

## CORRELATION OF SALIVARY CREATININE AND URIC ACID WITH SERUM CREATININE AND URIC ACID IN CHRONIC KIDNEY DISEASE

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### ABSTRACT:

**Background:** Chronic kidney disease (CKD) indicates a spectrum of pathophysiologic processes associated with abnormal kidney function. CKD is associated with accumulation of metabolic waste products and manifests as increased urea, creatinine, uric acid etc. Some systemic diseases like CKD can also affect contents of salivary secretion. Collection of blood is an invasive procedure causing anxiety and discomfort. Saliva has an advantage over serum because saliva collection is a non-invasive, simple and economic procedure that can be performed by the patient with minimal involvement of medical personnel, when required a repeat test be easily done and is suitable for all age groups.

**Aims and objectives:** Aim of our study is to estimate creatinine and uric acid in saliva and serum in Chronic kidney disease patients as well as in normal individuals.

**Methods and materials:** A hospital based observational study was conducted at a tertiary care hospital in Assam for 6 months with 50 individuals of randomly selected CKD patients and 50 healthy individuals of age group 40-70 years. Whole saliva was collected by spitting method after fasting for at least 2hours. The collected salivary and serum samples were centrifuged in a centrifuge machine for 10 minutes at the rate of 3000 rpm. Then the supernatant saliva and serum were separated and assayed in semi-automated analyser machine for creatinine and uric acid.

**Results:** Mean values of creatinine were 5.28 mg/dl in saliva and 8.09 mg/dl in blood of chronic kidney disease which were higher than that of control groups. Mean value of uric acid in saliva and serum were found 2.66 mg/dl and 7.81 mg/dl respectively in CKD patients which were slightly higher than that of healthy individuals. Statistical analysis of the results showed significant elevated levels in salivary and serum creatinine and uric acid in the cases with  $p < 0.05$ .

**Conclusion:** In our study, patients with CKD showed elevated levels of creatinine and uric acid in saliva as well as serum compared to the levels in healthy individuals. Therefore, salivary creatinine and uric acid could be taken as an alternative for serum creatinine and uric acid in chronic kidney disease.

**Keywords:** Chronic kidney disease, saliva, serum, creatinine, uric acid.

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**INTRODUCTION:** Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes which is associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR)<sup>1</sup>. The prevalence and incidence are increasing worldwide with leading categories of etiologies of disease such as diabetic nephropathy, glomerulonephritis, hypertension associated CKD (includes vascular and ischemic kidney disease and primary glomerular disease with associated hypertension), autosomal dominant polycystic kidney disease, other cystic and tubule interstitial nephropathy<sup>1,2</sup>. CKD patients require serum analysis frequently to diagnose and monitor therapeutic outcomes and to determine prognosis. Creatinine and uric acid are nitrogenous wastes, produced from protein metabolism and excreted by kidneys and their levels in serum are used as an index to renal function<sup>2,3</sup>.

Blood collection for serum analysis is an invasive method which causes anxiety and discomfort to the patients. Each dialysis procedure in CKD patients is associated with blood loss of around 20ml and also frequent blood sampling causes additional blood loss<sup>2</sup>.

Saliva is an exocrine secretion that is produced by 3 major salivary glands (parotid, submandibular and sub maxillary glands) and numerous minor salivary glands (labial and buccal gland, glossopalatine gland, palatine and lingual glands), can be used as a diagnostic tool<sup>4</sup>. Saliva analysis has advantages over serum analysis because saliva collection is easy to collect, noninvasive, simple and economic procedure that can be performed repeatedly by the patient with minimal involvement of medical personnel<sup>2</sup>. Saliva can also be used as a diagnostic medium for patients suffering from clotting disorders like haemophilia and in patients with compromised venous access<sup>2</sup>. There are many preliminary studies with promising results which showed that saliva can be used to detect various local diseases such as oral, head and neck cancers, lung, pancreatic, breast and ovarian cancers and in the diagnosis of systemic diseases such as type 2 diabetes mellitus<sup>5</sup>.

There is evidence that creatinine and uric acid are measurable in saliva. The diffusion of creatinine and uric acid through cell membrane or intracellular junctions of salivary ducts is considered difficult due to the low lipid solubility of creatinine and uric acid but could elevate when plasma levels are high<sup>6</sup>. Theoretically it was found that salivary glands could express transporters similar to those ones that in the epithelial cells of the renal tubule account for the renal excretion of creatinine and uric acid through tubular secretion<sup>6</sup>. The raised concentration of these analytes in saliva may be because of raised serum creatinine and uric acid creates increased concentration gradient which in turn increases their diffusion from serum to saliva in CKD patients<sup>2</sup>. Our study therefore was diagnosed to estimate creatinine and uric acid on saliva with specific focus on methodological aspects and on association between serum and saliva levels<sup>6</sup>.

**AIMS AND OBJECTIVES :** The study aimed to (1) correlate the serum and salivary creatinine and uric acid levels in CKD patients and normal individuals and to (2) evaluate the role of saliva as a non invasive alternative to serum for creatinine and uric acid estimation in CKD patients.

**METHODS AND MATERIALS :** This study was a case-control study which was conducted for 9 months from 10<sup>th</sup> March to 10<sup>th</sup> December, 2022 in the Biochemistry department collaborated with Nephrology department of Gauhati medical college and hospital, Guwahati, Assam. The study population consists of randomly selected 50 patients already diagnosed with chronic kidney disease (aged between 40 and 70 years). Exclusion criteria of cases were gout patients, pregnant females, patients using nephrotoxic drugs, having problem in oral cavity. 50 healthy volunteers of same age groups who had no complaints or no major illness in recent past were selected as controls. Ethical clearance was obtained from Institutional Ethics Committee to conduct this study. A written informed consent was obtained from every patients and healthy volunteers included in this study. After that, clinical examination of oral cavity was performed and details of cases and controls were recorded on a proforma.

Whole unstimulated saliva samples were collected under restful conditions between 8AM to 11AM to decrease the effect of diurnal variation. In CKD patients undergoing hemodialysis, the saliva samples were collected prior to dialysis. The participants were asked to refrain from eating and drinking for at least 90 minutes before the collection and to rinse mouth thoroughly with distilled water prior to collection of saliva. They were instructed to sit in a comfortable position with eyes open and head tilted slightly forward. Also they were instructed to prevent swallowing and oral movements during collection and to accumulate the saliva in the floor of mouth and spit every 60 seconds or when they feel an urge to swallow the accumulated fluid. 2ml of whole saliva was collected in a sterile graduated container by spitting method and then transferred to dry sterile centrifuge tube.

Immediately after collection of saliva sample, 5ml of venous blood was collected by means of sterile vein puncture and transferred to serum separator tubes/clot activator vial. The whole blood samples were allowed to clot at room temperature for an hour.

The collected saliva and whole blood samples were centrifuged for 10 minutes at 4000rpm for saliva separation from mucin and serum separation from clot. The clear supernatant serum and saliva were separated . Then creatinine and uric acid levels in saliva and serum were analysed on a Erba semi-autoanalyser by using standard reagent kits which uses enzymatic methods (Modified Jaffe’s reaction for creatinine and Modified Trinder peroxidase method using 2,4, 6-tribromo-3-hydroxy benzoic acid for uric acid estimation).

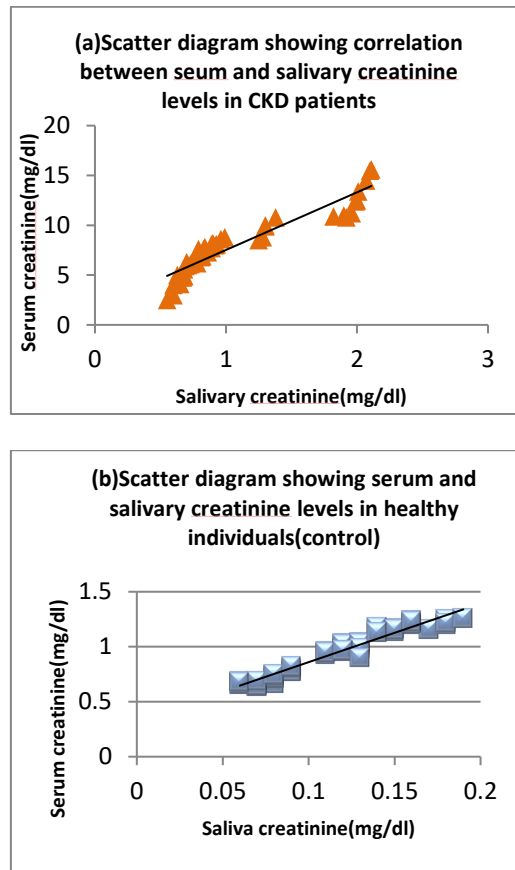
Data of creatinine and uric acid levels of serum and saliva for both CKD patients and healthy individuals were entered into MS Excel sheet. Student’s T-test was performed for paired observations to compare saliva and serum levels of creatinine and uric acid in both cases and controls. Pearson’s correlation coefficient (r) was used to test the correlation between serum and salivary creatinine and uric acid levels from salivary levels.

**RESULTS :** Out of 50 CKD cases, 36 were men and 14 were women with a mean age and standard deviation of the subjects was 45 +/-5. Control group comprised of 50 healthy volunteers among which 29 were men and 21 were women with mean age and standard deviation of subjects was 50 +/-4. Based on GFR estimation using Cockcroft-Gault formula, the cases (CKD patients) were found to be in stage 4 and 5 CKD. In CKD patients, serum creatinine ranged between 2.5 mg/dl and 15.6 mg/dl with a mean of 7.86 +/- 3.14 and salivary creatinine ranged between 0.6 mg/dl and 2.11 mg/dl with a mean of 1.06 +/- 0.51. Serum creatinine and salivary creatinine in healthy individuals ranged between 0.64 mg/dl to 1.25 mg/dl with mean 0.94 +/- 0.21 and 0.06 mg/dl to 0.18 mg/dl with a mean of 0.12 +/- 0.03 respectively. The mean of serum and salivary creatinine concentration were found significantly higher in CKD patients compared to controls (Table 1). There is a significant positive correlation was found between salivary and serum creatinine in CKD patients and healthy individuals, r=0.94 and r=0.98 respectively.

Table-1: Table showing correlation between salivary and serum creatinine in CKD patients and control using Pearson correlation

Groups	Parameters	Mean	Standard deviation	r-value	p-value
Cases (CKD patients)	Creatinine in saliva(mg/dl)	1.06	0.51	0.94	<0.01
	Creatinine in serum(mg/dl)	7.86	3.14		
Controls (healthy individuals)	Creatinine in saliva(mg/dl)	0.12	0.03	0.98	<0.01
	Creatinine in serum(mg/dl)	0.94	0.21		

Figure 1: Scatter diagram showing linear correlation between salivary and serum creatinine levels among CKD patients (a) and healthy individuals (b).

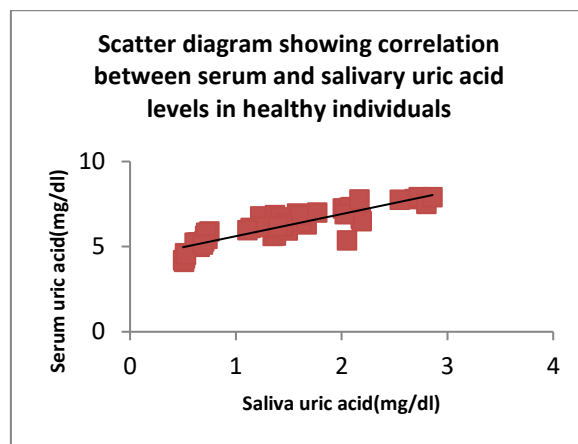
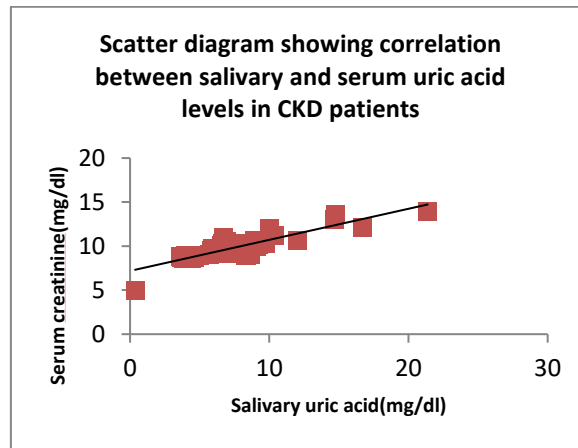


In CKD patients, serum uric acid was found between 5 mg/dl and 13.61 mg/dl with a mean of 9.83 $\pm$  1.47 and salivary uric acid was found between 0.36 mg/dl and 21.38 mg/dl with a mean of 7.5 mg/dl $\pm$  3.7. Serum uric acid and salivary uric acid in healthy individuals ranged between 4.11 mg/dl to 7.91 mg/dl with mean 6.19  $\pm$  1.01 and 0.5 mg/dl to 2.81mg/dl with a mean of 1.45  $\pm$  0.69 simultaneously. The mean of serum and salivary uric acid concentration were found significantly higher in CKD patients compared to controls (Table 2). There is a significant positive correlation was found between salivary and serum uric acid in CKD patients and healthy individuals,  $r=0.88$  and  $r=0.86$  respectively.

Table-2: Table showing correlation between salivary and serum creatinine in CKD patients and control using Pearson correlation

Groups	Parameters	Mean	Standard deviation	r-value	p-value
Cases (CKD patients)	Uric acid in saliva(mg/dl)	7.50	3.70	0.88	<0.01
	Uric acid in serum(mg/dl)	9.83	1.47		
Controls (healthy individuals)	Uric acid in saliva(mg/dl)	1.45	0.69	0.86	<0.01
	Uric acid in serum(mg/dl)	6.19	1.01		

Figure 2: Scatter diagram showing linear correlation between salivary and serum creatinine levels among CKD patients (a) and healthy individuals (b).



**DISCUSSIONS :** Creatinine and uric acid are waste products of protein metabolism that are primarily excreted by kidneys. The normal range of serum creatinine is 0.6-1.5 mg/dl and of salivary creatinine is 0.05-0.2mg/dl<sup>2,7</sup>. Normal range of serum uric acid is 3.5-8.5mg/dl and salivary uric acid is 0.5- 3mg/dl<sup>7</sup>.

In our study, we found that there is a strong positive correlation between serum creatinine and saliva creatinine in CKD patients and healthy individuals with  $r=0.94$  and  $0.98$  respectively and also between serum uric acid and saliva uric acid in CKD patients and healthy individuals with  $r=0.88$  and  $0.88$  respectively. There was significant difference between the studied groups with regard to serum and saliva levels of creatinine and uric acid ( $p<0.01$ ).

A similar study conducted by Giancarlo Bilancio, et al.<sup>6</sup> showed that saliva and plasma levels differed but correlated with plasma for creatinine ( $r=0.87$ ,  $p<0.01$ ) and uric acid ( $r=0.82$ ,  $p<0.01$ ). Another study conducted by Reda Sedkey Bader, et al.<sup>8</sup> showed significant positive correlation between serum creatinine and saliva creatinine in healthy people and CKD patients with  $r=0.83$  and  $0.68$ . ( $p<0.05$ ). Also a study conducted by Y. Xia et al<sup>9</sup> found that concentrations of creatinine and uric acid in both saliva and serum were positively correlated in healthy individuals and CKD patients ( $r = 0.932, 0.840$  and  $0.971, 0.920$ ) where levels of saliva creatinine and uric acid in CKD patients were significantly higher than those of healthy people ( $p<0.05$ ).

**CONCLUSION :** Salivary levels and serum levels of creatinine and uric acid are positively correlated in our study. The concentration of creatinine and uric acid in Saliva can reflect renal damage, monitor kidney function of CKD patients and help in the diagnosis of middle-stage to late-stage CKD. Our study has contributed to the existing data supporting the diagnostic potential of salivary creatinine and uric acid as a non-invasive tool in CKD patients.

**LIMITATIONS :** Though a satisfactory result was obtained but there are some limitations in this study also. The study group comprised of only stage 4 and 5 CKD patients (though not intentional). This study was

conducted in a single tertiary care center with limited number of patients, limited age group over a short duration which may fail to generalize for the whole CKD patients group. Therefore, including larger sample size over longer duration and increasing age interval of the groups (including pediatric and elder age group), in multiple care centers might be required for further validation.

**CONFLICT OF INTEREST :** There are no conflicts of interest.

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