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ORIGINAL RESEARCH

Salivary Flow Rates of Nigerian Patients with Chronic Kidney Disease: A Case-control Study

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ABSTRACT

Aims and objectives: The study determined the relationship between chronic kidney disease (CKD) and changes in salivary flow and the complications of reduced salivary flow among African subjects with CKD compared with the controls.

Materials and methods: One hundred and eighty patients, 90 CKD and 90 controls were recruited, interviewed and examined. Stimulated and unstimulated saliva collection was done with standardized spitting method. Urinalysis and blood creatinine levels were determined and glomerular filtration rate (GFR) of each patient was calculated from the blood creatinine using Cockcroft and Gault formula. Statistical analysis was done using STATA 11 software.

Results: The mean stimulated and unstimulated whole salivary flow rate among CKD subjects were 4.07 ± 1.91 and 2.34 ± 0.99 ml/5 min respectively and is significantly lower than that of the controls which were 8.05 ± 3.95 ml/5 min and 3.82 ± 2.27 ml/5 min for stimulated and unstimulated flow rates. Oral signs of reduced salivary flow were found in 80% of CKD patients. The commonest oral finding was taste abnormalities others are burning sensation, halitosis and difficulty in mastication.

Conclusion: Patients with CKD had reduced stimulated and unstimulated salivary flow rate. Reduced salivary flow was associated with oral lesions in majority (80%) of CKD patients, the commonest finding being taste abnormalities.

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INTRODUCTION

Several factors influence salivary flow rate. They include medications, salivary gland diseases, chronic stress, and level of hydration of the body. Others are systemic diseases, such as diabetes mellitus, hypertension, depression and chronic kidney disease (CKD). The effects of CKD on salivary tissues are enormous and partly due to the pathophysiology of renal disease or the effects of instituted therapy or both factors.[1] Chronic kidney disease is an irreversible deterioration in the renal functions which classically develop over a period of 3 months to a year.[2] The prevalence of CKD is increasing annually with 337 per million reported in US population.[1] In Nigeria, much higher prevalence of 1.8 to 10% (1,800-10,000 per million population) has been reported and it represents 27.17% of all medical outpatients' clinic attendance.[3] Consequently, more CKD patients may be presenting to dentists.[4]

Approximately, 90% of CKD patients have at least one or more oral symptom.[4] These include: periodontitis, burning sensation, halitosis, mucosal lesions and xerostomia. These lesions have been associated with reduced quality of life in affected patients due to the bidirectional relationship reported between the oral lesions and the underlying systemic diseases.[5]

An average healthy adult has resting flow rate of 0.82 ± 0.1 ml/min for whole saliva, while the stimulated whole salivary (SWS) flow rate is 2.17 ± 0.14 ml/min.[6] Generally,

when resting whole saliva (RWS) and SWS becomes less than 1 ml and 1.5 ml/min respectively, subjective and objective sign of impaired salivary flow will be evident. In CKD, impaired salivary flow (the extreme of which is considered xerostomia) is a frequently observed symptom in 33 to 76% of CKD patients.[7] Saliva performs several vital functions, such as lubrication of the oral mucosa, aid mastication and deglutition, antibacterial functions, aid oral cleansing and caries prevention. These vital functions will be lost or impaired in patients experiencing impaired/reduced salivary flow.[7,8] Chronic kidney disease patients with reduced salivary flow have significantly reduced quality of life compared with controls.[9] In addition, qualitative changes in saliva, which was also widely reported in CKD patients, affects oral functions as well and this tends to improve as the kidney functions returns.

Of the several reports available in the scientific literature, none has described salivary flow changes in the African population. The higher prevalence of CKD in African countries coupled with poor dental awareness and subsequent oral health neglect is common in this region. This study determined salivary flow rates of CKD subjects compared with controls as well and the oral lesions associated with the reduced salivary flow. Findings from this study are expected to educate the public and care givers on the importance of paying attention to the oral aspects of CKD during management.

MATERIALS AND METHODS

Study Design

The study was designed as a case control study comparing salivary flow rates in chronic kidney patients attending the renal clinic of the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile Ife, Nigeria, with the controls from the General Medical Outpatient Clinic of the same hospital between September 2011 and March 2012.

Ethical Issues

Ethical clearance for the study was obtained from the Ethics and Research Committee (ERC), OAUTHC, Ile-Ife, Nigeria.

Subjects

This consisted of two populations. The first group (Group A) consisted of patients diagnosed with chronic renal failure and end stage renal disease (CKD group). This group was randomly selected from the pool of patients being managed by the Renal Unit of the OAUTHC Ile-Ife. The control group (Group B) comprised of patients who presented at the general out patients' clinic of OAUTHC for routine medical check-up including those for pre-employment and preadmission medical check-up. They were also randomly selected. The inclusion criteria for group A was patients diagnosed of CKD and aged 18 years and above while the inclusion criteria for the group B were patients with normal glomerular filtration rate (GFR) (as calculated from blood creatinine) and aged 18 years and above. Patients who had other systemic disease and those who did not give their consent were excluded.

Sample Size Estimation

Sample size was calculated using Stata statistical software (version 11).[10] The paramenters for sample size estimation were alpha of 5%, power of 90%, and a known prevalence of xerostomia in normal adult population of 20%[11] and projected to be 45% in renal patients. Sample size was calculated to be 80 subjects in each group.

Methods

Patients who met the inclusion criteria were informed about the study after which a signed consent of those willing to participate was obtained. Information on patients' biodata, such as name, age, gender, address, ethnicity, marital status and occupation was obtained from the participants. Relevant information on past medical history, history of salivary gland diseases and drug history were obtained and recorded.

Salivary collection and measurements: Collection of saliva for objective salivary measurements (unstimulated whole saliva (UWS) and SWS was done using standardized spitting method.[12] Each subject was told to abstain from eating and drinking 30 minutes before salivary collection done between 7 and 8:30 am each day. Patients were asked to spit continuously into the sputum jars for 5 minutes after which the volume of the collected saliva was measured with graduated pasture pipette. Mechanical stimulation was done by asking the patients to chew continuously on a standard weighed paraffin wax and the collection and measurement was similar to the unstimulated. The chemical stimulation was also done by delivering a drop of lime juice on the dorsum of the tongue with the aid of drop applicator at interval of 1 minute during the 5 minutes saliva collection and the volume also measured with pasture pipette. The mean value of the stimulated salivary flow for each subject was calculated by finding the average of mechanical and chemical stimulated salivary flow rate.

Oral soft tissues: The tongue, floor of the mouth, buccal mucosa, orifices of major salivary gland ducts, pharynx and palatal mucosa were also examined for dryness, depapillation, ulceration, and hyperemia, paleness,

fissuring, crusting and any other abnormalities. Other oral examinations were done and appropriate referral made where necessary.

Urinalysis was done for each patient using Combic 9® urinalysis kit. Mid stream urine was collected using urine sample bottles. The urinalysis kit was dipped inside urine. The color change on the strips was used to match the standard color changes as indicated by the manufacturer. The presence/absence of the various urine parameter were indicated. The parameters include: protein, bilirubin, ketones, acidity (pH), blood, glucose and bilirubinogen.

Blood creatinine: Blood sample was taken from each subject for the assessment of blood creatinine level from which the estimated glomerular filtration rate (eGFR) of each subject was calculated using Cockcroft and Gault equation[13] as follows:

$$\text{Estimated creatinine clearance (ml/min)} = \frac{(140\text{-age}) \times \text{body weight}}{72 \times P_{cr}\ (\text{mg/dl})}$$

For females multiply the answer by 0.85 (Gender correlating factor).

STATISTICAL ANALYSIS

Data analysis was done using Stata 11 statistical software (Statacorp, College Station, Texas). Descriptive statistics was used to characterize sociodemographic variables, such as age, sex, marital status and occupation. For descriptive continuous variables, the mean, median, minimum value, maximum value and appropriate measures of variability were determined depending on if they are normally distributed or not. For descriptive variables that are categorical, simple frequency and percentages was determined.

Bivariate analysis, such as t-test, Fisher's exact and Chi-square statistics or their non-parametric equivalent was used as appropriate to compare between two groups. Statistical significance was inferred at $p < 0.05$ and confidence interval was set at 95% for all the analysis. Logistic regression was used for determining the role of the predictor and confounders on the primary outcome.

Table 1: Salivary production in subjects

Salivary flow rates	*CKD patients vol. (ml)/ 5 min (SD)*	*Controls vol. (ml)/ 5 min (SD)*	*p-value*
Mean unstimulated whole saliva (mean UWS)	2.34 (0.99)	3.82 (2.27)	<0.001*
Mean stimulated whole saliva (mean SWS)	4.07 (1.91)	8.05 (3.95)	<0.001*

Mann-Whitney rank sum test; *statistically significant, $p < 0.001$

RESULTS

Salivary Production in Subjects

Salivary flow was significantly lower in CKD subjects than in the controls (Table 1).

Relationship between Age and Salivary Flow Rate in all Subjects

Salivary flow rate was greatest in patients below the age of 20 years, sharply comes down in patients between 21 and 30 years and gradually increase up to 50 years after which it gradually comes down as the patients approach old age (Graph 1).

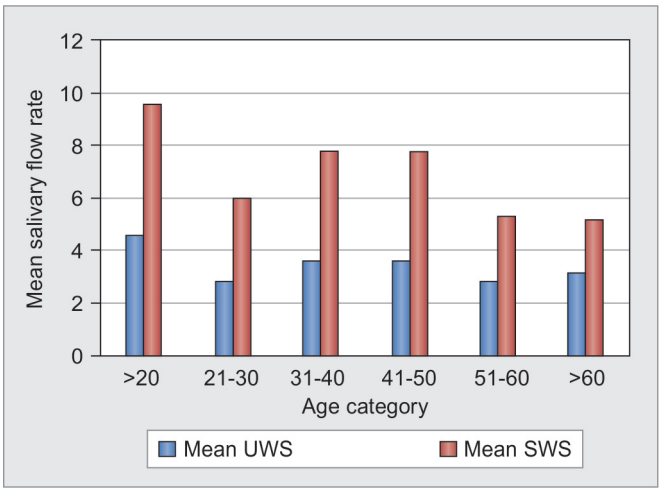
Oral Signs of reduced Salivary Flow Rate/Dry Mouth in Subjects

Majority (80%) of CKD patients have oral signs of reduced salivary flow. The most frequent oral sign was taste impairment. Other signs include burning sensation, halitosis, and difficulty in mastication and halitosis (Table 2).

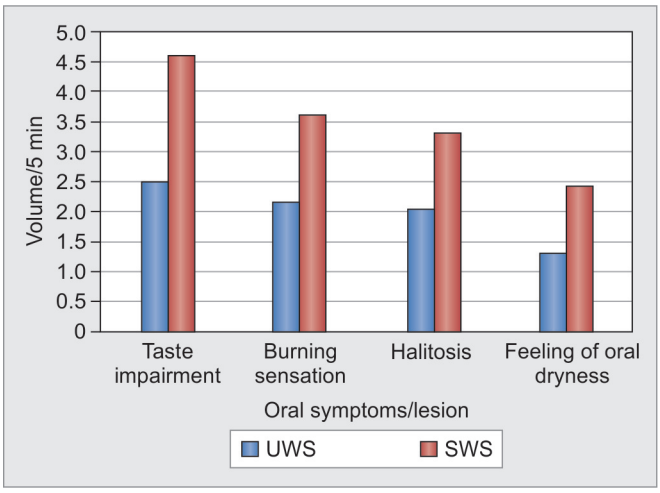
Table 2: Oral signs of reduced salivary flow rate/dry mouth in subjects

	CKD subjects (%) n = 90	*Controls (%) n = 90*	*All subjects N = 180*	*p-value*
Taste impairment	23 (26%)	1 (1.1%	24 (13.3%)	<0.001*
Speech difficulty	4 (4.5%	0 (0%)	4 (2.2%)	0.121
Burning sensation	16 (18%)	0 (0%)	16 (8.89%)	<0.001*
Halitosis	11 (12%)	1 (1%)	12 (7%)	0.005*
Difficulty in mastication	6 (6.7%	0 (5)	6 (3.3%)	0.029
Thick saliva	5 (5.6%)	1 (50)	6 (3.3%)	0.211
Difficulty in swallowing	1 (1.1%)	0 (0%)	1 (0.5%)	1.000
Prominent/dry papillae	4 (4.5%)	0 (0%)	4 (2.2%)	0.121
Salivary gland swelling	1 (1.1%)	0 (0%)	1 (0.5%)	1.000
Dry and sticky mucosa	1 (1.1%)	1 (1.1%))	2 (1.1%)	1.000
Those with no signs	18 (20%)	86 (4.4%)	22 (12.2%)	<0.001*
Total	90 (100%)	90 (100%)	180 (100%)	

*Statistically significant, $p < 0.05$



Graph 1: Relationship between age and salivary flow rate in all subjects



Graph 2: Salivary production and common oral complaints/lesions in CKD patients

Table 3: Relationship between salivary production/flow rates and common oral complaints in all subjects

Symptoms	*CKD patients vol. (ml)/5 min (SD)*	*Controls vol. (ml)/5 min (SD)*	*p-value*
Taste impairment			
UWS	2.4 (1.4)	3.2 (1.9)	< 0.001*
SWS	4.6 (2.6)	6.2 (3.5)	
Burning sensation			
UWS	2.2 (0.6)	3.2 (1.9)	<0.001*
SWS	3.6 (1.2)	6.2 (3.6)	
Halitosis			
UWS	2.1 (1.1)	3.2 (1.9)	0.0025*
SWS	3.3 (1.7)	3.3 (1.7)	
Oral dryness			
UWS	1.3 (0.5)	3.2 (1.8)	<0.001*
SWS	2.4 (0.9)	6.2 (3.5)	

Mann-Whitney rank sum test; *statistically significant, p < 0.005

Subjects with complaints of oral dryness have the least stimulated and unstimulated salivary flow rates (Graph 2). Salivary flow rates of subjects with CKD are significantly lower than controls (Table 3).

The Effects of Age and Sex in Salivary Flow in CKD Subjects

Table 4 shows the association between CKD and reduced salivary flow that adjusted for the differences due to age and sex. The likelihood of developing reduced saliva flow was significantly higher in subjects with CKD compared with controls (Odds ratio 37.68, 95% C.I (8.47-167.6), p < 0.001). Also, every 1 year increase in age is associated with about one fold increase in risk of having reduced saliva flow, this observation was not statistically significant p = 0.31 (Table 4).

Table 4: Role of chronic kidney disease on development of reduced salivary flow—using a logistic regression model for age and sex

Covariate	*Odds ratio*	*Standard error*	*95% CI*	*p-value*
Chronic kidney disease	37.7	28.7	8.47-167.6	<0.001*
Sex	0.64	0.28	0.26-1.51	0.31
Age	0.99	0.01	0.97-1.03	1.03

*Statistically significant, p < 0.001, CI: Confidence interval

Both age and sex did not have a significant relationship with the likelihood of developing oral lesion.

DISCUSSION

Chronic kidney diseases are associated with diverse complications, involving virtually all the organs in the body. Oral manifestations of CKD have been widely reported, majority of which are focused on oral mucosa lesions, dental and periodontal changes but information on salivary flow rate changes in the African population is scanty.

In our study, chronic kidney patients were most frequently seen within the age category of 41 to 60 years, with male predilection. This age and sex distribution findings is in agreement with some studies, the close association between the age of occurrence of the common etiological agents of CKD and the age category and male sex predilection are possible explanation for the findings.[1,4] However, CKD has also been reported in children, in this case congenital problems (e.g. polycystic kidney disease) has been strongly implicated among others.[14]

The mean unstimulated salivary flow rate among CKD subjects and controls in the present study were 2.34 ± 0.99 ml/5 min and 3.82 ± 2.27 ml/5 min respectively, equivalent to 0.764 and 0.48 ml/min respectively. This showed a significantly lower salivary flow in CKD subjects and control. These findings are similar to a Nigerian study that reported a mean UWS of 0.75 ml/min for the controls/health patients while comparing the salivary flow and composition in diabetic and non-diabetic patients.[15] Other studies that presented similar results include Kho et al,[8] Bayraktar et al,[16] Skopouli et al[17] and Elishoov et al.[18] Several reports attributed the reduced salivary flow rate in CKD patients to fluid restriction, dehydration, electrolyte imbalance and possibly the effect of overwhelming infection observed in CKD patients on salivary glands.[1,8] The same trend of lower salivary flow in CKD subjects was also found in SWS flow rate findings. Consistent with many studies, the SWS from the present study was 4.07 ± 1.91 and 8.05 ± 3.95 ml/5 min among CKD subjects controls respectively. These findings showed that the percentage reduction in the mean stimulated salivary flow rate in CKD patients is higher (49.4% reduction) that the mean unstimulated salivary flow (30% reduction) in the same group of patients. This may suggest nerve damage (neuropathy) as one of the major mechanisms explaining changes in salivary flow in CKD patients as 70% of renal patients present with uremic polyneuropathy.[19]

Patients with reduced salivary flow usually show associated oral signs and symptoms as a result of the reduced quantity of saliva.[20] In the present study, 80% of the CKD had oral sign suggestive of reduced salivary flow. These oral signs and symptoms are pointer to salivary changes that may lead to other dental/oral problems. The severity of the lesions could also be used as an indicator to estimate the severity of the underlying renal disease.[21] Oral signs of reduced salivary flow found in this study include taste impairment in 26% CKD patients, burning sensation (18%), halitosis (12%), difficulty in mastication (6.7%) and speech difficulty (4.5%) consistent with many reports.[1,22] Carious lesion which was reported by some researchers[1,23] to be partly due to reduced salivary flow and partly poor oral hygiene in CKD patients was not found in this study. These oral signs are well documented in CKD patients and have influence on patients' quality of life.[1,4]

Salivary flow rate of patients also appears to differ with different lesion in the mouth. This study showed that patients with observable oral dryness had the lowest flow rate (1.5 ml/5 min for RWS) and is highest in patients with taste impairment. This further stressed the potential role of oral signs as indicators of severity of underlying renal diseases. While taste impairment may indicate a mild salivary flow change and a lower stage of renal damage, dry oral mucosa, candidiasis may indicate a severe problem and will require further investigation to achieve optimal patients' care.

Although association between salivary flow rate and age has been widely reported,[24] Smith et al,[25] however, reported no association. Likewise, the present study which showed reduction in salivary flow as the age increases also showed with logistic regression for sex and age that the net effects effect of age and sex in accounting for reduced salivary flow was found to be statistically insignificant. These findings appear not to necessarily negate the earlier findings that increasing age and sex differences affect salivary flow rates, but rather removing the effects of sex and age as a cofounder in causing reduced salivary flow among CKD subjects.

CONCLUSION

Findings from this study had established a significant relationship between CKD and reduction of both stimulated and unstimulated whole salivary flow rate in an African population. Furthermore, majority (80%) of CKD patients suffer from oral effects of reduced salivary flow in the mouth, the most frequent of the oral effect is abnormal taste sensation seen in 26% of CKD patients. Other oral lesions include taste impairment, burning sensation, and difficulty in mastication, speech problems and halitosis. Salivary evaluation (Sialometry) is therefore helpful for all CKD patients in the course of their management.

REFERENCES

1. Proctor R, Kumar N, Slein A, Moles D, Porter S. Oral and dental aspect of chronic renal failure. J Dent Res 2005;84: 199-208.
2. Levey A, Eckkardt K, Tsukamoto Y. Definition and classification of chronic kidney disease: a position statement from kidney disease improving Global Outcome. Kidney Int 2005;67:2089-2100.
3. Ulasi I, Chinwuba K. The enormity of chronic renal disease in Nigeria. The situation in a teaching Hospital in South-East Nigeria. J Tropical Med volume 2010 Article ID 501957, 6 pages doi: 101155/2010/501957.
4. Santosh P, Suneet K, Bharati D, Farzan R, Sumita K. Oral manifestations in chronic renal failure patients attending two hospitals in North Karnataka, India. OHDM 2012;11:100-106.
5. Monica AF, George WT, Brady TW, Ellen TM. Bi-directional relationship between chronic kidney and periodontal disease: a study using structural equation modelling. Kidney Int 2011;79:347-355.
6. Cedric J, Bulur N, Berrin O, Satman I, Yilmaz MTJ, Malaisse W, et al. Salivary glucose concentration and excretion in normal and diabetic subjects. J Biomedic Biotechnol 2009;2009: 1-6.

7. Porter S, Hegarty A, Scully C. An update of the etiology and management of xerostomia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;97:28-46.
8. Kho H, Lee S, Chung S, Kim Y. Oral manifestations and salivary flow rate, PH, and buffer capacity in patients with end-stage renal disease undergoing haemodialysis. Oral Surg Oral Med Oral Pathol 1999;88:316-319.
9. Esra G, Hilai U, Bahar T, Dilek T. Oral health related quality of life and periodontal health status in patients undergoing haemodialysis. JADA 2009;140.
10. Corp S. Stata statistics/data analysis. Version 10 (1984-2007), Special Edition. Texas 77845 USA. Available at: http://wwwstatacom.
11. Keles M, Tozoglu U, Uyanik A, Eltas A, Bayindir Y, Cetinkaya R, et al. Does peritoneal dialysis affect halitosis in patients with end-stage renal disease? Perit Dial Int 2011;31:168-172.
12. Navazesh M, KS S. Measuring salivary flow challenges and opportunities. J Am Dent Association 2008;139:355-405.
13. Amira C. Assessment of glomerular filtration rate in clinical practice in Nigeria. Med Practionner 2007;52:76-81.
14. Al Nowaiser A, Roberts G, Trompeter R, Wilson M, Lucas V. Oral health in children with chronic renal failure. Pediatr Nephrol 2003;18:39-45.
15. Lasisi TJ, Fasanmade AA. Salivary flow and composition in diabetic and non-diabetic subjects. Niger J Physiol Sci 2012;27:79-82.
16. Bayraktar G, Kazancioglu R, Bozfakioglu S, Yildiz A, Ark E. Evaluation of salivary parameters and dental status in adult hemodialysis patients. Clin Nephrol 2004;62:380-383.
17. Skopouli F, Siouna-Fatourou H, Ziciadis C, Moutsopoulos H. Evaluation of unstimulated whole saliva flow rate and stimulated parotid flow as confirmatory tests for xerostomia. Clin Exp Rheumatol 1989;7:127-129.
18. Elishoov H, Wolff A, Volovikov A, Gorsky M. Evaluation of unstimulated and stimulated parotid salivary flow rate in Israeli healthy subjects aged 60 years and older. Refuat Hapeh Vehashinayim 2005;22:44-48.
19. Aggarwal H, Sood S, Jain D, Kaverappa V, Yadav S. Evaluation of spectrum of peripheral neuropathy in predialysis patients with chronic kidney disease. Ren Fail 2013;35:1323-1329.
20. Kaushik A, Reddy S, Umesh L, Devi BKY, Santana N, Rakesh N. Oral and salivary changes among renal patients undergoing hemodialysis: a cross-sectional study. Ind J Nephrol 2013;23:125-129.
21. Epstein S, Mandel I, Scopp I. Salivary composition and calculus formation in patients undergoing hemodialysis. J Periodontol 1980;51:336-338.
22. De la Rosa G, Mondragon-padilla, Irigoyen-Camacho M, Bustamante-Ramirex M. Oral lesion in group of kidney transplant patients. Med Oral Pathol Oral Cir Bucal 2005;10:196-204.
23. Dawes C. How much of saliva is enough for avoidance of xerostomia? Caries Res 2004;38:236-240.
24. Percival R, Challacombe S, Marsh P. Flow rates of resting whole and stimulated parotid saliva in relation to age and gender. J Dent Res 1994;73:1416-1420.
25. Smith C, Boland B, Daureeawoo Y, Donaldson E, Small K, Tuomainen J. Effect of aging on stimulated salivary flow in adults. J Am Geriatr Soc 2013;61:805-808.