Clinical Medicine and Health Research Journal (CMHRJ)
Volume 05, Issue 02, March - April, 2025
Page No. 1168-1172,

Research Article

Determining the Association Between Severities of Periodontitis and Chronic Kidney Disease Severities Among Pre-Dialysis Patients.

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Received: 01 February, 2025 : Accepted: 04 March, 2025 : Published: 09 March 2025

Abstract:

Background: Different studies have looked at the effect of periodontitis on chronic kidney disease but only few studies have evaluated the effect of severities of periodontitis on severities of Chronic Kidney Disease (CKD) especially among predialysis patients. This study revealed the association between the severities of periodontitis and severities of CKD among predialysis patients and findings from this study may be applied to the management of CKD especially among predialysis CKD patients.

Methods: A cross-sectional study involving 120 pre-dialysis CKD participants. Full periodontal examination was carried out on the participants and severities of periodontitis assessed using American Academy of Periodontology, 2005 Classification modified by Eke and Page 2012. The severity of CKD was grouped into 5 stages based on estimated glomerular filtration rate (eGFR). Data collected were subjected to descriptive analysis, measures of central tendency, and analysis of variance (ANOVA). Regression analysis was also done to adjust for confounders such as age, gender, and socioeconomic status. Statistical significance was set at $p < 0.05$.

Results: Mild Periodontitis participants had the highest mean eGFR (62.6ml/min/1.73m^2) indicating better renal function while severe Periodontitis had the least mean eGFR (34.8ml/min/1.73m^2). Participants with high sensitivity C-reactive protein hsCRP (hsCRP <1mg/L and hsCRP >3mg/L) had mean eGFR values of 58.7ml/min/1.73m^2 and 42.1ml/min/1.73m^2 respectively suggestive of worsening renal function with progression of periodontitis.

Conclusion: This study revealed that severities of periodontitis may have effect on the severities of CKD.

Keywords: **Severities of Periodontitis, Severities of Chronic Kidney Disease, Estimated Glomerular Filtration Rate.**

Introduction

Periodontal diseases are a group of conditions that involve certain complex interactions between pathogenic bacteria, the environment and host causing inflammation and destruction to the supporting structures of the teeth.[1] Periodontitis results in pocket formation and progressive loss of alveolar bone around teeth that if left unattended leads to tooth mobility, and eventual tooth loss.[2] Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for ≥ 3 months.[3, 4] Chronic kidney disease has become a public health problem evident by its global prevalence and increasing morbidity and mortality especially in developing countries like Nigeria. It is estimated that by 2030 more than 2 million people in the United States of America will be on dialysis or need a kidney transplant.[5]

An association has been proposed by a number of studies between periodontitis and chronic kidney disease.[6, 7] Some cross-sectional studies and clinical trials have revealed the effect of CKD on periodontitis.[8, 9] Poor oral hygiene and increased level of periodontal inflammation have been reported in many haemodialysis patients and these have been linked to neglected oral care especially in end stage renal disease, ESRD.[9] Also, CKD patients because of their uraemic state are immunosuppressed which contribute to the rate of infection among them.[10, 11] This is attributable to functional abnormalities of monocytes, neutrophils, and dendritic cells.[12] One of such infections is periodontitis which is a polymicrobial infection predominantly caused by gram-negative bacteria. This relationship between CKD and periodontitis is however a double-edged sword. While CKD patients are predisposed to periodontitis, there is also accruing evidence that periodontitis could affect CKD. The proposed pathogenesis for the effect of periodontitis on CKD has been linked with systemic inflammation.[13, 14]

Studies have looked at the effect of periodontitis on chronic kidney disease but only few studies have evaluated the effect of severities of periodontitis on severities of CKD especially among predialysis patients.

The aim of this study is to determine the association between severities of periodontitis and CKD severities among predialysis patients. We hypothesized that there would be a positive association between progression of periodontitis based on severities and worsening renal function in predialysis CKD patients as assessed by eGFR.

Materials and Methods

Study design and setting:

This is a cross-sectional study conducted in both the Renal unit, Department of Medicine, and the Periodontology unit, Preventive and Community Dentistry department, Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile- Ife, Osun State, a Tertiary Hospital in the South Western geopolitical zone of Nigeria. The study was conducted between June 2019 and December 2020.

Participants:

The study comprised of consenting, consecutive participants aged 18 years and above recruited from the Nephrology Unit, Department of Medicine, Obafemi Awolowo University Teaching Hospitals Complex, Ile- Ife, Osun State Nigeria for a period of 19 months (June 2019 to December 2020) who had been diagnosed of Chronic Kidney Diseases for at least 3 months and undergoing conservative management (pre-dialysis patients). The participants were informed about the details of the study before enrolment into the study. The participants were informed that they were free to withdraw from the study without any consequence on their treatment and written informed consent was obtained from each participant. The participants were recruited based on the classification of Centers for Disease Control and Prevention in partnership with the American Academy of Periodontology, 2005; modified by Eke and Page, 2012. Severities of Periodontitis classified into mild, moderate, and severe periodontitis using the PPD and CAL. Mild periodontitis as ≥2 interproximal sites with CAL ≥3 mm and ≥2 interproximal sites with PD ≥4 mm (not on the same tooth) or one site with PD ≥5 mm, Moderate periodontitis as ≥2 interproximal sites with CAL ≥4 mm and ≥2 interproximal sites with PD ≥5mm (not on the same tooth), and Severe periodontitis as ≥2 interproximal sites with CAL ≥6 mm (not on the same tooth) and ≥1 interproximal site with PD ≥5mm.

The potential systemic impact of periodontal inflammation on general health, that is, the burden of periodontal inflammation as an inflammatory co-morbidity in predialysis CKD patients was assessed using the inflammatory burden marker, high sensitivity C-reactive protein (hsCRP). Low was inflammatory burden marker, hsCRP <1mg/L, moderate as hsCRP between 1-3mg/L while high was hsCRP >3mg/L.

The severity of CKD was grouped into 5 stages based on GFR.[3] The grouping criteria were developed by National Kidney Foundation as part of its Kidney Disease Outcomes Quality Initiative (NKF KDOQI): Stage 1: normal eGFR = 90 mL/min per 1.73m^2 and persistent albuminuria, Stage 2: eGFR between 60 to 89 mL/min per 1.73m^2, Stage 3: eGFR between 30 to 59 mL/min per 1.73m^2, Stage 4: eGFR between 15 to 29 mL/min per 1.73m^2, and Stage 5: eGFR of < 15 mL/min per 1.73m^2 or end-stage renal disease. Other inclusion criteria were participants who had never smoked cigarette and those who quitted cigarette smoking more than 5 years, and participants with minimum of 15 teeth. The exclusion criteria include patients who currently smoke or quitted smoking within the last five years, female patients who are pregnant, patients with possible immunosuppression (immunosuppressive drugs, tuberculosis, malnutrition, Acquired Immune Deficiency State, long-term steroid use), patients living with diabetes or with diabetic nephropathy as the cause of CKD, patients who had undergone non-surgical periodontal therapy within the last six months, patients on long term use of anti-inflammatory drugs especially non-steroidal anti-inflammatory drugs, patients with the history of use of antibiotics within the last six months.

Variables

Independent variables:

periodontal status, renal function

Sociodemographic factors:

gender, socio-economic staus, highest educational attainment.

Dependent variables:

PPD, CAL, hsCRP, eGFR

Data sources/measurement:

Each participant was given an appointment in the Periodontology clinic. On each appointment day, full periodontal examination was carried out in six sites per tooth by the researcher for the estimation of PPD and CAL and participants were grouped based on the estimated values. Mild periodontitis as ≥2 interproximal sites with CAL ≥3 mm and ≥2 interproximal sites with PD ≥4 mm (not on the same tooth) or one site with PD ≥5 mm, Moderate periodontitis as ≥2 interproximal sites with CAL ≥4 mm and ≥2 interproximal sites with PD ≥5mm (not on the same tooth), and Severe periodontitis as ≥2 interproximal sites with CAL ≥6 mm (not on the same tooth) and ≥1 interproximal site with PD ≥5mm.

The potential impact of periodontal inflammation as an inflammatory co-morbidity in predialysis CKD patients was assessed using the inflammatory burden marker, high sensitivity C-reactive protein (hsCRP). Low was inflammatory burden marker, hsCRP <1mg/L, Moderate as hsCRP between 1-3mg/L while High was hsCRP >3mg/L.

Blood samples were collected for serum creatinine (for the estimation of GFR) for both groups and were sent to the Chemical Pathology Laboratory (Point of Care Testing and Metabolic Research Unit) of Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC) Ile Ife, Osun State, Nigeria.

Blood samples were collected for serum hsCRP and creatinine (for the estimation of GFR) and sent to the Chemical Pathology Laboratory (Point of Care Testing and Metabolic Research Unit) of OAUTHC Ile Ife. Blood sample was collected using a tourniquet and a 5cc disposable syringe with a 21G needle from the antecubital fossa after skin preparation with methylated spirit in all participants. Five millilitres of blood was taken into a plain (non-anticoagulated) bottle and transported within 2 hours of collection to the Chemical Pathology laboratory (Point of Care Testing and Metabolic Research Unit) of OAUTHC

where sample processing, storage and analysis were done. All the laboratory procedures were carried out by a single Chemical Pathologist who was actively assisted by the researcher at the Chemical Pathology laboratory (Point of Care Testing and Metabolic Research Unit), OAUTHC. Blood sample collected in a plain (non-anticoagulated) bottle was allowed to stay for one hour to allow for clot retraction and was centrifuged at 3000 rev/sec for 10 minutes. The resulting supernatant (the serum) was separated into 2mls graduated plain (non-anticoagulated) cryobottle and refrigerated at -80°C for storage. For laboratory analysis of hsCRP, the serum was analysed according to Accubind ELISA® microwells High Sensitivity C-reactive Protein (hsCRP) test kit instruction. Serum level of hsCRP was based on a study of an apparent normal population and established references of a normal range for hsCRP AccuBind ELISA Microplate Test System established as follows: low risk (<1mg/L), normal (1-3mg/L), and high risk (>3mg/L). For the laboratory analysis of serum creatinine for the estimation of eGFR, serum creatinine was analysed according to Randox Laboratories Ltd test kit instructions.

The estimation of GFR was done using the Cockcroft-Gault(CG) equation.

This was based on the estimating equation that Ccr = [(140 −age) × weight/](72 × Scr) × 0.85 (if the subject is female), where Ccr is expressed in milliliters per minute, age in years, weight in kilograms, and serum creatinine (Scr) in milligrams per decilitre. Standardisation of this procedure was achieved by sending all blood specimens to the same diagnostic laboratory as stated above.

Study size: The sample size was determined and estimated to be 120 participants.

Quantitative data analysis and statistical methods: The data for each patient was recorded by the researcher on a standardised data collection form. Data collected were analysed using IBM SPSS Statistics 23.0. Data were subjected to descriptive analysis, measures of central tendency, and analysis of variance (ANOVA). Regression analysis was also done to adjust for confounders such as age, gender, and socioeconomic status. Statistical significance was set at $p < 0.05$.

Ethical considerations: The Ethics and Research Committee (ERC) of the Obafemi Awolowo University Teaching Hospitals Complex, Ile Ife, Osun State, Nigeria (ERC/2018/10/14) approved the study (31/10/2018).

Results

The age range for the total participants was 19–83 years with their mean age being 45.7 (SD = 16.63) years. The mean age of the males was 45.97 (SD = 18.00) years and 45.44 (SD = 14.83) years for the females.

Participants with mild periodontitis exhibited the highest mean eGFR (62.6 ml/min) **Table 1**, indicating better kidney function. The relatively low standard deviation (15.5) suggests that eGFR values within this group are more consistent and less variable. However, in Moderate periodontitis, the mean eGFR reduced significantly to 41.0 ml/min. **Table 1**. This reduced eGFR suggests worsening kidney function as periodontitis progresses from Mild to Moderate. The higher standard deviation (17.5) compared to Mild indicates greater variability in kidney function within this group. Participants with severe periodontitis showed the lowest mean eGFR (34.8 ml/min) **Table 1** indicating worsening kidney function. The lower standard deviation (11.1) compared to the other mild and moderate periodontitis suggests that the participants in this group consistently experience severe reductions in kidney function.

Table 1: Association between severities of periodontitis and severities of CKD as assessed by eGFR

Summary of baseline Glomerular Filtration Rate ml/min

Baseline PPD	Mean eGFR	Standard Deviation	Frequency
Mild Periodontitis	62.6	15.5	59
Moderate Periodontitis	41.0	17.5	55
Severe Periodontitis	34.8	11.1	6
Total	51.3	19.7	120

Table 2 The ANOVA revealed significant differences in the mean eGFR across the different severities of periodontitis. The F-value of 28.0, coupled with a p-value of 0.00, indicates that the differences observed are statistically significant, meaning that the severity of periodontitis is associated with varying degrees of chronic kidney disease severity as measured by eGFR.

Table 2: ANALYSIS OF VARIANCE

Source	Sum of Squares	Degree of freedom	Mean Square	F	P > F
Between groups	14920.7	2	7460.4	28.0	0.00
Within groups	31152.8	117	266.3		
Total	46073.5	119			

P- Probability, F- F-test

Participants with low hsCRP levels had the highest mean eGFR at 58.7 ml/min **Table 3**, indicating relatively better kidney function. The standard deviation of 15.9 suggests some variability in kidney function within this group. Participants with Moderate hsCRP levels showed a mean eGFR of 55.0 ml/min. **Table 3** The reduction in eGFR compared to those with Low hsCRP levels indicates a decline in kidney function as the burden of inflammation increases. The standard deviation of 19.0 reflects more variability in kidney function among these participants, potentially due to a mix of factors influencing their CKD progression. Participants with the high hsCRP levels had the lowest mean eGFR at 42.1 ml/min, **Table 3** indicating more advanced kidney disease. The higher standard deviation of 19.8 suggests that while all participants in this group have reduced kidney function, the severity of CKD varies more widely among them.

Table 3: Potential systemic impact of periodontal inflammation on eGFR.

Summary of baseline Glomerular Filtration Rate ml/min

Baseline hsCRP(mg/L)	Mean eGFR	Standard Deviation	Frequency
Low	58.7	15.9	40
Moderate	55.0	19.0	34
High	42.1	19.8	46
Total	51.3	19.7	120

The ANOVA revealed that the differences in eGFR with varying burden of inflammation from periodontitis were statistically significant (F = 9.7, p = 0.00). **Table 4**

Table 4: ANALYSIS OF VARIANCE

Source	Sum of Squares	Degree of freedom	Mean Square	F	P > F
Between groups	6549.7	2	3274.8	9.7	0.00
Within groups	39523.8	117	337.8		
Total	46073.5	119			

P- Probability, F- F-test

Discussion

This study assessed the association between the different severities of periodontitis and CKD severities among predialysis patients in a tertiary care centre in Nigeria. The key findings revealed that severities of periodontitis affect the severities of CKD in predialysis CKD patients as evidenced by decreasing eGFR values. Participants with mild Periodontitis have the highest mean value of eGFR while those with severe periodontitis have the least. The renal function as assessed by eGFR was also found to reduce with increasing burden of inflammation and rate of progression of periodontitis as assessed by hsCRP. Participants with Low have the highest mean value of GFR while those with high have the least.

The strengths of this present study include looking at the effect of severities of periodontitis on renal function compared to putting all the groups together which were found in most studies. Also, selecting predialysis CKD participants with less severities of CKD revealed the possible advantage and potential beneficial effects of periodontal therapy in this group compared to those undergoing dialysis or that will need renal transplantation. One of the limitations is that the study design (being a cross-sectional study) could not establish a cause-effect relationship in these participants.

Participants with mild Periodontitis have the highest frequency also has the highest mean eGFR in this study while those with High hsCRP levels have the highest frequency and with the least eGFR also. This was similar to the findings of JS Schuetz et al. in Brazil.[15] This could possibly explain further that untreated periodontitis will progress and this progression continues to leave a deteriorating effect on the renal function of predialysis CKD patients. The mean value of hsCRP used in this study was found to increase with severities of CKD. Those with high levels of hsCRP have the worst eGFR. This was similar to the findings of JS Schuetz et al.[15] where stages 3 and 4 CKD have mean CRP of 8.79mg/dl and 10.35mg/dl respectively. This also further shows the possible effect of increased inflammatory burden on the severities of CKD. A study from Malaysia[16] also reported similar findings of worsening renal function with increasing inflammatory burden (hsCRP of 1.71mg/dl with eGFR of 89.6ml/min/1.73m^2 and hsCRP of 3.07mg/dl with GFR of 25.9ml/min/1.73m^2).

This association between periodontitis and CKD has been attributed to persistent immune response from periodontitis which leads to low grade inflammation and eventually contributes to reduced renal function.[15] However, because of many shared risk factors such as age, smoking, diabetes mellitus, cardiovascular diseases between these conditions, it is still very difficult to define the true strength of association.[15]

The findings from this present study may be applied to the management of CKD especially among predialysis CKD patients.

Conclusion

This study revealed the possible association between the severities of periodontitis and severities of CKD among predialysis patients. It is recommended that periodontal screening should be part of routine evaluation for CKD patients. Future studies should also focus on the possible beneficial effects of periodontal therapy in predialysis CKD patients.

Added value of this study

This study revealed the association between the different severities of periodontitis and severities of CKD among predialysis patients and findings from this study may be applied to the management of CKD especially among predialysis CKD patients.

Clinical implications

Altering the progression of periodontitis through treatment of early stages of periodontitis may go a long way in reducing burden of inflammation in predialysis CKD patients and thereby improving renal function.

Conflicts of Interest: There are no conflicts of interest

Sources of Funding: Nil

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