DIFFERENCE BETWEEN PERIODONTAL PATHOGENS IN STAGE III AND IV PERIODONTITIS PATIENTS WITH CHRONIC KIDNEY DISEASE: A PILOT STUDY

Suthasinee Udomwitthayaphiban[1], Nuntiya PAHUMUNTO[1], Mutita WONGSUWANLERT[1], Praphansri RUANGSRI[1] and Supontep TEERAKANOK[1]

1 Faculty of Dentistry, Prince of Songkla University, Thailand;
suthasinee.u1234@gmail.com (S. U.); nuntiya.p@psu.ac.th (N. P.)

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ABSTRACT

This study aimed to investigate difference between periodontal pathogens stage III and IV periodontitis patients with chronic kidney disease (CKD) as a pilot study. 21 participants were included and divided into 2 groups (Stage III periodontitis n=12, Stage IV periodontitis n=9) then periodontal, renal parameters were measured. Saliva, supragingival plaque and subgingival plaque were collected and measured by real-time PCR. The results showed that P. gingivalis from supragingival plaque of stage III and IV patient with CKD was significantly different at P value < 0.05. The richness of oral microbiota is different in stages of periodontitis which may also increase the severity of CKD.

Keywords: Stage III and IV Periodontitis, Periodontal Pathogen, Chronic Kidney Disease

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INTRODUCTION

The oral cavity is a route for microbial transmission to body system. Immune systems are a key to balancing these microbiotas in healthy state (symbiosis). If it cannot be maintained, it will be turned to the unbalanced stage (dysbiosis). This would finally cause a pathologic disease.

Chronic kidney disease (CKD) is a progressive condition with significant global health implications, often associated with systemic inflammation and comorbidities. Increasing evidence highlights the role of chronic inflammatory conditions, such as periodontitis, in exacerbating systemic diseases, including CKD. Periodontitis, a chronic and severe gum infection driven by pathogenic bacteria like *Porphyromonas gingivalis (P. gingivalis), Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans)* and *Tannerella forsythia (T. forsythia)*, results in the breakdown of tooth-supporting tissues and triggers systemic inflammatory responses.

The systemic impact of periodontitis stems from the dissemination of periodontal pathogens and their virulence factors into the bloodstream, causing persistent inflammation. Elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), are shared markers in both periodontitis and CKD. These cytokines not only exacerbate local periodontal damage but also contribute to systemic diseases by promoting chronic inflammation and endothelial dysfunction.

There was a significant correlation between periodontitis and CKD in literature. Some reported that when CKD patients with periodontitis received periodontal treatment, their kidney condition significantly improved (Almeida et al., 2017; França et al., 2017; Parsegian et al., 2022). Understanding the link between periodontitis and systemic conditions like CKD becomes crucial for identifying pathogenesis pathways. Despite growing evidence of this association, the precise role of periodontal pathogens in different stages of periodontitis patient with CKD remains unclear. The objective of this study is to investigate the differences between periodontal pathogens in stage III and IV periodontitis patients with chronic kidney disease.

LITERATURE REVIEWS

Periodontal disease and CKD

Periodontal diseases are an inflammatory disease involving periodontal supporting tissue which includes gingiva, periodontal ligament, cementum, and alveolar bone. Periodontitis is a periodontal disease that is characterized by progressive destruction of the teeth-supporting apparatus, including the periodontal ligament and alveolar bone (Kwon et al., 2021) which can be caused by the imbalance of periodontal pathogen, *P. gingivalis,* A. *actinomycetemcomitans* and *T. forsythia* in oral cavity. These pathogens induce inflammatory responses and periodontal tissue destruction that lead to inflammation in oral and body tissue. Periodontal disease is one of non-communicating diseases (NCDs) that affect the difficulties of eating or speaking and general well-being of the global population. In 2019, severe periodontal disease had been increased significantly between 1990 and 2019 (Organization, 2022). Estimated case numbers were almost 1 billion or 18.82% of world population. The South-East Asia region had been reported to have prevalence of periodontal disease among population around 20.77% or 307 million people. From 7th (2012) (Bureau of dental heath, 2012), 8th (2017)(Bureau of dental heath, 2017), and 9th (2023) (Bureau of dental heath, 2023) Thailand national dental health survey, there was a significantly growing number of periodontitis among Thai adults at age range from 35 to 44 and elderly at age from 60 to 74 years old especially in the Southern region of Thailand.

According to 2018 American Academy of Periodontics (AAP) classification, staging of periodontitis was classified into 4 stages. Stage III and stage IV periodontitis were considered as severe condition but stage IV periodontitis patients are the most advanced and required more multidisciplinary treatment including complex rehabilitation to re-establish a functional

dentition to improve quality of life (Kebschull et al., 2025; Sanz et al., 2020; Tonetti et al., 2018).

Chronic kidney disease (CKD) is defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m2, persisting for 3 months or more, irrespective of the cause, and can be classified into 5 stages (Vaidya & Aeddula, 2025) which is one of the health problems that many countries are facing. The global prevalence of CKD was 13.4% (Lv & Zhang, 2019), up to an estimated 7.0%-34.3% or 434.3 million adults had CKD in Asia (Liyanage et al., 2022). CKD can be developed from other diseases such as diabetes mellitus, hypertension or risk factors, smoking, obesity, NSAIDs drugs, alcohol, and heavy metal poisoning.

Periodontal pathogens and CKD

Red microbial complexes in subgingival biofilm, especially *P. gingivalis* is considered as a key stone pathogen in periodontitis. Oral bacteria can migrate into periodontal epithelium and blood circulation and some periodontal pathogens such as *A. actinomycetemcomitans, P. gingivalis, and Fusobacterium nucleatum* are involved in cancers, adverse pregnancy outcomes, cardiovascular diseases, or Alzheimer disease (Teles et al., 2022). A study showed an increased frequency of *P. gingivalis* ($P = 0.008$), *T. forsythia* ($P = 0.013$), and *T. denticola* in CKD patients (Bastos et al., 2011). *P. gingivalis, T. forsythia, F. nucleatum and T. denticola* genomic DNA were also positive in the kidney, heart, and aorta of TLR2 and TLR4 deficiency mice (Chukkapalli et al., 2018).

Lipopolysaccharide (LPS) from *P. gingivalis* may lead to diabetic renal inflammation, glomerulosclerosis, tubulitis via glomerular overexpression of vascular cell adhesion molecule-1 (VCAM-1) and E-selectin. Additionally, LPS from *P. gingivalis* can induce M1 and M2 macrophages through toll-like receptor 2 (TLR2) causing proteinuria, increasing inteleukin-6 (IL-6), tumor necrotic factor-alpha (TNF-α), transforming growth factor beta (TGF-β) expression in renal cortex of glomeruli in mice. Decreasing IL-8 in endothelial cells which caused by LPS can affect kidney function, local chemokine paralysis and uncontrolled immune response (Kajiwara et al., 2021). Gingipain from *P. gingivalis* is also a major virulence factor that can induce inflammatory response in neutrophils, macrophages, T cells and has an impact on kidney function (Chen et al., 2023; Wei et al., 2024). The effect of uremia in CKD patients led to a higher salivary pH which was favorable for periodontal pathogens such as *P. gingivalis* and *F. nucleatum* (Parsegian et al., 2022). Moreover, the patients with diabetic nephropathy presented greater amout of *A. actinomycetemcomitans* compared to non-diabetic nephropathy (Murakami et al., 2013).

RESEARCH METHODOLOGY

All the participants were received dental treatment at Postgraduation Periodontics clinic, Dental hospital, Prince of Songkla University and Nephrology clinic, Songklanagarind Hospital, Prince of Songkla University with stage III and IV periodontitis patient with chronic kidney disease patient age >20 years old target population. Inclusion criteria were chronic kidney disease patients aged 20-70 years old who had stage III or IV periodontitis**.** Exclusion criteria were patients with fewer than 15 remaining teeth, patients who have received any periodontal treatment within the last 6 months, patients with a history of acute renal failure within the last 3 months, patients currently using immunosuppressive drugs, pregnant patients, patients with hematocrit (Hct) level below 30%, patients with chronic diseases such as chronic heart disease or diabetes mellitus. Sample size was calculated by G*power 3.1.9.7. from previous studies (Kolte et al., 2019; Palathingal et al., 2022).

This study is a part of the evaluation of non-surgical periodontal treatment in patients with chronic kidney disease stages 2-5 which was approved by the ethical committee from the Faculty of Medicine (REC.64578-14-1) and the Faculty of Dentistry (EC6506-025), Prince of

Songkla University. The study was registered in the Thai Clinical Trials Registry (TCTR20240516002), Thailand. The participants of this study were the volunteers from the evaluation of non-surgical periodontal treatment in patients with chronic kidney disease stages 2-5 project. Chronic kidney disease assessment by the nephrologist with these data collection gender, age, weight, height, medical record, serum creatinine, eGFR, Blood Urea Nitrogen (BUN) and urine analysis.

The periodontal condition was assessed by three certified periodontists with a full-mouth clinical examination, 6 surfaces in each tooth (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, distolingual). Recording bleeding on probing (bleeding on probing by Silness & Loe, 1964), probing depth (PD), gingival margin, then clinical attachment level is calculated. The classification of stage III and IV periodontitis was categorized according to 2018 American Academy of Periodontics (AAP) classification. Group I for stage III periodontitis patients with chronic kidney disease (n=12), Group II for stage IV periodontitis patients with chronic kidney disease (n=9).

Periodontal pathogens DNA Detection

Before intraoral examination, unstimulated saliva was collected 1 ml in a centrifuge tube. Pool plaque from 6 teeth was collected from 16, 11, 26, 36, 31, and 46 (if any of these representative teeth were extracted, then use a similar one). DNA of periodontal pathogens (*A. actinomycetemcomitans*, *F. nucleatum, P. gingivalis* and *C. albicans*) was extracted from pool plaque and saliva by PureDirex (Bio-Helix) and then the levels of periodontal pathogens were measured using real-time PCR (CFX96 TouchTM Real-Time PCR detection system (Bio -Rad, USA) with specific primers of each species, *A. actinomycetemcomitans* and (Pahumunto et al., 2022) *F. nucleatum* and (Wanitsuwan et al., 2024), *P. gingivalis* (Pg-forward and Pg-reverse) (Gafan et al., 2004), *C. albicans* (Ca-forward and Ca-reverse) (Galan et al., 2006). The real-time PCR condition was 95°C for 10 minutes, 50°C for 2 minutes and 40 cycles of 95°C for 20 seconds, annealing temperatures (60°C for *P. gingivalis*, *F. nucleatum*, *and A. actinomycetemcomitans* as well as 56°C for *C. albicans*) for 20 seconds, and polymerizing temperature at 72°C for 25 seconds. The levels of periodontal pathogens were calculated using a standard curve to interpret the amount of each periodontal pathogen.

Statistical analysis

Descriptive statistics were used to describe Demographic information. Categorical information was shown in numbers and percentages. Continuous variable was reported in mean and standard deviation. Mann-Whitney U test with P value < 0.05 was used to describe the difference between in different stage of periodontitis.

RESEARCH RESULTS

A total of 21 participants were included, comprising 12 with Stage III periodontitis and 9 with Stage IV periodontitis. In these numbers, 10 participants had stage III periodontitis with stage 3 CKD. 6 participants had stage III periodontitis with stage 4 CKD. Two participants with stage III periodontitis and stage 4 CKD. 3 participants with stage IV periodontitis and stage 4 CKD. Table 1 showed that stage IV periodontitis patients had a significantly (*P value* < 0.05) higher percentage of sites with ≥4 mm pocket depth ($46.78 \pm 32.50\%$) than Stage III ($13.18 \pm 11.64\%$). While shallow pockets (<3 mm) were more prevalent in Stage III ($86.82 \pm 11.64\%$) than Stage IV ($53.22 \pm 32.50\%$). Clinical Attachment Loss (CAL) was significantly (*P value* < 0.05) higher in Stage IV periodontitis patients with sites presenting ≥5 mm CAL ($54.56 \pm 29.25\%$) than in Stage III periodontitis patients ($17.01 \pm 11.47\%$). Sites with 1-2 mm CAL were more frequent in Stage III ($29.17 \pm 22.70\%$) than in Stage IV ($9.98 \pm 9.63\%$). The mean percentage of bleeding on probing was higher in Stage IV periodontitis patients ($83.07 \pm 24.65\%$) than in Stage III ($68.03 \pm 28.79\%$).

Table 1 Demographic data and dental examination

Periodontitis / Clinical parameters	Stage III (n=12)	Stage IV (n=9)
Participants	12	9
Sex		
- Male (%)	9(42.86)	7(33.33)
- Female (%)	3(14.29)	2(9.52)
Age (years)	53.9±7.85	62.3±8.00
Teeth (number)	27.00±2.34	20.11±4.40*
% Pocket depth		
- ≤3 mm.	86.82±11.64	53.22±32.50*
- ≥4 mm.	13.18±11.64	46.78±32.50*
% CAL		
- 1-2 mm.	29.17±22.70	9.98±9.63
- 3-4 mm.	53.82±17.06	35.46±24.16
- ≥5 mm.	17.01±14.47	54.56±29.25*
%BOP	68.03±28.79	83.07±24.65

Table 2 showed renal function indicators varied in periodontitis stages. GFR was lower in Stage IV periodontitis (33.86 ± 18.35 mL/min/1.73 m²) than Stage III (39.40 ± 11.15). Serum creatinine levels were higher in Stage IV periodontitis patients (2.31 ± 0.88 mg/dL) than Stage III (1.86 ± 0.65 mg/dL). Mean BUN was similar in all groups 25.35 ± 6.84 in Stage III and 27.47 ± 13.26 in Stage IV. Urine Protein Creatinine Ratio (UPCR) was elevated in Stage IV (2.95 ± 3.15) relative to Stage III (0.49 ± 0.55).

Table 2 CKD parameters according to the stage of periodontitis

CKD / Periodontal parameter	Stage 3 (n=11)	Stage 4 (n=10)
Teeth	24.00±4.94	24.20±4.82
% Pocket depth		
- ≤3 mm.	74.77±26.35	64.92±35.23
- ≥4 mm.	25.23±26.35	35.08±35.23
% CAL		
- 1-2 mm.	16.88±16.52	33.96±27.83
- 3-4 mm.	46.40±22.79	44.52±21.21
- ≥5 mm.	36.72±30.68	21.53±18.70
%BOP	70.76±28.94	86.34±20.32

Periodontal conditions were also classified by CKD severity in Table 3. A higher percentage of shallow pockets (<3 mm) was found in CKD Stage 3 (74.77 ± 26.35%) than CKD Stage 4 (64.92 ± 35.23%). Deeper pockets (≥4 mm) were more prevalent in CKD Stage 4 (35.08 ± 35.23%) compared to Stage 3 (25.23 ± 26.35%). CAL ≥5 mm. was higher in CKD Stage 4 (44.52 ± 21.21%) than Stage 3 (36.72 ± 30.68%). Sites with 1-2 mm CAL were higher in Stage 3 (16.88 ± 16.52%) than Stage 4 (33.96 ± 27.83%). Bleeding on probing was more extensive in CKD Stage 4 (86.34 ± 20.32%) than Stage 3 (70.76 ± 28.94%).

Table 3 Periodontal parameters according to CKD

Periodontitis / CKD parameters	Stage III	Stage IV
GFR (mL/min/1.73 m²)	39.40±11.15	33.86±18.35
Serum Creatinine (mg/dL)	1.86±0.66	2.31±0.88
BUN	25.35±6.84	27.47±13.26
UPCR	0.49±0.55	2.95±3.15

The mean bacterial quantities in saliva, supragingival plaque, and subgingival plaque samples in total and stratified by periodontitis stages III and IV were presented in table 4. *Aggregatibacter actinomycetemcomitans* was undetected in most samples. The mean values were negligible with zero detection in subgingival plaque samples. A small increase was noted in supragingival plaque in stage IV periodontitis patients (0.58 ± 1.73 log CFU/ml) but statistically insignificant difference. *Fusobacterium nucleatum* was detected at high levels in all samples. In total samples, values ranged from 5.07 ± 1.87 (saliva) to 7.22 ± 2.44 (subgingival plaque). In stage III periodontitis patients, subgingival plaque contained 6.58 ± 3.10 log CFU/ml, while stage IV periodontitis patients showed an increase to 8.07 ± 0.42 log CFU/ml. *Porphyromonas gingivalis* were found prevalence in all plaque samples. Overall, it was more abundant in plaque than saliva. In periodontitis stage III patients, supragingival plaque contained 6.59 ± 0.77 log CFU/ml, increasing to 7.29 ± 0.65 in stage IV. Subgingival plaque in stage IV showed the highest levels at 7.64 ± 0.96 log CFU/ml. Moreover, *Porphyromonas gingivalis* supragingival plaque were found significantly different between stage III and IV periodontitis patients. *Candida albicans* were detected in all sample types with relatively high levels. In total samples, values ranged from 6.05 ± 1.77 (saliva) to 7.33 ± 1.75 (supragingival plaque). In stage IV periodontitis patients, supragingival and subgingival plaques presented mean levels of 7.72 ± 0.37 and 7.77 ± 0.75 log CFU/ml.

Table 4 Bacteria quantities in different stages of periodontitis

Bacteria	**Total bacteria** (log CFU/ml) mean±SD, median (min, max)			**Periodontitis Stage III** (log CFU/ml) mean±SD, median (min, max)			**Periodontitis stage IV** (log CFU/ml) mean±SD, median (min, max)		
	Saliva	Supragingival plaque	Subgingival plaque	Saliva	Supragingival plaque	Subgingival plaque	Saliva	Supragingival plaque	Subgingival plaque
A. actinomycetemcomitans	0.24±0.50 0.00 (0.00, 1.66)	0.25±1.13 0.00 (0.00, 3.18)	0.00±0.00 0.00 (0.00, 2.33)	0.24±0.54 0.00 (0.00,1.66)	0.00±0.00 0.00 (0.00,0.00)	0.00±0.00 0.00 (0.00,0.00)	0.24±0.48 0.00 (0.00,1.23)	0.58±1.73 0.00 (0.00,5.2	0.00±0.00 0.00 (0.00,0.00)
F. nucleatum	5.07±1.87 5.1461 (3.2, 11)	7.11±1.63 5.4853 (4.46, 5.04)	7.219±2.438 5.54 (5.04, 6.30)	4.42±1.54 4.96 (3.2,5.46)	7.35±1.43 7.805 (3.18,8.53)	6.58±3.10 7.675 (0,8.67)	5.92±2.01 5.17 (4.52,11)	6.79±1.89 7.62 (4.03,8.05)	8.07±0.42 8.17 (7.56,8.82)
P. gingivalis	4.12±1.57 4.73 (0.60,5.70)	6.89±0.79 4.66 (2.39,6.07)	6.69±2.46 5.45 (3.10,6.23)	3.59±1.79 3.68 (0.6, 5.59)	6.59±0.77* 6.67 (6.19, 7.59)	5.97±3.00 6.11 (0, 9.05)	4.82±0.88 4.95 (4.53,5.7)	7.29±0.65* 7.38 (6.68,8.45)	7.64±0.96 7.91 (7.83,8.68)
C. albicans	6.05±1.77 5.68 (4.10,11.35)	7.33±1.75 5.39 (0.00,6.26)	6.76±2.54 5.21 (0.80,6.37)	6.48±2.27 5.85 (4.1,11.35)	7.05±2.29 7.625 (7.07, 8.56)	6.01±3.14 7.35 (0, 8.56)	5.54±0.66 5.49 (5.19,6.83)	7.72±0.37 7.74 (6.97,8.19)	7.77±0.75 7.94 (7.72,8.9)

* Statistically significant at 0.05 level

DISCUSSION & CONCLUSION

Stage IV periodontitis patients showed worse clinical periodontal parameters, such as remaining teeth, probing depth, and CAL than Stage III patients. These findings support that stage IV periodontitis is characterized by more tooth loss and functional impairment(Kinane et al., 2017). Moreover, bleeding on probing (%BOP), an indicator of gingival inflammation, was elevated in Stage IV cases ($83.07 \pm 24.65\%$).

Renal parameters were impaired in Stage IV periodontitis patients, with reduced glomerular filtration rate (GFR: 33.86 ± 18.35 mL/min/1.73 m²), increased serum creatinine (2.31 ± 0.88 mg/dL), and urinary protein/creatinine ratio (UPCR: 2.95 ± 3.15). As systemic inflammation driven by chronic periodontitis may be associated with renal injury and accelerate CKD

progression (Kshirsagar et al., 2005), and reduced GFR may be an indicative predictor for periodontitis (Ghanem, 2025).

CKD Stage 4 patients showed a higher proportion of deep periodontal pockets and CAL ≥5 mm compared to Stage 3. In contrast, shallow pockets (≤3 mm) and minimal attachment loss were more common in CKD Stage 3. These results are consistent with prior reports indicating that worsening renal function is associated with more severe periodontal deterioration (Chambrone et al., 2013). Furthermore, bleeding on probing was more extensive in CKD Stage 4 than Stage 3, indicating a more inflammatory response.

Microbial analysis showed that *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, and *Candida albicans* were present at higher levels in Stage IV periodontitis patients. *P. gingivalis*, a keystone pathogen in periodontitis, was significantly elevated in the supragingival plaque of Stage IV patients (7.29 ± 0.65).

This study found a plausible association between periodontitis and chronic kidney disease. Patients with Stage IV periodontitis demonstrated significantly poor periodontal health, by increased probing depths, greater CAL, and higher bleeding on probing compared to those with Stage III periodontitis. The results of renal parameters in stage IV periodontitis patients were also shown by impaired renal parameters, reduced GFR, elevated serum creatinine, and increased UPCR. Furthermore, CKD Stage 4 patients exhibited more severe periodontal breakdowns and higher inflammatory responses compared to Stage 3 CKD patients. The richness of oral microbiota is different in stages of periodontitis which may also increase the severity of CKD when Stage IV periodontitis patients had higher levels of periodontal pathogen than Stage III periodontitis patients. All of these may suggest a bidirectional link between periodontitis with CKD patients.

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