https://doi.org/10.48047/AFJBS.7.2.2025.786-803

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Can salivary creatinine and urea levels be used as a biomarker to diagnose chronic kidney disease among periodontitis patients

1)DR.REENA EVANGELINE KONATHAM, 2)DR.L.VAMSI KRISHNA REDDY, 3)DR.P.SIVA KUMAR, 4)DR. POTTEM NAGARJUNA, 5)DR.PICHIKA SWATHI

post graduate in the department of public health dentistry, Anil neerukonda institute of dental sciences, Visakhapatnam-531162, gmail:drreenaevangeline@gmail.com- 7396098698
PROFESSOR & HOD , department of public health dentistry, Anil neerukonda institute of dental sciences, Visakhapatnam-531162, gmail: drvamsired@gmail.com-9908200033
PROFESSOR, department of public health dentistry, Anil neerukonda institute of dental sciences, Visakhapatnam-531162, gmail:Shiva.mds@hotmail.com-9885121123
READER ,dept of public health dentistry, Anil neerukonda institute of dental sciences, Visakhapatnam-531162, gmail:pottemnagarjuna45@gmail.com -8985268420
READER, Dept Of Public Health Dentistry, Anil Neerukonda Institute Of Dental Sciences,Visakhapatnam531162,Contact No: 8790253269. pichika.swathi@gmail.com.-8790253269

Volume 7, Issue 02, Jan 2025

Received: 15 Dec 2024

Accepted: 05 Jan 2025

Published: 29 Jan 2025

doi:10.48047/AFJBS.7.2.2025.786-803

ABSTRACT

INTRODUCTION: A bidirectional relationship between kidney disease and periodontitis has been proposed a link to endothelial dysfunction and decrease of renal function. Patients with periodontitis have a significantly higher risk of chronic kidney disease than do healthy individuals. Salivary creatinine and urea could be used as non-invasive markers for assessment of kidney function and diagnostics of renal failure.

OBJECTIVE:

To assess and correlate the salivary urea and creatinine levels among patients with and without periodontitis in diagnosing chronic kidney disease.

METHODOLOGY:

This case-control study was conducted among patients attending a tertiary hospital in the age group of 40–60yrs with 26 samples in each group with periodontitis and without periodontits. All participants were instructed to avoid eating or drinking for 2 hours before collection of saliva. Whole saliva was collected by spitting method. Saliva samples were stored at -20°C until laboratory analysis. Samples were defrosted at room temperature and then centrifuged at 3000 rpm for 10 min before being used for the analysis in order to remove contaminants.

RESULTS: The mean values of salivary creatinine levels were 0.71mg/dl and salivary urea levels were 94.28 mg/dl among cases. The mean values of salivary creatinine level were 0.09mg/dl and salivary urea levels were 16.28 mg/dl among controls.

CONCLUSION: There was a positive correlation between salivary creatinine and urea levels among Chronic Kidney Disease patients thus stating saliva can be used as a non-invasive diagnostic tool for estimating the urea & creatinine level among periodontitis patients with Chronic Kidney Disease.

KEY WORDS: Salivary creatinine, Salivary urea, periodontitis, chronic kidney disease.

1. INTRODUCTION:

A chronic inflammatory disease of the periodontium, periodontitis can lead to numerous negative systemic repercussions, such as diabetes mellitus, poor pregnancy outcomes and respiratory disorders. Microbial plaque is the main cause of periodontal disorders, along with issues including poor oral hygiene, smoking, and drug abuse. [1-5]

An alteration in the composition of the oral microbiota is one of the primary causes of periodontitis. It has been suggested that renal disease and periodontitis are correlated in both directions. It has been demonstrated that endothelial dysfunction and a decline in renal function are related to bacterial spread and inflammation.[6-8]

Compared to healthy people, patients with periodontitis are far more likely to have chronic renal disease. On the other hand, uraemia in kidney disease patients makes them more vulnerable to infections and may result in bacterial dysbiosis, which can cause periodontitis. One of the systemic conditions that can impact the contents of salivary discharges is chronic renal disease. [12-15]

The buildup of metabolic waste products and involvement of multiple organs are linked to chronic kidney disease. A decreased glomerular filtrate rate and thus higher salivary creatinine concentrations are also more likely to occur in patients with untreated periodontal disorders, according to the findings.[16-18]

Many benefits of using saliva as a diagnostic fluid have been linked to the analysis of salivary creatinine and urea in CKD patients. When compared to healthy groups, studies on individuals with chronic renal failure showed higher levels of PPD and CAL. Serum samples from dialysis patients with severe periodontitis showed elevated levels of antibodies against P. gingivalis.[1-2]

Therefore, periodontitis, which could occur in patients with kidney disease, could be one of the potential biases influencing the concentrations of the salivary markers of kidney disease thus might prevent their use in practice.

Salivary urea and creatinine may be employed as non-invasive indicators to diagnose renal failure and evaluate kidney function. The salivary glands secrete a multi-component biologic fluid called saliva, which is the primary factor influencing dental health. Saliva collection has an advantage over serum since it is a straightforward, cost-effective, and non-invasive technique that patients may do on their own with little assistance from medical professionals. All age groups can use it, and a repeat sample is simple to get when needed. Additionally, it offers a financially sensible method for screening big populations. Patients with coagulation problems such as haemophilia and those with impaired venous access would benefit greatly from the use of saliva as a diagnostic medium. [3-5]

Due to their ability to screen quickly, many salivary biomarkers are employed for screening and predicting early changes in periodontal tissue. Given the significance of saliva in host immunity and dental biofilm production, produced saliva may be a significant factor in the onset and progression of periodontal diseases. For a periodontium to be healthy, adequate salivary flow and salivary urea concentration are crucial factors.

Several systemic disorders, such as chronic kidney disease (CKD), have been shown in numerous studies to cause notable, observable alterations in saliva[18]. Salivary creatinine and urea analysis in patients with chronic kidney disease (CKD) has several benefits that have been linked to its usage as a diagnostic biofluid. The use of saliva as a diagnostic fluid is still being researched because it can be influenced by a variety of circumstances.

In lieu of the above controversy, this study was undertaken to evaluate the possible association between the periodontal status of the systemically healthy individuals and the salivary creatinine and urea level to assess the role of periodontitis on renal function.

2.AIMS AND OBJECTIVES

The present study aimed to assess salivary urea and creatinine levels in patients with periodontitis and without periodontitis to determine if salivary creatinine and urea levels can be used to diagnose chronic kidney disease.

3.MATERIALS & METHODS:

This was a case-control study of patients with periodontitis and with out periodontitis attending a tertiary hospital as cases & controls respectively. The study includes 52 patients in the age group of 40–60 yrs with 26 samples in each group visiting the department of public health dentistry in a tertiary care hospital. This study was approved by Anil neerukonda Institute of dental sciences, Visakhapatnam, AP Institutional Ethical committee . The study was conducted by the joint efforts of the Departments of Nephrology, Medical College, and the Department of public health dentistry, NRI institute of medical sciences. Through out the study, confidentiality of data was preserved. The study protocol was explained and written informed consent was signed by each patient before commencement of the study. The sample size for the present study has been estimated using the software G Power v. 3.1.9.4. Considering the effect size to be measured (d) at 80% for Two-tailed Hypotheses, power of the study at 80% and the alpha error at 5%, the sample size obtained is 52. Thus, each group will comprise of 26 samples.

Inclusion Criteria:1) Patients who has given informed consent.2)Age of 40-60 Years.3) Patients with periodontitis in one group and with out periodontitis in the other group visiting the tertiary care hospital. **Exclusion criteria:** 1)Patients with history of any antibiotics, anti-inflammatory or immunosuppressive drug therapy six months prior to the study, 2)History of

periodontal treatment in the last six months, salivary gland diseases, any apparent oral infections (i.e. herpes or candidiasis), 3)History of radiation therapy, pregnant and lactating women, chronic smokers, tobacco users, alcohol users, aggressive periodontitis and denture wearers and patients with blood pressure variables >130/90, BMI >25.0, and postprandial glucose levels >140 mg/dL were excluded.

Saliva collection:

For all the subjects initially recruited, body mass index (BMI), systolic and diastolic blood pressure, and serum glucose (PP) was analyzed. For the study subjects, the following periodontal parameters were recorded: probing pocket depth (PPD) and clinical attachment level (CAL).

William's markings on calibrated periodontal probes were used to do the periodontal examination. Probing Pocket Depth (PPD), gingival recession, and clinical attachment level (CAL) measures from four locations on each tooth (buccal, mesial, lingual/palatal, and distal) were used to assess the periodontal health. PPD was calculated as the separation between the gingival margin and the gingival sulcus/periodontic pocket base.

The distance between the cemento-enamel junction and the gingival margin was used to quantify gingival recession. The values for CAL were then indirectly obtained by adding these scores. According to the criteria put forth by the Centers for Disease Control and Prevention's joint working group with the American Academy of Periodontology in 2003, all of the participants were divided into three groups (Mild/No Periodontitis, Moderate Periodontitis, and Severe Periodontitis) based on CAL and PPD measurements.

Based on the periodontal finding, the subjects were divided into two groups: Group I (n =26) subjects with periodontitis and Group II (n= 26) periodontally healthy subjects.

After obtaining a written informed consent, a clinical examination of the oral cavity was performed and the case details were recorded on a special proforma. Samples of whole, unstimulated saliva were collected. To reduce the impact of diurnal variation, all samples were taken between 9:00 and 11:00 a.m. Using the spitting technique, 3 mL of saliva was collected while the subject was at rest in a sterile graduated container. In order to prevent swallowing and oral movements during collection, they were instructed to sit comfortably with their eyes open and their head slightly forward. They were also instructed to collect their saliva in the pit and floor of their mouth every 60 seconds or whenever they felt the need to swallow the accumulated fluid. This was carried out until three milliliters of complete saliva were collected.

After collecting, the samples were immediately transferred to a vaccine carrier with ice pack to avoid biochemical changes and carried to the laboratory. The saliva samples were kept at -20 degrees Celsius until they were analyzed in a lab. To eliminate impurities, samples were centrifuged for 10 minutes at 3000 rpm after being defrosted at room temperature before being utilized for analysis.

A variation of Jaffe's method was used to assess the quantities of creatinine in saliva, while the urease method was used to estimate the levels of urea. An auto analyzer (Beckman AU 5800, Beckman Coulter Inc., Brea, CA) and commercially available kits (Beckman Coulter Diagnostics) were used for the measurement. because saliva has been the subject of these techniques in past research. The creatinine levels were determined calorimetrically using the RANDOX Reagents (USA) creatinine Assay Kit in accordance with the manufacturer's instructions.

Levels of urea were also determined using Urea Assay Kit from RANDOX Reagents (USA). The absorbance was measured at 510 nm and 580 nm for creatinine and urea respectively using

spectrophotometer 300 (Thermo Scientific, USA). These methods have been standardized for saliva in previous studies .

Statistical analysis:

The Statistical Analysis was done using SPSS v.26 software IBM., Corp. Data was entered in the excel spread sheet. A descriptive analysis of the data was presented as frequency, mean and percentage distribution of study variables. The level of significance was set at $P<0.05$.

4.RESULTS

There were a total of 52 subjects with a median range age of 40-60 years and there were 26 males (55.7%) and 26 females (44.2%). The mean salivary creatinine levels were significantly higher in the group with periodontitis than in the control group ($p<0.05$) (Table 2) and the mean salivary urea level was significantly higher in the group with periodontitis than in the control group(Table3). The serum and salivary creatinine levels in both groups were estimated using linear regression analysis, which revealed a linear association between the urea and salivary creatinine levels. Comparison between salivary creatinine levels and salivary urea levels in cases and controls was depicted in the figure 1 and 2.

Table 1 shows demographic parameters in cases and control groups

	Cases(n=26)	**Controls(n=26)**
Age(years)	**14.49±3.15**	**14.86±3.11**
Male(n)	**15**	**14**
Female(n)	**11**	**12**

Table 2 shows higher salivary creatinine levels in patients with periodontitis when compared to patients with out periodontitis.

Table 2:

Group	N	Mean	Std	95% confidence levels		t-value	p- value
				Lower	Upper		
Cases	26	0.71	0.289	0.503	0.739	10.570	0.000*
controls	26	0.09	0.049	0.5005	0.742		

Table 3 shows higher salivary urea levels in patients with periodontits when compared to patients with out periodontitis.

Table 3:

Group	N	Mean	Std	95% confidence levels		t-value	p- value
				Lower	Upper		
Cases	26	94.28	13.4	8.403	19.99	4.925	0.000*
controls	26	16.28	5.25	8.321	20.07		

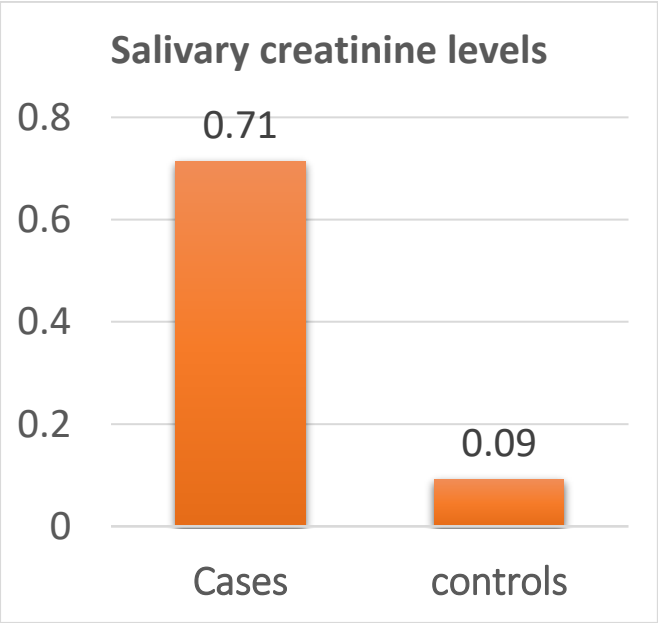


Fig 1: Comparison of Salivary creatinine levels in cases and controls.

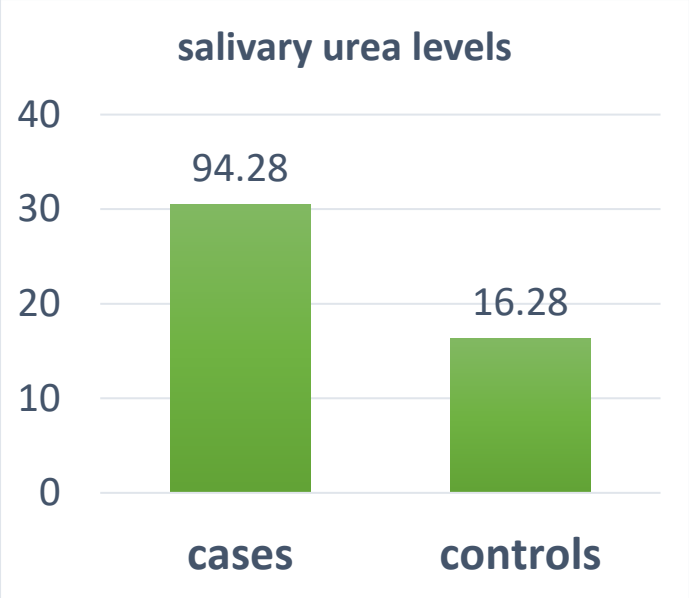


Fig 2: Comparison of salivary urea levels in cases and controls.

ROC analysis was used to ascertain the reciprocal link between chronic renal disease and periodontitis, i.e., to accurately divide the test group into patients with periodontitis and controls(Figure 3a and figure 3b). The total AUC was 0.9 for salivary creatinine and 1.0 for salivary Urea (Table 4).

Table 4

Group	Area	Standard Error	p-value	95% confidence level	
				Lower bound	Upper bound
Creatinine	**0.9**	0.048	0.000*	0.823	1.000
Urea	**1.0**	0.000	0.000*	1.000	1.000

Fig 3a- Receiver operating characteristic curve for salivary creatinine

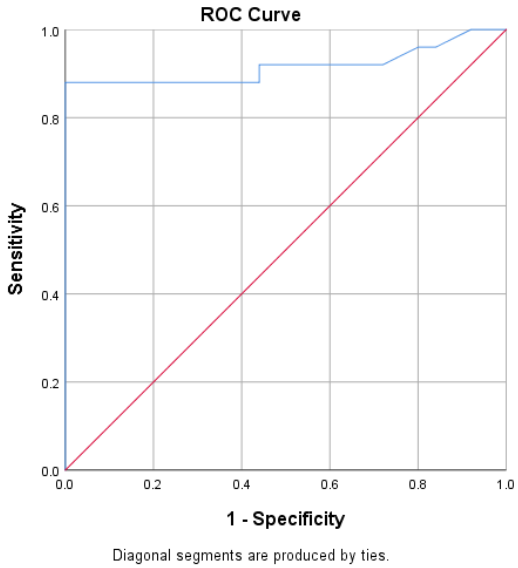
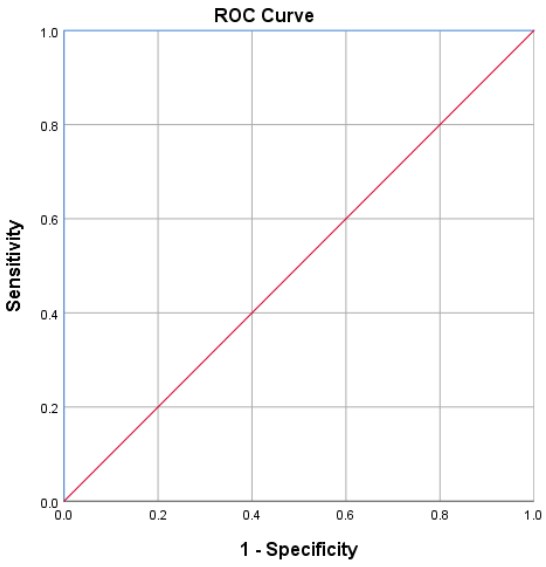


Fig 3b- Receiver operating characteristic curve for salivary urea



5.DISCUSSION:

Numerous epidemiological studies demonstrate that the systemic chronic inflammatory load of periodontal disease, possibly through the action of acute phase reactants, contributes to endothelial damage and atherosclerosis.[28-33] Prior research has demonstrated that in end-stage renal disease (ESRD) patients receiving haemodialysis, persistent inflammation plays a role in the development of progressive atherosclerosis. [34-39]

Based on available data, it appears that the acute phase response and pro-inflammatory cytokines are key factors in the development of cardiovascular problems and malnutrition in these patients.[41] Recent data also indicates that periodontal disease may be a hidden cause of systemic inflammation in these people and may actually predict the onset of overt nephropathy and end-stage renal disease (ESRD) in diabetes patients.[42] According to a new longitudinal study, one important nontraditional risk factor for chronic renal disease is periodontal disease..[43]

The current study's findings suggest that people with renal failure have a higher prevalence and severity of periodontal disease. In the group with periodontitis, the mean salivary urea level was substantially higher (94.28) than in the control group (16.28), and the mean salivary creatinine levels were significantly higher (0.71) than in the control group (0.09) ($p<0.05$). Conflicting reports exist, despite the fact that other earlier writers have produced findings that are similar,[10-18] and they have not found any differences in the periodontal health of haemodialysis patients.[19-23]

The area under the ROC curve is used to quantify accuracy. According to our study, salivary creatinine has a higher area under the curve (0.967), which indicates that it is a useful alternative diagnostic test for differentiating between those with chronic kidney disease and healthy people. The area under the curve that Xia et al. obtained was 0.897.[50]

According to a recent study in a Japanese population, older adults who live in the community may be more likely to have severe periodontal disease due to the higher incidence of chronic renal failure that comes with aging.[44] The authors also hypothesize that prolonged renal insufficiency, which results from inadequate bone metabolism, influences periodontal disease. Previous research indicates that vitamin D polymorphisms may increase the risk of developing periodontitis and chronic kidney disease. Therefore, there is a chance that the risk factors for chronic renal disease and periodontal disease are similar. [45]

Sreeram et al. found that patients with periodontitis had higher mean C-Reactive protein and serum urea levels and lower estimated glomerular filtration rate, uric acid, and total antioxidant capacity. They also found that patients with periodontitis were more likely to develop chronic kidney disease. Chronic renal disease and periodontitis are positively correlated, according to a 2013 comprehensive study.[6] There was also a beneficial effect periodontal therapy on estimated glomerular filtration rate.[7]

There was no difference between the groups in a study that evaluated the bacterial buildup in renal patients with periodontitis and those with systemically healthy periodontitis.[9] The majority of the clinical periodontal markers did not significantly differ between people with and without chronic renal failure. According to study articles published between 2000 and 2012, Wahid et al. (2014) demonstrated that there is a reciprocal relationship between periodontal disease and chronic renal disease.[46] Additionally, Taylor et al. found that serum urea levels remained unchanged even after all of the teeth in patients with periodontitis were extracted.[8]

According to the Brotto et al. study, kidney function markers (urea, creatinine, uric acid, and albumin levels) were assessed in the serum of both periodontitis controls and periodontally healthy individuals. The levels of markers did not differ between the test and control groups.

Additionally, it was suggested that renal function was unaffected by periodontal disorders.[48] In a similar vein, Shimazaki Y et al. investigated the periodontal health of middle-aged Japanese men with normal SCR levels and discovered a strong unfavorable correlation..[49]

In patients with chronic kidney disease (CKD), saliva collection is a non-invasive way to obtain diagnostic fluid. It can lessen the anxiety and discomfort related to blood collection and be used to enable more frequent monitoring of the patients' overall health over time in order to identify morbidities early.

An established method for determining kidney health is the measurement of urea and creatinine, which is well suited to the creation of a salivary assay. For patients with renal disorders, saliva is therefore a first step and has the potential to complete5ly transform the diagnostic process. The study's key discovery is that saliva can be utilized as a non-invasive diagnostic tool to measure the amounts of urea and creatinine in the saliva of patients with and without periodontitis that are associated with chronic kidney disease.

Patients with chronic kidney disease have higher serum creatinine and urea levels, which also raise salivary creatinine and urea levels because renal failure prevents the kidneys from excreting creatinine, which raises blood levels. Dry mouth, uremic breath, tongue coating, and other oral consequences of chronic kidney disease are brought on by elevated salivary creatinine and urea.

6.CONCLUSION

This study aimed to use saliva as a non-invasive diagnostic fluid in patients with chronic kidney disease. It has the potential to significantly lower the anxiety and discomfort associated with blood sampling procedures and increase the patients' willingness to undergo routine health examinations, which will significantly improve the chances of tracking their overall health over time and identifying morbidities early on. All age groups can benefit from saliva sampling

rather than blood sampling, which also lowers the dangers to laboratory workers' safety. The positive outcome of our investigation indicates that saliva can be utilized as a non-invasive diagnostic method to measure the amounts of urea and creatinine in the saliva of patients with chronic renal disease. Nevertheless, there are several restrictions on this study. To genuinely claim that saliva may be used to detect chronic kidney disease, a study with patients at every stage of the disease as well as healthy controls should be conducted. This will set the groundwork for future investigators.

REFERENCES:

1. Velayutham A, Muthu J, Balu P, Ravindran S. Association between Serum Creatinine and Periodontal Disease Severity—A Comparative Clinicobiochemical Study. J Sci Den 2020;10(1):3–6.
2. Gaal Koval cıkova A ,Pan cıkova A, Konecn a B, Klam arov a T, Novak B, Kovalova E, Podracka L, Celec P, T othov a L, Urea and creatinine levels in saliva of patients with and without periodontitis, Eur J Oral Sci 2019; 000: 1–8.
3. Taye Jemilat Lasisi , Yemi Raheem Raji and Babatunde Lawal Salako, Salivary creatinine and urea analysis in patients with chronic kidney disease: a case control study,. BMC Nephrology (2016) 17:10
4. Rahime R, Can salivary creatinine and urea levels be used to diagnose chronic kidney disease in children as accurately as serum creatinine and urea levels? A case–control study renal failure, (2017)39:1,452–57
5. Bagalad BS, Mohankumar KP, Madhushankari GS, Donoghue M, Kuberappa PH. Diagnostic accuracy of salivary creatinine, urea, and potassium levels to assess dialysis need in renal failure patients. Dent Res J 2017;14:13-8
6. Sreeram M, Suryakar AN, Dani NH, Kulkarni MB, Is periodontitis associated with decreased glomerular filtration rate, with oxidative stress as an important link? IOSR J Dent Med Sci (IOSR-JDMS) 2013;12(3):41–47.
7. Chambrone L, Foz AM, Guglielmetti MR, Pannuti CM, Artese HP, Feres M. Periodontitis and chronic kidney disease: a systematic review of the association of diseases and the effect of periodontal treatment on estimated glomerular filtration rate. J Clin Periodontol 2013;40(5):443–456.

8. Taylor BA, Tofler GH, Carey HMR, Morel-Kopp MC, Philcox S, Carter TR, et al. Full-mouth tooth extraction lowers systemic inflammatory and thrombotic markers of cardiovascular risk. J Dent Res 2006;85(1): 74–78.
9. Yamalik N, Delilbasi L, Gulay H, Caglayan F, Haberal M, Caglayan G. The histological investigation of gingiva from patients with chronic renal failure, renal transplants, and periodontitis: a light and electron microscopic study. J Periodontol 1991;62(12):737–744.
10. Rahmati MA, Craig RG, Homel P, Kaysen GA, Levin NW. Serum markers of periodontal disease status and inflammation in hemodialysis patients. Am J Kidney Dis. 2002;40:983-9.
11. Davidovich E, Davidovits M, Eielman E, Schwartz Z, Bimstein E. Pathophysiology, therapy, and oral implications of renal failure in children and adolescents: an update. Pediatr Dent. 2005;27:98-106.
12. Duran I, Erdemir EO. Periodontal treatment needs of patients with renal disease receiving haemodialysis. Int Dent J. 2004;54:274-8.
13. Chen LP, Chiang CK, Chan CP, Hung KY, Huang CS. Does periodontitis reflect inflammation and malnutrition status in hemodialysis patients? Am J Kidney Dis. 2006;47:81522.
14. Chuang SF, Sung JM, Kuo SC, Huang JJ, Lee SY. Oral and dental manifestations in diabetic and nondiabetic uremic patients receiving hemodialysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;99:689-95.
15. Naugle K, Darby ML, Bauman DB, Lineberger LT, Powers R. The oral health status of individuals on renal dialysis. Ann Periodontol. 1998;3:197-205.
16. Yoshino M, Craig RG, Kuhlmann MK, Kshirsagar AV, Offenbacher S, Beck JD et al. Prevalence of periodontitis in hemodialysis (HD) patients at 2 sites. J Am Soc Nephrol. 2005;16:507A.
17. Cengiz MI, Bal S, Gökçay S, Cengiz K. Does periodontal disease reflect atherosclerosis in continuous ambulatory peritoneal dialysis patients? J Periodontol. 2007;78:1926-34.
18. Borawski J, Wilczyńska-Borawska M, Stokowska W, Myśliwiec M. The periodontal status of pre-dialysis chronic kidney disease and maintenance dialysis patients. Nephrol Dial Transplant. 2007;22:457-64.
19. Nunn JH, Sharp J, Lambert HJ, Plant ND, Coulhtard MG. Oral health in children with renal disease. Pediatr Nephrol. 2000;14:997-1001.

20. Marakoglu IK, Gursoy KD, Demirer S, Sezer H. Periodontal status of chronic renal failure patients receiving hemodialysis. Yonsei Med J. 2003;44:648-52.
21. Castillo A, Mesa F, Liébana J, García-Martinez O, Ruiz S, García-Valdecasas J et al. Periodontal and oral microbiological status of an adult population undergoing haemodialysis: a cross-sectional study. Oral Diseases. 2007;13:198-205.
22. Bots CP, Poorterman JH, Brand HS, Kalsbeek H, van Amerongen BM, Veerman EC et al. The oral health status of dentate patients with chronic renal failure undergoing dialysis therapy. Oral Diseases. 2006;12:176-80.
23. Bayraktar G, Kurtulus I, Duraduryan A, Cintan S, Kazancioglu R, Yildiz A et al. Dental and periodontal findings in hemodialysis patients. Oral Diseases. 2007;13:393-7.
24. Greene JC, Vermillion JR. The simplified oral hygiene index. J Amer Dent Assoc 1964; 68:7-13
25. Lobene RR, Weatherford T, Ross NM, Lamm RA, Menaker L. A modified gingival index for use in clinical trials. Clin Prev Dent. 1986;8:3-6.
26. Page RC, Eke PI. Case definitions for use in population-based surveillance of periodontitis. J Periodontol. 2007;78:1387-99.
27. Craig RG, Kotanko P, Kamer AR, Levin NW. Periodontal diseases--a modifiable source of systemic inflammation for the end-stage renal disease patient on haemodialysis therapy? Nephrol Dial Transplant. 2007;22:312-5.
28. Mehta JL, Saldeen TG, Rand K. Interactive role of infection, inflammation and traditional risk factors in atherosclerosis and coronary artery disease. J Am Coll Cardiol. 1998;31:121725.
29. Iacopino AM, Cutler CW. Pathophysiological relationships between periodontitis and systemic disease: recent concepts involving serum lipids. J Periodontol. 2000;71:1375-84.
30. De Nardin E. The role of inflammatory and immunological mediators in periodontitis and cardiovascular disease. Ann Periodontol. 2001;6:30-40.
31. Herzberg MC. Coagulation and thrombosis in cardiovascular disease: plausible contributions of infectious agents. Ann Periodontol. 2001;6:16-9.
32. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105:1135-43.
33. Chun Y-HP, Chun K-RJ, Olguin D'A, Wang H-L. Biological foundation for periodontitis as a potential risk factor for atherosclerosis. J Periodont Res. 2005;40:87-95.

34. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int. 1999;55:648-58.
35. Craig RG, Spittle MA, Levin NW. Importance of periodontal disease in the kidney patient. Blood Purif. 2002;20:113-9.
36. Yeun JY, Levine RA, Mantadilok V, Kaysen GA. C-reactive protein predicts all cause and cardiovascular mortality in hemodialysis populations. Am J Kidney Dis. 2000;35:469-76.
37. Stenvinkel P, Alvestrand A. Inflammation in end-stage renal disease: sources, consequences, and therapy. Semin Dial. 2002;15:329-37.
38. Stenvinkel P. Interactions between inflammation, oxidative stress, and endothelial dysfunction in end-stage renal disease. J Ren Nutr. 2003;3:144-8.
39. Yao Q, Axelsson J, Heimburger O, Stenvinkel P, Lindholm B. Systemic inflammation in dialysis patients with end-stage renal disease: causes and consequences. Minerva Urol Nefrol. 2004;56:237-48.
40. Yao Q, Pecoits-Filho R, Lindholm B, Stenvinkel P. Traditional and non-traditional risk factors as contributors to atherosclerotic cardiovascular disease in end stage renal disease. Scand J Urol Nephrol. 2004;38:405-16.
41. Peter Stenvinkel. Inflammation in end-stage renal failure: could it be treated? Nephrol Dial Transplant. 2002;17:33-8.
42. Shultis WA, Weil EJ, Looker HC, Curtis JM, Shlossman M, Genco RJ et al. Effect of periodontitis on overt nephropathy and end-stage renal disease in type 2 diabetes. Diabetes Care. 2007;30:306-11.
43. Fisher MA, Taylor GW, Shelton BJ, Jamerson KA, Rahman M, Ojo AO et al. Periodontal disease and other nontraditional risk factors for CKD. Am J Kidney Dis. 2008;51:45-52.
44. Yoshihara A, Deguchi T, Hanada N, Miyazaki H. Renal function and periodontal disease in elderly Japanese. J Periodontol. 2007;78:1241-8.
45. de Souza CM, Braosi AP, Luczyszyn SM, Avila AR, de Brito RB Jr, Ignácio SA et al. Association between vitamin D receptor gene polymorphisms and susceptibility to chronic kidney disease and periodontitis. Blood Purif. 2007;25:411-9.
46. Wahid A, Chaudhry S, Ehsan A, Butt S, Ali Khan A. Bidirectional relationship between chronic kidney disease & periodontal disease. Pak J Med Sci 2013;29(1):211–215. DOI: 10.12669/pjms.291.2926.

47. Barbudo-Selmi GR, Carvalho MB, Selmi AL, Selmi AL, Martins SEC. Periodontal disease characterization in dogs with normal renal function or chronic renal failure. Ciênc Rural 2004;34(1):113–118. DOI: 10.1590/S0103-84782004000100017.
48. Brotto RS, Vendramini RC, Brunetti IL, Marcantonio RAC, Ramos APP, Pepato MT. Lack of correlation between periodontitis and renal dysfunction in systemically healthy patients. Eur J Dent 2011;5(1):8–18. DOI: 10.1055/s-0039-1698853.
49. Shimazaki Y, Kushiyama M, Murakami M, Yamashita Y. Relationship between normal serum creatinine concentration and periodontal disease in japanese middle-aged males. J Periodontol 2013;84(1): 94–100. DOI: 10.1902/jop.2012.110528.
50. Xia J, Wang L, Ma Z, Zhong L, Wang Y, Gao Y, He L, Su X. Cigarette smoking and chronic kidney disease in the general population: a systematic review and meta-analysis of prospective cohort studies. Nephrol Dial Transplant. 2017 Mar 1;32(3):475-487. doi: 10.1093/ndt/gfw452. PMID: 28339863.