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Salivary creatinine is a promising noninvasive biomarker for chronic kidney disease: a case-control study

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Informed consent: Written informed consent was taken from all study participants after providing a comprehensive explanation of study objectives.

Patient consent for publication: consent was taken from patients to publish research data while maintaining the confidentiality of their personal information.

Availability of data and materials: the data used during the current study are available upon reasonable request from the corresponding author.

Abstract
Chronic kidney disease (CKD) is associated with irreversible and progressive renal dysfunction. Our study aimed to assess whether salivary creatinine can be used as an alternative noninvasive biomarker for serum creatinine. Hence, a case-control study was conducted at Al-Gadarif Hospital for kidney disease in Eastern Sudan. The study included 40 hemodialysis patients as a case group and 40 healthy individuals as a control group. Significantly higher serum and salivary creatinine levels were reported in the case group (10.9±2.65 mg/dL; 2.2±1.3 mg/dL) than in the control group (0.88±0.15 mg/dL; 0.23±0.14 mg/dL). The serum and salivary creatinine levels were significantly higher in males (8.6±5.4 mg/dL; 1.7±1.5 mg/dL) than in the females (3.6±4.2 mg/dL; 0.83±1.1 mg/dL) in the patient group. Age was significantly correlated with serum ($r=0.68$, $p=0.001$) and salivary creatinine ($r=0.48$, $p=0.001$) in CKD patients. A significantly strong positive correlation was reported between serum and salivary creatinine. The sensitivity and specificity of salivary and serum creatinine were 100%. Therefore, our study revealed that salivary creatinine may serve as a potential noninvasive biomarker in CKD patients.

Introduction

Chronic kidney disease (CKD) is a progressive condition that affects more than 10% of the general population worldwide.[1] Along with the rise in diabetes and hypertension, the prevalence and incidence of CKD are rising globally.[2] CKD is defined by the presence of kidney damage or decreased kidney function for at least 3 months, irrespective of the cause.[3] The irreversible kidney dysfunction in CKD patients is associated with the accumulation of non-protein nitrogenous substances.[4,5]

The diagnosis of CKD relies mainly on the estimation of the glomerular filtration rate, using filtration biomarkers like serum creatinine or cystatin C along with various formulas. Additionally, albuminuria is one of the biomarkers that is used to evaluate disease progression and outcomes.[6,7] Creatinine is a waste product of muscle metabolism that is mainly eliminated by the kidneys and its serum level is used as an index to renal function.[8] Patients on dialysis usually need close laboratory monitoring; however, one of the main causes of blood loss in these patients is the frequent and extensive blood sampling for diagnostic tests.[9] Additionally, the patients undergoing dialysis are at a greater risk of developing hepatitis B and C. Furthermore, this potentially increases the risk of health care professionals to blood borne diseases.[10,11] Simple noninvasive diagnostic test that provides a reliable evaluation of disease status and stages would be of value to both the clinicians and the CKD patients.

Saliva, a multi-constituent biologic fluid secreted by the salivary glands, is the major contributor of oral health.[12] Researchers have recently investigated saliva as a noninvasive way to diagnose and monitor disease.[13,14] In comparison to serum because saliva collection is a noninvasive, simple, and economic procedure that can be performed by the patient with minimal involvement from medical personnel. When required, a repeat sample can be easily obtained and is suitable for all age groups.[15,16] There are several preliminary studies with promising results which show that saliva can be used to detect lung cancer, pancreatic cancer, breast cancer, and type II diabetes.[17-20] A study suggests that saliva has the potential to become a first-line diagnostic sample of choice.[16] Our study aimed to examine salivary and serum creatinine levels in CKD patients, comparing these levels to those of a control group. Additionally, we aimed to evaluate the potential of salivary creatinine as an alternative biomarker for serum creatinine in CKD.

Materials and Methods

Study population

A case control hospital-based study was conducted in Al-Gadarif Hospital for Kidney Disease in Eastern Sudan during the period from July 2023 to July 2024. A total of 80 subjects were enrolled in the study; 40 were patients and classified as a case group, and 40 were apparently healthy subjects and classified as a control group. According to the duration of disease, the case group was divided into patients with a duration of ≤5 years, which included 10 patients, and those with a duration of more than 5 years, which comprised 30 patients.

Inclusion and exclusion criteria

Patients who had been clinically diagnosed with CKD and had begun hemodialysis sessions were included. However, patients who had oral infections, cancer, oral bleeding, and those who had pathological conditions affecting serum or saliva creatinine levels were excluded. The control group included apparently healthy subjects who were selected randomly from the same geographical area, and they met the same exclusion criteria as the case group.

Sampling and data collections

Serum and salivary samples were collected from patients and controls at 7am to 2pm in a non-fasting state and before half an hour of hemodialysis in the case group. Saliva was collected from the subjects using the spitting method. The subjects were asked to spit 1 ml of saliva into a dry, clean, plain container.

The collected saliva sample was centrifuged for 5 minutes at 4000 rpm, after which the supernatant was separated and analyzed. Venous blood samples were collected into heparin containers and centrifuged at 4000 rpm; then, the supernatant was separated and analyzed immediately. Serum and salivary creatinine levels were estimated by the Jaffe reaction method using the semi-automated analyzer Mindray BA-88A.

Ethical consideration

The research approval was obtained from the Faculty of Medicine and Health Science, University of Gadarif ethical committee. Written informed consent was taken from each study participants after providing a comprehensive explanation of study objectives.

Statistical analysis

Data was analyzed by using the statistical package for social sciences (SPSS) version 25. Pearson's correlation analysis was used to assess the correlations between age, serum creatinine, and salivary creatinine levels. A one-way analysis of variance test was used to compare the mean differences in the study subgroups. Chi-square was also used to evaluate the distribution of gender variables in the case and control group. The results were considered significant if the p-value was less than or equal to 0.05.

Results

The majority of patients (75%) had a duration of disease for less than 5 years; however, 25% had the disease for more than 5 years, as shown in Figure 1.

The distribution of patients considering the gender groups showed that the male gender was more prevalent (32.5%) in the case group in comparison to the control group (13.8%). However, the female showed a lower percentage in the case group (17.5%) than the control group (36.3%), with a p-value of 0.001, as shown in Table 1.

The mean age was significantly higher in the cases (47.7±15.4 years) group than in the control (25.2±2.54 years), p=0.000. Significantly higher serum creatinine and salivary creatinine levels were reported in cases (10.9±2.65 mg/dL; 2.2±1.3 mg/dL) than their counterpart controls (0.88±0.15 mg/dL; 0.23±0.14 mg/dL), respectively, with p=0.000 (Table 2).

Considering the duration of the disease, patients were classified into two groups: a case group with a duration of ≤5 years and a case group with a duration >5 years. Our results showed that the mean age was higher in the cases group with the longer duration of disease (53±13.8 years) than those who had a short duration of disease (45.8±15.8 years), p=0.19. No significant differences were shown in serum and salivary creatinine levels in the case group with a duration of disease ≤5 years (10.7±2.8 mg/dL; 2.3±1.4 mg/dL) in comparison to the case group that had a duration of disease for >5 years (11.5±1.6 mg/dL; 2.04±0.75 mg/dL); the p-values were 0.27 and 0.41, respectively (Table 3).

Based on gender, the mean age was higher in males in the patient group (41.3±17.3 years) in comparison to females (31.9±12.9 years), p=0.010. As well, significantly higher serum and salivary creatinine were seen in males (8.6±5.4 mg/dL; 1.7±1.5 mg/dL) than in females (3.6±4.2 mg/dL; 0.83±1.1 mg/dL) with p-values of 0.001 and 0.005, respectively (Table 4).

The correlation analysis revealed a significant positive correlation between age and serum creatinine in the patient group (r=0.68, p=0.001). A significant positive correlation was reported between age and salivary creatinine in the patient group (r=0.48, p=0.001). Furthermore, salivary and serum creatinine were significantly positively correlated in the patients (r=0.75, p=0.000), as presented in Table 5.

Receiver operating characteristic (ROC) curve analysis was used in the current study to evaluate the potential of salivary creatinine as a diagnostic biomarker as well as serum creatinine for CKD (Figure 2). The total area under the curve of salivary and serum creatinine was 1.000. (p=0.000, 95% confidence interval=1.000-1.000). Sensitivity and specificity for different values of salivary and serum creatinine were established, and a cutoff was determined Table 6.

Discussion

CKD is a common disorder and an important growing public health problem worldwide. Various factors contribute to this increase, including increased prevalence of diabetes and hypertension.[21,22] Noninvasive tests are required for diagnosis and follow-up of CKD, since they usually suffer from bleeding and anemia. The main objective of our study was to evaluate the levels of serum creatinine and salivary creatinine levels in CKD patients and to compare them with the healthy control. Moreover, to examine whether salivary creatinine could be used as an alternative test for serum creatinine in CKD patients. Our study showed that the serum and salivary creatinine were significantly higher in CKD patients than control group. The serum and salivary creatinine were significantly higher in males than females in CKD patients. The age was positively correlated with serum and salivary creatinine in CKD patients. Our study also revealed that salivary creatinine is positively correlated with the levels of creatinine in serum. Similar findings had been reported in many previous studies.[23-25] The elevated levels of salivary and serum creatinine observed in patients with CKD are reflections of the blood levels as confirmed by the positive correlations. The positive correlation between serum and salivary creatinine observed in this study was consistent with Venkatapathy *et al.* and Xia *et al*.,[24,26] and it could be explained by the increased concentration of creatinine in patients with CKD which creates a concentration gradient that facilitates increased diffusion of creatinine from serum into saliva.[27] These suggest that analysis of salivary and serum creatinine could be an appropriate method for diagnosis, monitoring the efficacy of hemodialysis, and progression of the CKD. Salivary creatinine concentrations above 8.5µmol/L may identify patients with CKD and should prompt referral for further diagnostic evaluation.[23]

The accuracy of the new test depends on how well it separates the group being tested into those with the disease or without the disease.[28] Sensitivity and specificity are the basic methods to determine the accuracy of a diagnostic test.[29] Hence ROC analysis is used to ascertain the diagnostic potential of a tool as an alternative to a standard method. A study found that Area under the curve for salivary creatinine was found to be 0.967. A cut-off value of 0.2 mg/dL gave a sensitivity of 97.1% and specificity of 86.5%.[24] In our study a cut-off value of salivary creatinine 0.65 mg/dL gave a 100% sensitivity and specificity. Consequently, our study suggests that saliva can be used as a non-invasive diagnostic tool for estimating serum creatinine in CKD patients.

Limitations

Our findings suggest that salivary creatinine may be a valuable biomarker for CKD and a potential substitute for serum creatinine. However, the study had limitations, including a small sample size and the accuracy and precision of salivary creatinine results. Additionally, our study did not consider the different stages of CKD. The sex and age of the control group were not matched, which are both confounding factors that can affect creatinine level. Future research should be done to examine the precision and accuracy of our findings, addressing all previously mentioned limitations.

Conclusions

The serum and salivary creatinine levels were higher in patients with CKD than in the healthy individuals. Additionally, salivary creatinine showed a strong positive correlation with serum creatinine levels in patients with CKD. The ROC analysis displayed that salivary creatinine has comparable diagnostic accuracy to serum creatinine in CKD. Accordingly, it is suggested that salivary creatinine could be promising as a potential alternative noninvasive biomarker for serum creatinine in CKD patients.

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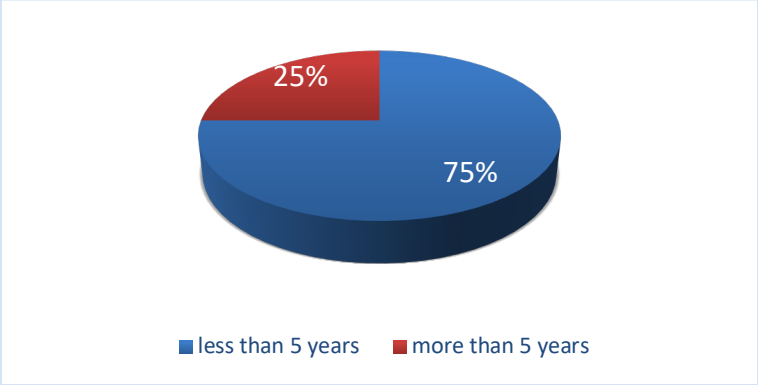

Figure 1. Distribution of patients according to disease duration.

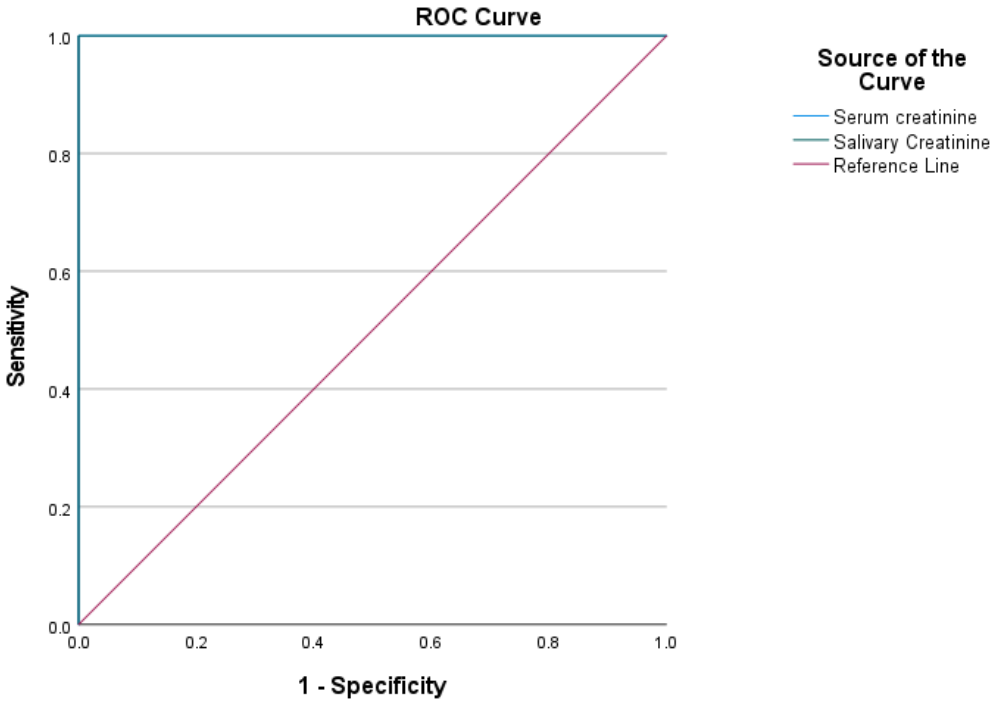

Figure 2. Receiver operating characteristic (ROC) curve for salivary creatinine levels.

Table 1. Distribution of gender among study groups.

Gender	Case group	Control group	p	Chi squire
Male	26 (32.5%)	11 (13.8%)	0.001	11.7
Female	14 (17.5%)	29 (36.3%)		

Table 2. Comparison of mean age and creatinine between case and control group.

Variables	Case group Mean ± SD (n=40)	Control group Mean ± SD (n=40)	p
Age (years)	47.7±15.4	25.2±2.54	0.000
Serum creatinine (mg/dL)	10.9±2.65	0.88±0.15	0.000
Salivary creatinine (mg/dL)	2.2±1.3	0.23±0.14	0.000

SD, standard deviation.

Table 3. Comparison of mean age and creatinine in case group according to disease duration.

Variables	Duration ≤5 years Mean ± SD (n=10)	Duration >5 years Mean ± SD (n=30)	p
Age (years)	45.8±15.8	53±13.8	0.19
Serum creatinine (mg/dL)	10.7±2.8	11.5±1.6	0.27
Salivary creatinine (mg/dL)	2.3±1.4	2.04±0.75	0.41

SD, standard deviation.

Table 4. Comparison of mean age and creatinine according to gender in patients.

Variables	Male Mean ± SD (n=26)	Female Mean ± SD (n=14)	p
Age (years)	41.3±17.3	31.9±12.9	0.010
Serum creatinine (mg/dL)	8.6±5.4	3.6±4.2	0.001
Salivary creatinine (mg/dL)	1.7±1.5	0.83±1.1	0.005

SD, standard deviation.

Table 5. Correlation analysis of age, serum creatinine, and salivary creatinine in patients.

Variable	Age (years)	Serum creatinine (mg/dL)	Salivary creatinine (mg/dL)
Age (years)	0	r=0.68**	r=0.48**
Serum creatinine (mg/dL)		0	r=0.75***
Salivary creatinine (mg/dL)			0

**p≤0.001; ***p≤0.0001; r, correlation.

Table 6. The sensitivity and specificity of salivary and serum creatinine levels in chronic kidney disease patients.

Test variable	Area	Cutoff value	p	95% confidence interval		Sensitivity	Specificity
				Lower bound	Upper bound		
Serum creatinine mg/dL	1.000	3.2	0.000	1.000	1.000	100%	100%
Salivary creatinine mg/dL	1.000	0.65	0.000	1.000	1.000	100%	100%