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ORIGINAL ARTICLE

Salivary Creatinine is Complementary to Serum Creatinine in Patients with Chronic Kidney Disease

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Abstract

Background: *Chronic kidney disease (CKD) diagnosis and staging requires glomerular filtration rate (GFR), which can be estimated by serum creatinine using various equations. Frequent monitoring of serum creatinine and other blood-based renal function tests necessitates repeated venipuncture, which causes anxiety and discomfort to the patient and also contributes to anemia. So, a non-invasive alternative to serum creatinine for screening, diagnosis and monitoring of CKD will be of much value.*

Objective: *This study is planned to assess diagnostic utility of salivary creatinine as complementary to serum creatinine in patients with CKD.*

Methods: *This cross sectional study was conducted in Dhaka Medical College Hospital. A total of 226 participants, comprising 153 cases (group 1) of CKD and 73 healthy controls (group 2) were included in the study by purposive sampling technique. Unstimulated whole saliva and venous blood were collected following standard procedure. After centrifugation, saliva supernatant and serum was analyzed for creatinine concentration by auto-analyzer using Jaffe's method.*

Results: *Both serum and salivary creatinine levels were significantly higher in CKD patients than that of controls. Among CKD patients, both serum and salivary creatinine levels were incremental across the stages G1-G5. The correlation between serum and salivary creatinine was very weak in controls ($r=0.065$, $p=0.593$), but strong in CKD patients ($r=0.606$, $p<0.001$). The correlation is significant in stage G4 ($r=0.67$, $p<0.001$) and stage G5 ($r=0.861$, $p<0.001$). Linear regression analysis of serum and salivary creatinine for CKD patients was significant in CKD stages G3-G5. An area under curve (AUC) of 0.685 was obtained for salivary creatinine and a cut-off value of 0.29 mg/dL yielded sensitivity 62%, specificity 70% PPV 75% and NPV 59%.*

Conclusion: *Salivary creatinine can be used as complementary to serum creatinine in patients with CKD especially in stages G4 and G5.*

Keywords: *Chronic Kidney Disease (CKD), Serum creatinine, Salivary creatinine*

Introduction

Chronic kidney disease (CKD) prevalence is growing rapidly around the world mostly due to the rising prevalence of diabetes mellitus and hypertension[1]. The global prevalence of CKD is 13.4% overall and 10.6% in stages G3–G5[2]. In Bangladesh, prevalence of CKD is 22.48% overall and 19.8% in stages G3-G5, which are much higher than the global prevalence[3,4].

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CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. It is categorized into stages G1-G5 based on glomerular filtration rate (GFR)[5]. The assessment of GFR is an important part of the diagnosis and staging of CKD. GFR can be directly measured by the clearance of exogenous filtration markers (e.g. inulin and iohexol) or can be worked out by the clearance of endogenous filtration markers (e.g. serum creatinine and cystatin C). Estimated GFR (eGFR) calculated with serum creatinine using various equations remains the most widely used method in clinical practice[6]. The cut-off value of serum creatinine for a GFR of less than 60 ml/min/1.73 m^2 is 137 ìmol/L (1.55 mg/dL) for male with sensitivity 90% and specificity 93% and 104 µmol/L (1.12 mg/dL) for female with sensitivity 88% and specificity 90%[7].

If CKD remains untreated, it may progress to end stage renal disease (ESRD), where life cannot be sustained without renal replacement therapies (RRT), which are too much costly. CKD is also a major risk factor for cardiovascular disease and cardiac death[8]. Early diagnosis of CKD by screening creates the opportunity for early intervention, which can slow, if not halt, the progression of CKD to ESRD and reduce cardiovascular mortality and morbidity[9]. Generally, tests used to screen for CKD in high-risk population are serum creatinine based eGFR and urinary albumin-creatinine ratio (uACR) or urine dip-stick for albumin[10]. But, serum creatinine is less suitable for population screening for its invasive method of sampling[11]. Sampling of blood with venipuncture causes anxiety and discomfort to the person[12].

Iron depletion due to blood loss is one of the important causes of anemia in CKD patients. Chronic bleeding, blood trapping in hemodialysis apparatus and frequent blood sampling contributes to iron depletion[13]. Every 10 mL of blood sampling removes 5 mg of iron and causes decrease in hemoglobin concentration of 0.07 gm/dL[14]. On the other hand, patients with CKD are at increased risk for blood borne infections such as hepatitis B & C, HIV, associated with contaminated blood and blood product transfusion and exposure to contaminated hemodialysis equipment during treatment[15]. It potentially puts the health care professionals at risk of blood borne diseases, while handling the patients with CKD. Thus, a reliable non-invasive diagnostic test would be of value to both the patients and the clinicians[12]. Saliva is an ultrafiltrate of blood, composed of various hormones, proteins, enzymes, antibodies, antimicrobial constituents and cytokines. Some molecules expressed in saliva are due to transcellular or paracellular transfer of molecules from the blood. Studying saliva from a diagnostic point of view has been the area of interest in recent times. It has several established biomarkers. Saliva is considered to be an alternative to serum as a diagnostic medium for the following reasons: easy non-invasive sampling, feasibility of multiple sampling, safer to handle, less infectious, easy storage and transport, good patient compliance etc[16].

Salivary concentration of biomarkers may be affected by various factors including age, sex, diet, oral conditions, saliva flow rate, saliva collection method. In fact, saliva flow rate may be the most significant factor in the determination of saliva biomarkers and is itself determined by a variety of factors, such as hydration status, stress response, age, genetic influence, drug composition, diurnal changes, or the effects of oral and facial movements[17]. Drugs causing hypersalivation include antipsychotics e.g. clozapine, olanzapine, quetiapine etc. and cholinergic agents e.g. rivastigmine, pyridostigmine etc. On the other hand, there are many drugs causing hyposalivation, such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), beta blockers, clonidine, methyldopa, diuretics, antimuscarinics, antihistamines, opioids etc[18].

Various studies have investigated the role of saliva as a substitute for serum or plasma in the diagnosis of CKD. A number of studies have shown the correlation of salivary and serum concentration of different markers including creatinine, urea, uric acid, potassium, calcium and phosphate in patients with CKD[19]. Earlier studies have revealed that salivary creatinine levels are about 10-15% of the serum levels[20]. Few studies have determined cut off values but a standardized value is still not established for salivary creatinine that could replace serum as a diagnostic medium. Currently, no study has determined salivary creatinine levels in comparison to their serum levels in a stage (G1-G5) wise manner of CKD[16].

With this background, our study has been planned to evaluate the correlation of salivary and serum creatinine in all stages of CKD as well as in healthy individuals to determine the ability of salivary creatinine to identify patients with CKD.

Materials and Methods

This cross sectional study was carried out in Dhaka Medical College Hospital (DMCH), Dhaka over a period of 18

months. Specify A total of 226 adult participants, of which 153 were CKD patients (group 1) and 73 were healthy volunteers (group 2), were included in this study. Already diagnosed patients of CKD according to the KDIGO criteria was considered to be included in group 1, which was further divided into 5 subgroups comprising 5 stages of CKD. First two subgroups consisted of 30 patients & last three subgroups consisted of 31 patients. The stages of CKD were determined by eGFR using '2021 CKD-EPI creatinine' equation. Patients with acute kidney injury (AKI) on CKD, diseases of the oral cavity, gum and teeth, taking drugs causing decreased or increased salivation were excluded from the study. Individuals with no history of kidney disease, diabetes mellitus, hypertension, systemic disease that may affect kidneys, oral disease or dry mouth and no family history of CKD were considered as healthy controls.

Before starting the study, approval was taken from the ethical review committee (ERC) of Dhaka Medical College (DMC). Following counseling about the study aim, objectives and procedure, informed written consent was taken from each participant. A standardized questionnaire was used to collect demographic data, clinical presentation, associated medical conditions and laboratory findings. History taking and physical examination was done as per standard protocol.

For collection of saliva, participants were instructed to refrain from eating and drinking at least 60 min before collection and to thoroughly rinse their mouths with water, prior to the sample collection. About 2 mL of unstimulated whole saliva was collected in a clean graduated container by spitting method. Participants had to sit in a comfortable position with eyes open and head tilted slightly forward and to avoid swallowing or other oral movements during collection. The pooled saliva in the floor of the mouth had to be spat into the container every 60 seconds or just before they experienced an urge to swallow the accumulated saliva. This process was repeated until 2 mL of whole saliva was obtained. Immediately after saliva sample collection, 2 mL of blood was collected from patients' antecubital veins into serum separator tubes. In case of patients on hemodialysis, samples were collected before hemodialysis. Blood samples were allowed to clot at room temperature for one hour. Then, all collected samples were centrifuged at 3000 RPM for 10 minutes. Saliva supernatant and serum were separated. The samples were assayed immediately in automatic analyzer (Erba Mannheim XL-1000) using creatinine estimation kit by Jaffe's kinetic reaction. These tests were done in Department of Clinical Pathology, DMCH, Dhaka.

Statistical Analysis

Data were entered into Microsoft Excel and Statistical Package for Social Sciences (SPSS) version 25 was used for statistical analyses. All categorical data were expressed as frequency. All normally distributed continuous data were expressed as mean ± standard deviation (SD) and the non-normal continuous data were expressed as median with interquartile range (IQR). Spearman rank correlation was used to identify any correlation between one normally and one non-normally distributed continuous group of data. Kendall tau correlation analysis was done to find any correlation between two non-normally distributed continuous data. Correlation is considered strong at a correlation coefficient (r) of 0.5 - 1.0, moderate at 0.3 - 0.5, weak at 0.1 - 0.3 and very weak or no correlation at <0.1. Result is considered significant at p value <0.05. A linear regression analysis was used to formulate a regression equation to predict serum creatinine value from salivary creatinine. Receiver operating characteristic (ROC) curve analysis was performed to find whether salivary creatinine levels can distinguish the CKD group from controls. The overall performance was determined by the area under the curve (AUC). The cut-off value was determined based on the best trade-off between the sensitivity and specificity. Positive predictive value (PPV) and negative predictive value (NPV) were also determined.

Results

A total of 226 participants, of which 153 were CKD patients (group 1) and 73 were healthy volunteers (group 2), were included in this study. Group 1 was further divided into 5 subgroups according to the staging of CKD. Stages G1 and G2 included 30 patients each and stages G3-G5 included 31 patients each. In group 1, 76 were males and 74 were females. In group 2, 44 were males and 26 were females. The mean ages of group 1 and group 2 were 42.51±14.68 years and 35.17±10.42 years respectively (Table I).

In group 1, serum creatinine value was significantly higher than that of group 2. The salivary creatinine was also significantly higher in the group 1 (Table II). Across different stages of group 1, the salivary creatinine value was incremental and was highest in stage G5 patients which is 1.26 mg/dL (0.87-1.79) (Table III). A correlation analysis was done to find any correlation of serum and salivary creatinine between groups 1 & 2. In group 1, correlation coefficient r=0.606, p<0.001 indicating a strong

Table-I

Demographic characteristics of the study population (N=226).

Characteristics	CKD patients (Group 1)						Control
	Stage G1	Stage G2	Stage G3	Stage G4	Stage G5	All stages	(Group 2)
Sex[a]							
Male	11 (36.7)	11 (36.7)	19 (61.3)	19 (61.3)	17 (54.8)	77 (50.3)	44 (60.3)
Female	19 (63.3)	19 (63.3)	12 (38.7)	12 (38.7)	14 (45.2)	76 (49.7)	29 (39.7)
Age[b]	30.77±10.99	31.07±8.91	49.48±12.97	53.61±8.85	47.86±13.27	42.51±14.68	35.17±10.42

[a] = n (%), [b] = Mean±SD

Table-II

Comparison of serum creatinine, salivary creatinine and salivary-serum creatinine ratio between groups 1 & 2 (N=226).

	Group 1 (n=153)	Group 2 (n=73)	p-value
Serum creatinine (mg/dL)	3.38±4.12[a]1.78 (1.06-3.08)[b]	1.06±0.19[a]1.11 (0.9-1.21)[b]	<0.001
Salivary creatinine (mg/dL)	0.51±0.57[a]0.33 (0.18-0.57)[b]	0.24±0.19[a]0.24 (0.08-0.34)[b]	<0.001
Salivary-serum creatinine ratio (%)	18.04±14.14[a]14.14 (10.7-21.66)[b]	23.38±21.89[a]19.7 (7.18-32.75)[b]	0.218

[a] = Mean±SD, [b] = Median (IQR)

Table-III

Comparison of serum creatinine, salivary creatinine and salivary-serum creatinine ratio among subgroups of group 1 (n=153).

	Serum creatinine (mg/dL)	Salivary creatinine (mg/dL)	Salivary-serum creatinine ratio (%)
Stage G1 (n=30)	0.85±0.15[a]	0.19 (0.07-0.31)[b]	19.11 (7.68-24.29)[b]
Stage G2 (n=30)	1.12±0.17[a]	0.18 (0.08-0.28)[b]	14.64 (6.89-24.22)[b]
Stage G3 (n=31)	1.82±0.27[a]	0.31 (0.2-0.42)[b]	17.96 (11-21.94)[b]
Stage G4 (n=31)	2.91±0.34[a]	0.41 (0.35-0.51)[b]	13.89 (12.7-18.02)[b]
Stage G5 (n=31)	10.27±4.76[a]	1.26 (0.87-1.79)[b]	12.66 (10.61-16.85)[b]
p-value	<0.001	<0.001	0.402

[a] = Mean±SD, [b] = Median (IQR)

positive correlation. In group 2, r=0.065, p=0.593 indicating no correlation (Table IV). To see any association of serum and salivary creatinine across different stages of CKD, Spearman correlation was done. In CKD stages G4 and G5, there were strong positive correlations with an r=0.67, p<0.001 and r=0.861, p<0.001 respectively (Table V).

A linear regression equation was performed to estimate serum creatinine levels from salivary creatinine values. The equations in the CKD group and overall population were found to predict serum creatinine accurately from salivary creatinine in 85.2% and 82.6% cases, respectively (Figure 1, 2, 3; Table VI). A linear regression equation was performed to estimate serum creatinine levels from salivary creatinine values across different stages of CKD. The equations in CKD stages G4 and G5 can predict serum creatinine accurately from salivary creatinine in 32.1% and 74.6% cases, respectively (Table VII). A receiver operating characteristic (ROC) analysis was performed to assess the diagnostic potential of saliva when compared to serum creatinine between the CKD and control group. An area under curve (AUC) of 0.762 and 0.685 was obtained for serum and salivary creatinine respectively (Figure 4, Table VIII). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for different levels of salivary creatinine were

Table-IV

Correlation between serum and salivary creatinine in groups 1 & 2 (N= 226).

	CKD patient (Group 1)	Controls (Group 2)
Correlation coefficient (r)	0.606	0.065
p-value	<0.001	0.593

Table-V

Spearman correlation analysis of serum and salivary creatinine in subgroups of group 1 (n=153).

	Stage G1	Stage G2	Stage G3	Stage G4	Stage G5
Correlation coefficient (r)	0.28	0.18	0.456	0.67	0.861
p-value	0.128	0.341	0.11	<0.001	<0.001

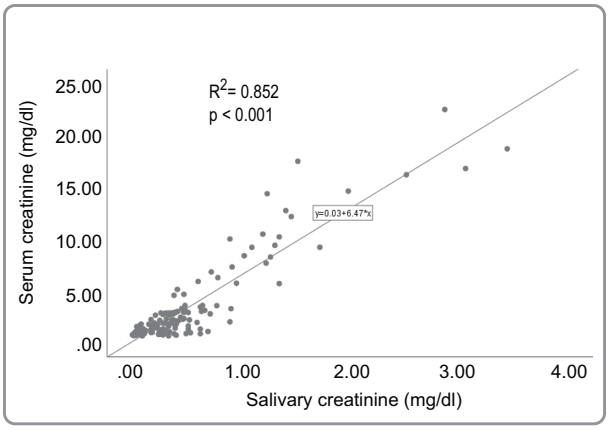

Figure 1: *Scatter plot showing linear regression between salivary and serum creatinine of group 1 (n=153).*

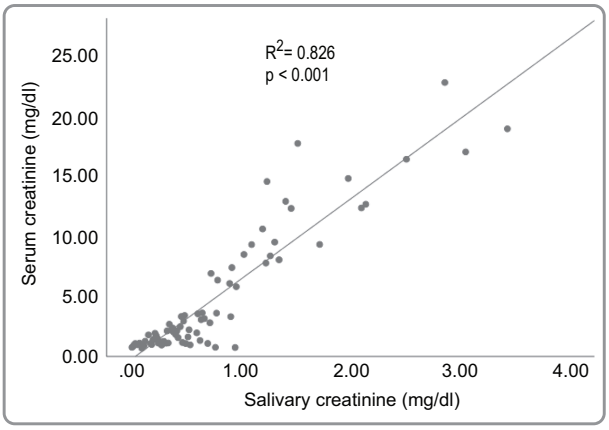

Figure 3: *Scatter plot showing linear regression between serum and salivary creatinine levels of both groups 1 & 2 (N=226).*

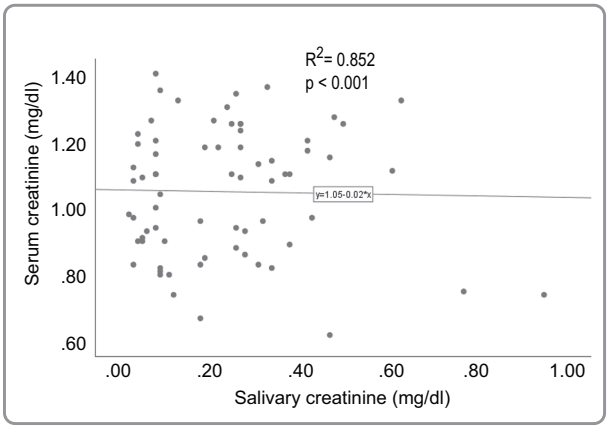

Figure 2: *Scatter plot showing linear regression between salivary and serum creatinine of group 2 (n=73).*

Table-VI

Linear regression analysis to predict serum creatinine from salivary creatinine in groups 1 & 2 (N=226).

Group	Linear regression equation	R^2	R^2 (%)	p-value
Group 1	Y= 0.03 + (6.47) x (Salivary Cr)	<0.001	0.852	85.2%
Group 2	Y= 1.05 + (-0.02) x (Salivary Cr)	0.856	0.01	1%
Both group 1 & 2	Y= -0.06 + (6.31) x (Salivary Cr)	<0.001	0.826	82.6%

Table-VII

Linear regression analysis to predict serum creatinine from salivary creatinine in subgroups of group 1 (n=153).

Stage	Linear regression equation	R^2	R^2 (%)	p-value
Stage G1	Y= 0.8 + (0.25) x (Salivary Cr)	0.111	0.088	8.8%
Stage G2	Y= 1.1 + (0.09) x (Salivary Cr)	0.671	0.007	0.7%
Stage G3	Y= 1.64 + (0.58) x (Salivary Cr)	0.04	0.143	14.3%
Stage G4	Y= 2.35 + (1.21) x (Salivary Cr)	0.001	0.321	32.1%
Stage G5	Y= 2.88 + (5.28) x (Salivary Cr)	<0.001	0.746	74.6%

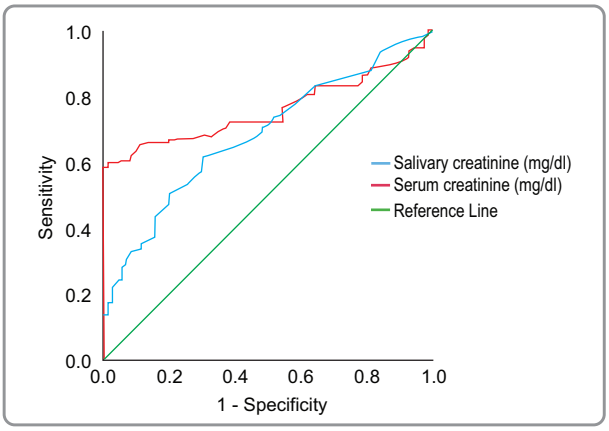

Figure 4: *ROC for serum and salivary creatinine.*

Table-VIII

Area under the ROC curve for serum and salivary creatinine.

Test result variables	Area	Standard error	p-value	95% confidence interval	
				Lower bound	Upper bound
Serum creatinine	0.762	0.031	<0.001	0.701	0.823
Salivary creatinine	0.685	0.036	<0.001	0.613	0.756

Tabl-IX

Different values of salivary creatinine (mg/dL) with sensitivity, specificity, PPV and NPV.

Salivary creatinine	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
0.25	68.7	52.9	75.7	44
0.26	66.7	55.7	76.3	43.8
0.27	64.7	60	77.6	44.2
0.28	62.7	67.1	80.3	45.6
0.29	62	70	75	59
0.30	58	70	80.6	43.8

established and a cut-off value of 0.29 mg/dL was determined as it gave the best trade-off between a sensitivity of 62% and a specificity of 70%. It also yielded PPV of 75% and NPV of 59% (Table IX).

Discussions

In the present study, the normal range of salivary creatinine was 0.08 - 0.34 mg/dL and found to be less than that of the serum level with a range of 0.9 - 1.21 mg/dL. The data obtained are in accordance to Lloyd et al., Venkatapathy et al. and Xia et al.[20, 12, 21]. Venkatapathy et al. found normal range of salivary creatinine 0.1 – 0.3 mg/dL and that of serum creatinine 0.9 – 1.4 mg/dL[12].

The mean serum creatinine values were 1.06±0.19 mg/dL in controls and 3.38±4.12 mg/dL in CKD patients. The mean salivary creatinine levels were 0.24±0.19 mg/dL in controls and 0.51±0.57 mg/dL in CKD patients. The differences of both salivary and serum creatinine between cases and controls were statistically significant (p <0.001). The result is consistent with the previous studies[19, 22, 23, 24, 25].

In this study, there was positive linear correlation between the salivary and serum creatinine levels. Similar observation was made by previous studies[26,22,12,27]. Under normal condition, metabolic degradation of products such as urea, creatinine is excreted by the

kidneys into the urine. In diseased kidneys, these compounds accumulate in the systemic circulation and get into saliva, either directly or are excreted by salivary glands. In CKD patients, the highly increasing creatinine levels in serum lead the disparity of the gradient concentration between serum and saliva thus increasing diffusion ability to saliva from serum[25,12].

The correlation between serum and salivary creatinine in controls was found to be positive, r = 0.065 but was not statistically significant (p = 0.593). These result is concordant with Bagalad et al., Nagarathinam et al., Bader et al. and Pandya, Nagrajappa & Ravi, who found a positive correlation between serum and salivary creatinine in patients without kidney disease, but discordant with Venkatapathy et al., who reported a negative correlation[19,28,29,24,12]. These differences may be due to the presence of factors such as diabetes mellitus, hypertension and other systemic diseases which can influence the diffusion of creatinine from serum into the salivary glands[24].

The correlation between serum and salivary creatinine in CKD patients showed a significant positive correlation (r = 0.606, P <0.001). This correlation is lower than the result of Yajamanam et al. (r = 0.96), Padwal et al. (r = 0.95), Pham (r = 0.9), Lasisi, Raji & Salako (r = 0.69) and Bagalad et al. (r = 0.65), but higher than the results of Bader et al. (r = 0.58), Poposki et al. (r = 0.549) and Nagarathinam et al. (r = 0.523)[27,23,25,22,19,29,30,28]. Although the results were different, they showed there was rather strong correlation between salivary and serum creatinine[25].

This study reported a progressive increase in salivary creatinine levels from CKD stages G1–G5, consistent with the findings of Nagarathinam et al., Temilola et al., Bader et al. and Lasisi, Raji & Salako[28,31,29,22]. Linear regression demonstrated positive correlation between serum and salivary creatinine in all stages of CKD but relationship was statistically significant in CKD stages G4 & G5, with stage G5 having the highest coefficient of determination (R^2). This is in line with previous studies by Nagarathinam et al. and Temilola et al., in which a significant predictive relationship was found between serum and salivary creatinine in CKD stages G4 and G5[28,31]. In earlier stages of CKD, the relationship between serum and salivary creatinine was not significant and is thought to be due to the lower serum creatinine levels, with minimal movement of creatinine to saliva due to the lack of a large concentration gradient[31].

Before a salivary diagnostic test can replace a more conventional one, the diagnostic value of a new salivary test has to be compared with accepted diagnostic methods. The accuracy of this new test depends on how well it separates the group being tested into those with and without the disease. Sensitivity and specificity are the basic measures of the accuracy of a diagnostic test[12]. So, to ascertain the diagnostic potential of saliva as an alternative, ROC analysis was performed. In this study, ROC curve analysis showed area under curve (AUC) for salivary creatinine was 0.685 which was close enough of AUC of serum creatinine (0.762). Comparable large AUC were reported in previous studies such as Nagarathinam et al. (AUC = 0.858), Temilola et al. (AUC = 0.839), Xia et al. (AUC = 0.897), Bader et al. (AUC = 0.876) and Venkatapathy et al. (AUC = 0.967)[28,31,21,29,12]. As AUC for salivary creatinine is less than AUC for serum creatinine in this study, it can be inferred that, serum creatinine is still superior to salivary creatinine for diagnosing CKD. So, salivary creatinine cannot replace serum creatinine as diagnostic medium, rather it can complement serum creatinine.

In the present study, the optimal cut-off point for the diagnosis of CKD was determined to be a salivary creatinine concentration of 0.29 mg/dL, which provided good sensitivity (62%) and specificity (70%) in our cohort of participants. This suggests that salivary creatinine could be used as a non-invasive tool in diagnosing CKD and that people with values above 0.29 mg/dL should be referred for further diagnostic evaluation and appropriate management. Similar cut off value was reported by Pham (0.24 mg/dL), Padwal et al. (0.2 mg/dL), Nagarathinam et al. (0.18 mg/dL)[25, 23, 28]. A lower cut-off value was suggested by Temilola et al. (8.5 ìmol/L H" 0.1 mg/dL), which may be due to that they included no healthy control in their study[31]. A higher cut-off value was found in study of Bagalad et al. (0.69 mg/dL) and Lasisi, Raji & Salako (0.55 mg/dL)[19, 22]. This difference may be due to that Bagalad et al. included only patients on hemodialysis and Lasisi, Raji & Salako included only stages G4 & G5 CKD patients[19,22].

Conclusion

Salivary creatinine has positive correlation with serum creatinine in patients with CKD particularly in the later stages (stages G4 and G5). It shows considerably good AUC. In addition, cut-off value of salivary creatinine yielded good sensitivity and specificity. So, this study suggests that salivary creatinine can be used as a

noninvasive diagnostic tool in addition to serum creatinine in patients with CKD.

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