

Assessment of Periodontal Disease Severity among Patients at Different Stages of Chronic Kidney Disease

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How to cite the article:

Tawfig A, Jamal B, Eskandrani R, AlDayel L, AlTwaijry S, AlGhamdi E, Ahmed B. Assessment of periodontal disease severity among patients at different stages of chronic kidney disease. J Int Oral Health 2016;8(3):307-312.

Abstract:

Background: To assess the periodontal status in relation to chronic kidney disease (CKD) using the regular diagnostic methods, in addition to alkaline phosphatase (ALP) enzyme and pH value as biological markers. Most evidence suggests that a bi-directional relationship exists between periodontitis and systemic diseases in general.

Materials and Methods: Comparative study with the cross-sectional design having a sample size of 120 participants in Riyadh city, Saudi Arabia. CKD patients ranged from 20 to 65-year-old, dentate (≥ 10 teeth) are assigned in one of three study groups: (1) Pre-dialysis, (2) on dialysis, and (3) transplant with an $n = 30$ in each group. Exclusion criteria: Those who refused to consent, patients who have an additional systemic disease such as diabetes, hepatitis, smokers, pregnancy, patients with history of any periodontal treatment and/or antibiotic therapy in previous 6 months. The non-invasive oral examination was performed to evaluate the gingival index, plaque index, and clinical attachment loss (CAL). Salivary sample collection in 10 ml sterile test tube.

Results: The mean age of the patients was 41.90 ± 12.08 years. There were a total of 55.8% ($n = 67$) males and 44.2% ($n = 53$) females. The highest percentage of mild gingival inflammation was found in the hemodialysis patients 70% ($n = 21$). Moderate and severe periodontitis were distinctly higher in the dialysis group. Kruskal-Wallis *H*-test showed no statistically significant difference in the ALP and pH between the groups ($P > 0.05$). The overall correlation between CAL, ALP, and pH value showed a positive statistical significance at the level of 0.01.

Conclusion: On the basis of results of this study, it can be concluded that the activity of ALP enzyme and pH levels were increased in the saliva of patients with dialysis therapy as a consequence of severe periodontal destruction in this group specifically.

Key Words: Alkaline phosphatase level, chronic periodontitis, dialysis, kidney diseases

Introduction

Periodontitis is a collection of inflammatory diseases affecting the periodontium causing the destruction of the alveolar bone and loss of tissue attachment. One of the primary etiological factors is inadequate oral hygiene along with the continuous presence of Gram-negative, Gram-positive, and other microorganisms found in plaque biofilm, and their products causing a complex reaction to activate the host-derived immune and the inflammatory defense mechanism, releasing (interleukin-1, tumor necrosis factor, prostaglandin E2) which in turn amplify the inflammatory response causing connective tissue degeneration. Moreover, the triggering of the pro-inflammatory cytokines in response to lipopolysaccharides is responsible for the chronic systemic inflammation.^{1,2}

Its impact on the general health status, including systemic low-grade inflammation, development and progression of atherosclerosis, diabetes mellitus, pulmonary diseases, osteoporosis, and renal insufficiency is becoming increasingly apparent.³⁻⁸

Periodontal infections can act as focus of infection, aggravating the immunocompromised state of end-stage renal disease patients (ESRD).⁹

Chronic kidney disease (CKD) has five different stages are mainly measured based on estimated glomerular filtration rate (eGFR) which is the volume of fluid filtered from the kidney,¹⁰ in addition to alkaline phosphatase (ALP) which many clinicians use as a risk assessment tool to identify patients with higher risk for mortality and/or progression to ESRD.⁷ According to the National Kidney Foundation, normal results range from 90 to 120 ml/min/m². The primary causative agents for CKD are long-standing diabetes and hypertension which are often associated with low eGFR leading us to a stage three (eGFR 30-44 ml/min/m²) or stage four with (eGFR 15-29 ml/min/m²) kidney damage. The fifth stage and most severe condition is the ESRD, increasing the morbidity rate in the population, with a (eGRF <15 ml/min/m²), however, to prolong life span renal replacement therapy is indicated, either hemodialysis as an artificial means of removing nitrogenous and other toxic products of metabolism from the blood, or another alternative treatment which is renal transplant.¹¹ Patients on hemodialysis neglect their oral hygiene due to several factors which include the stress they are undergoing and prolong therapy session, so high periodontal destruction is

expected to be viewed in such patients, taking in consideration the various medications and supplements they are on such as erythropoietin, and cholecalciferol. While in renal transplant patients immunosuppressant drugs (cyclosporine and tacrolimus) to prevent the transplant rejection, yet they are well-known for their complication as they cause gingival hyperplasia which is still considered an obstacle for the dental population.^{12,13}

End stage renal failure can be associated with various clinical findings such as hyposalivation, impaired immunity and wound healing, alveolar bone destruction due to renal osteodystrophy and a general state of disability, attributed to unacceptable oral hygiene practices.^{4,5}

Further, there is a wide diversity of biochemical markers and enzymes that could act as a monitor for various biological alterations in the human body. The salivary fluid has an interest as a diagnostic medium in several studies. One of the salivary biomarkers for chronic periodontitis is ALP.¹⁴ It is a membrane-bound glycoprotein produced by many cells such as polymorphonuclear leukocytes, osteoblasts, macrophages, and fibroblasts within the area of the periodontium and into saliva, usually indicative of inflammation and/or destruction of the periodontal tissues. The level of ALP is positively correlated with the severity of the periodontal disease.¹⁵ Serum ALP is a marker for bone remodeling as well, frequently used to monitor bone metabolism in patients with renal impairment.¹⁶ Many studies conducted in the general population have shown that patients with CKD have higher ALP due to disturbances in the bone mineral disease. This could be considered as an eye opener that various systemic conditions are at risk due to periodontitis.

The statistical data from the Saudi Center for Organ Transplantation for the year 2014 has shown an increase in patients undergoing hemodialysis which reached up to 3398 patients in Riyadh while patients visiting the Renal Transplant Clinic regularly were 3815. Unfortunately, their periodontal status has not been monitored sufficiently, and data about the periodontal status of ESRD is very limited; yet, it could be very beneficial since most evidence suggests that a bi-directional relationship exists between periodontitis and systemic diseases in general.¹⁷ Therefore, the aim of this study is to assess the periodontal status in relation to CKD using the regular diagnostic methods, in addition to ALP as a biological marker.

Materials and Methods

This is a cross-sectional study in Riyadh city, involving $n = 120$ participants, after obtaining the approval from the Research Center of Riyadh Colleges of Dentistry and Pharmacy, in addition to a written consent for completion of a questionnaire about the general oral health, medical history, and drug history. A non-invasive oral examination along with a salivary sample collection from all the participants.

The clinical examination took place in two governmental hospitals of Riyadh, King Salman Center for Kidney Disease and Security Forces Hospital, both obtain large dialysis centers in their facilities, between the 15th of October and the 15th of December. The CKD patients ranged from 20 to 65-year-old, dentate (≥ 10 teeth) are the individuals targeted in our study. Those who refused to consent were excluded along with patients who have an additional systemic disease such as diabetes, hepatitis, smokers, pregnancy, patients with a history of any periodontal treatment in previous 6 months; also patients with history of antibiotic therapy in previous 6 months did not fit the inclusion criteria as well.

The control group ($n = 30$) are healthy individuals from both genders who age-matched the study group.

The study groups are patients who agreed to participate in the study with a CKD will be assigned to one of the following groups, 30 in each group.

- Group 1: Pre-dialysis patients
- Group 2: On dialysis patients
- Group 3: Transplant patients (the patients in the third group underwent renal transplantation 1 year ago).

Periodontal examination

Gingival index (GI by Loe and Silness, 1963), plaque index (PI by Silness and Loe, 1964), periodontal screening and recording, and clinical attachment loss (CAL) of the half mouth chart will be calculated.

Dental mouth mirror for visualization, WHO probe, and UNC periodontal probe are used to get the readings of six different sites (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, and distolingual) per tooth.

Laboratory

Patients will be asked to chew paraffin wax for 5 min, the stimulated saliva (10 ml) of the patient will be collected in a sterile test tube. The saliva sample will be stored in the refrigerator (2-8°C) until it is transported in an ice bag to the lab by the end of the day of the sample collection. Spectrophotometrically with the help of an autoanalyzer to determine the alkaline phosphatase level (ALP) as a biomarker, and pH.

Results

Total of 120 patients were Included in this study, (30 in each group). The mean age of the patients was 41.90 ± 12.08 years. There were a total of 55.8% ($n = 67$) males and 44.2% ($n = 53$) females. Chart 1 demonstrates the demographic data of the four groups. Table 1 shows the history of the systemic disease found in all the participants. Drug history specifically for antihypertensive such as calcium channel blocker for the 120 patients is demonstrated in Chart 2. Cyclosporine immunosuppressant intake by transplant patients shown in

Chart 3. Oral hygiene regarding the frequency of brushing is presented in Chart 4. Evaluation of the periodontal parameters (GI, PI, and CAL) as shown in Chart 5. Starting with the GI has shown that the highest percentage of mild gingival inflammation was found in the hemodialysis patients 70% ($n = 21$) followed by the control group 60% ($n = 18$), pre-dialysis 50% ($n = 15$), and least in transplant patients 40% ($n = 12$). On the other hand, the severe form of gingival inflammation in dialysis patients was 3.3% ($n = 1$) which is the least percentage in comparison to the other groups. The periodontal destruction (CAL) was higher in the dialysis patients. As shown in Table 2, among the total sample, the

prevalence of moderate and severe periodontitis increased stepwise across CKD stages. Distinctly in the dialysis stage. The mean \pm standard deviation values for GI, PI, and CAL scores are shown in Table 3. No statistically significant difference was observed ($P > 0.05$). Kruskal–Wallis H -test showed no statistically significant difference in the ALP (Table 4) and pH (Table 5) between the groups ($P > 0.05$).

Table 1: Distribution of the participants according to the history if underlying systemic diseases.

Systemic disease	Number of patients	Percentage
Hypertensions		
Control	0	0
Pre-dialysis	23	76.7
Dialysis	26	86.7
Transplant	20	66.7
Heart problems		
Control	0	0
Pre-dialysis	0	0
Dialysis	4	13.3
Transplant	1	3.3

Table 2: Distribution of periodontal disease severity (CAL) in the four groups.

Periodontal disease severity	CKD stages n (%)			
	Control	Pre dialysis	Dialysis	Transplant
No periodontitis	8 (26.7)	4 (13.3)	0 (0.00)	3 (10.00)
Mild	8 (26.7)	5 (16.7)	6 (20.0)	9 (30.00)
Moderate	10 (33.3)	12 (40.0)	14 (46.7)	11 (36.70)
Severe	4 (13.3)	9 (30.0)	11 (36.7)	7 (23.30)
Total	30 (100.0)	30 (100.00)	30 (100.00)	30 (100.00)

CKD: Chronic kidney disease, CAL: Clinical attachment loss

Table 3: Mean values for periodontal parameters in the four groups.

CKD stage	Mean \pm SD		
	Ginigival index	PI	CAL
Control	1.5 \pm 0.73	1.7 \pm 0.651	1.3 mm \pm 1.028
Pre-dialysis	1.6 \pm 0.718	1.9 \pm 0.548	1.8 mm \pm 1.008
Dialysis	1.3 \pm 0.547	2.2 \pm 0.626	2.1 mm \pm 0.73
Transplant	1.6 \pm 0.606	2.1 \pm 0.61	1.7 mm \pm 0.944
Total	1.5 \pm 0.66	2.0 \pm 0.642	1.7 mm \pm 0.968

SD: Standard deviation, PI: Plaque index, CKD: Chronic kidney disease, CAL: Clinical attachment loss

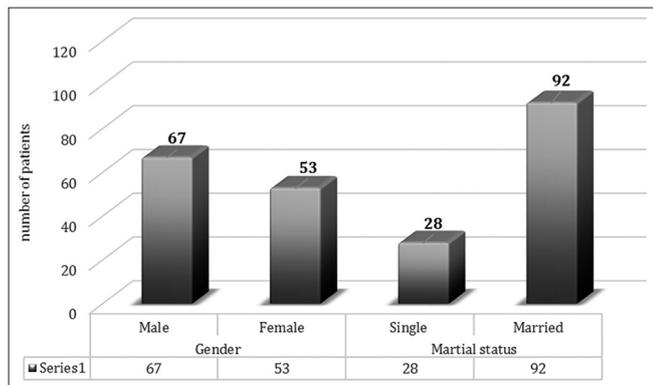


Chart 1: Demographic data of the participants.

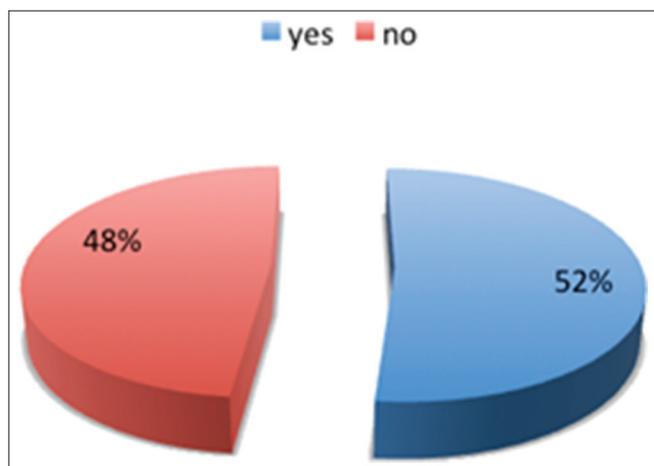


Chart 2: Calcium channel blocker.

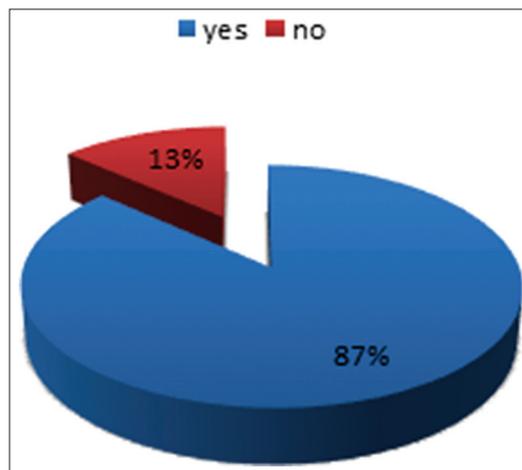


Chart 3: Cyclosporin.

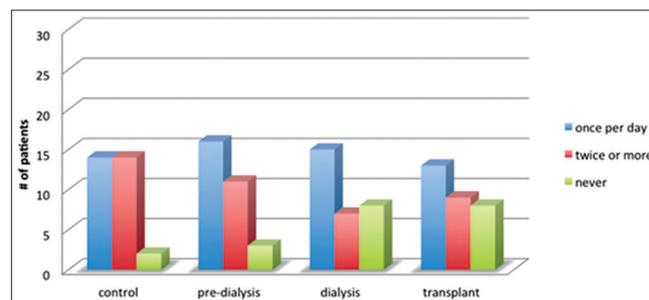


Chart 4: Brushing frequency.

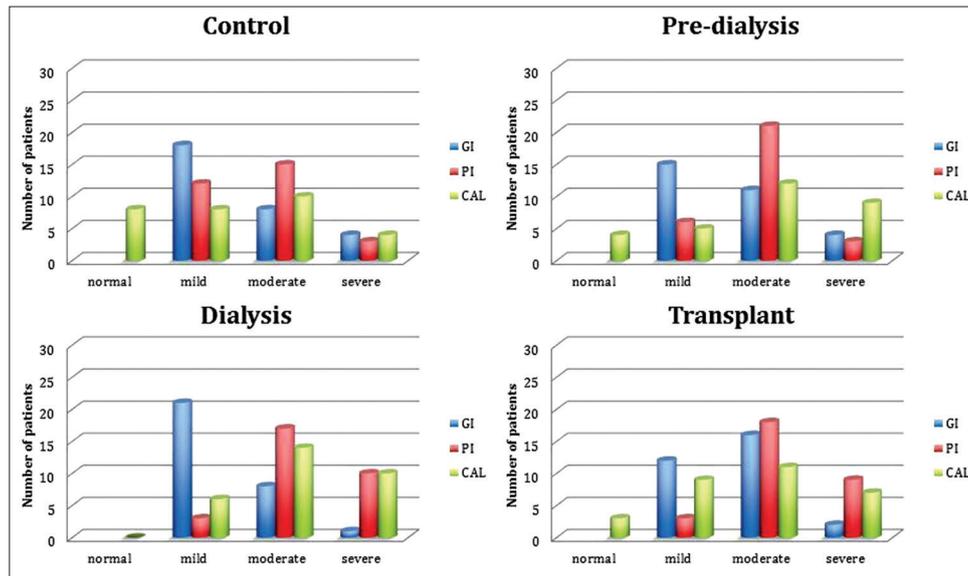


Chart 5: Evaluation of the periodontal parameters (GI, PI, CAL)

The overall correlation between charting, ALP, and pH value are presented in Table 6.

Discussion

The rapidly increasing number of patients with CKD combined with the unacceptably high morbidity and mortality in patients receiving dialysis or renal transplant points to an urgent understanding of the mechanisms responsible for the development of complications of CKD. From this point of view, the evaluation and promotion of oral health appear to be an important component of CKD care. It is necessary for the dental practitioner to thoroughly understand the special needs that arise from these patients.^{18,19}

Our study compared the periodontal health status of patients with different forms of renal disease to that of healthy controls in Riyadh city.

After statistical analysis, the moderate, severe GI parameter was least in dialysis patients. In the literature Davidovich *et al.*,²⁰ reported higher gingival inflammation and bleeding in the dialysis patients.

Tollefsen and Johansen²¹ and Oshrain *et al.* reported lower GI results in their studies. Insignificant change of GI may be due to suppression of immune system. According to Tollefsen and Johansen in laboratory conditions, blood lymphocytes of elderly patients react less effectively to dental plaque solution.

Other studies suggested that the uremic state in the hemodialysis patients may suppress inflammatory reactions in the tissues, which would result in infrequent detection of gingival inflammation.²² In contrast, the other investigations found that uremia would not retard gingival inflammation in hemodialysis patients,²³ with respect to this finding, our study

Table 4: The statistical mean value of salivary ALP U/L activity among the four CKD groups.

CKD stage	Mean±SD N=30
Control	3.93±5.483
Pre-dialysis	7.70±13.560
Dialysis	8.47±13.938
Transplant	3.37±4.979
Total	5.88±10.547

CKD: Chronic kidney disease, ALP: Alkaline phosphatase

Table 5: The statistical mean value of pH level among the four CKD groups.

CKD stage	Mean±SD
Control	7.20±1.095
Pre-dialysis	7.37±1.299
Dialysis	7.80±1.400
Transplant	7.63±1.351
Total	7.50±1.296

CKD: Chronic kidney disease

Table 6: The overall correlation between charting, alkaline phosphatase, and pH value.

Correlations			
Spearman's rho	CAL	ALP	pH
CKD stage n=120			
Correlation coefficient	0.153	-0.050	0.160
Significant (two-tailed)	0.095	0.587	0.081
CAL n=120			
Correlation coefficient	1.000	0.595**	0.195*
Significant (two-tailed)	0.000	0.000	0.033
ALP n=120			
Correlation coefficient	0.595**	1.000	0.181*
Significant (two-tailed)	0.000	0.000	0.49
pH n=120			
Correlation coefficient	0.195*	0.181*	1.000
Significant (two-tailed)	0.033	0.049	0.000

**Correlation is significant at the 0.01 level (two-tailed). *Correlation is significant at the 0.05 level (two-tailed). ALP: Alkaline phosphatase. PI: Plaque index, CKD: Chronic kidney disease, CAL: Clinical attachment loss

inducted 30 patients undergoing dialysis, and the results were in accordance that an inverse relationship exists between GI and dialysis. However, the gingival inflammation was assessed once and not over time; therefore, the association between GI and dialysis will need future studies for more clarification and solid evidence.

The periodontal destruction as evaluated by CAL levels is worse in the dialysis group, another indicative biomarker confirming the severity is ALP it was higher in dialysis group as well. It has been shown in different studies that higher ALP activity is related positively to periodontal disease.^{14,15,24}

Davidovich *et al.*²⁰ in their study on four renal failure groups provide evidence that the progression of the periodontal disease in chronic renal failure patients was correlated with bad oral hygiene. The results of our study are in agreement with the fact that oral hygiene has an impact on the periodontal status of CKD patients since 50% ($n = 15$) of the dialysis patients brush their teeth once per day. Furthermore, the high plaque levels of the dialysis patients indicate that they do neglect their oral self-care.²⁵

Another concern is the pH value of the saliva; the present study has shown the higher pH levels in the dialysis group (Table 5). Furthermore, the statistical analysis showed a positive correlation between the CAL level, pH value, and ALP enzyme level (Table 6).

This increase in pH value can be due to the urea concentration, which was diffused from saliva to the dental plaque. The urea is metabolized quickly by bacterial urease enzymes, producing ammonia and carbonic gas and causing an elevation in the pH of the saliva.²⁶ Ammonia can be cytotoxic for the periodontal tissue. 40% ($n = 12$) of the transplant patients had a score of 9 in the pH value which indicates high alkalinity this maybe in light of the fact that recent renal transplantation, since most of them had their surgery 1 year ago. Moreover, the prevalence of gingival enlargement secondary to immunosuppressant drug therapy and/or antihypertensive medications such as cyclosporine and calcium channel blocker is the most common oral manifestation.²⁷

Providentially, none of the transplant patients had a drug-induced gingival enlargement in spite of the fact that some of them have a drug history of cyclosporine due to the insufficient duration of drug consumption since this side effect needs a prolonged usage to take place. In this regard, further studies to analyze the effect of immunosuppressant's drug on periodontal status over longitudinal cohort basis are needed.

In summary, our study result verifies that a greater prevalence and severity of periodontal disease exists in the dialysis patients as compared to pre-dialysis, transplant patients, and systemically

healthy controls. It might be possible that severe periodontal destruction in CKD patients could have also altered their renal disease into a critical stage. The systemic disease could have also influenced the progression of periodontal disease in these patients. It has been already established that the chronic renal condition could have significant effects on the prevalence and severity of periodontal disease.²⁵ The complexity of the bi-directional systemic relationship needs well-controlled randomized clinical trials to clarify the mechanism of action. For the present time, our research provides promising results on how salivary ALP acts as a biomarker for periodontal disease severity in CKD patients.

Conclusion

On the basis of results of this study, it can be concluded that the activity of ALP enzyme and pH levels were increased in the saliva of patients with severe periodontal destruction, this is possibly a consequence of the dialysis therapy for ESRD patients specifically. Therefore, it is necessary that efforts should be made to motivate the renal patients to improve their oral hygiene practices to reduce the incidence of periodontal diseases among this population. Awareness oral health programs in dialysis centers would be very beneficial.

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