKD and periodontitis	It has been demonstrated that the prevalence of periodontitis in CKD patients is double that of non-CKD individuals.
11	Kitamura et al, 2019 <sup>38</sup>	Review article	To determine the impact of periodontal disease on several clinical states in CKD and Kidney Transplantation (KT) patients	The findings shown that there is higher risk in CKD patients with periodontitis to have other pathological conditions such as diabetes, hypertension, liver diseases and atherosclerosis.

including its gene expression and polymorphism.

### Conflicts of Interest

The authors declare no potential conflicts of interest for this article.

### Data Availability

All the data are available in the manuscript.

Source of Fund:

This research was funded by Ministry of Education Malaysia (MOE) through, the Fundamental Research Grant Scheme (FRGS/1/2019 /SKK08/USM/02/14).

### Authors' Contribution

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