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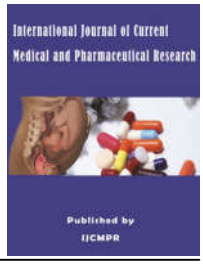

CORRELATION OF SALIVARY UREA AND SALIVARY CREATININE WITH BLOOD UREA AND SERUM CREATININE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiological processes associated with abnormal kidney function and progressive decline in glomerular filteration rate, leading to abnormal blood urea, creatinine levels and electrolyte disturbances. It is a worldwide medical and public health challenge due to high risk of progression to end stage renal disease (ESRD), increased cardiovascular burden and high management costs. Patients with CKD are subjected to repeated blood sampling to measure blood urea and serum creatinine, resulting in more pronounced anaemia. Frequent drawing of blood also adds to the psychological trauma to the patients. So to assess renal function in patients with CKD, an alternative sample source, other than blood is being investigated. Human saliva is a unique fluid secreted by major and minor salivary glands. Whole saliva is composed of components that originate from salivary glandular and non salivary glandular source. Various components of saliva are either passively diffused or actively transported directly from serum into the saliva through oral mucosa. Hence concentration of various solutes in saliva reflects the concentration of that solute in the serum. Collection of saliva being an easily accessible and non-invasive sample source is less painstaking for the patients. Thus, estimation of urea and creatinine in saliva may be considered an alternative to serum estimation and same may be used for following up patients with CKD. When the patients with CKD undergo dialysis, fall in blood urea and serum creatinine is expected. Our study was aimed to assess the correlation of salivary urea and creatinine with blood urea and serum creatinine in patients with CKD and to assess the change in salivary urea and creatinine with blood urea and serum creatinine in patients with CKD undergoing dialysis.

INTRODUCTION

Kidneys are the main excretory organs of the body and are vital for maintaining homeostasis. Renal disease is one of the major causes of global morbidity and mortality.¬¬1 Chronic kidney disease (CKD) is an internationally recognised public health problem affecting 5-10% of the world population.2,3 The incidence of renal failure has doubled in the last 15 years.4 In India, approximately 7.85 million people are suffering from chronic renal failure making it a devastating medical, social and economic problem.4 It is estimated that 1,00,000 new patients of end stage renal disease (ESRD) enter renal replacement programmes annually in India.5

CKD is characterised by progressive and chronic deterioration of nephron leading to impaired functioning of kidneys, resulting in an increase in blood urea, serum creatinine, fluid and electrolyte disturbances which is present for more than 3 months. Leading causes of CKD include diabetes mellitus, hypertension, glomerulonephritis, interstitial nephritis, pyelonephritis, obstructive uropathy etc.7 According to guidelines of KDIGO, CKD can be classified as follows:7

GFR category	eGFR (ml/min/1.73m^2)	Terms
G 1	>90	Normal or high
G 2	60-89	Mildly decreased
G 3a	45-59	Mildly to moderately decreased
G 3b	30-44	Moderately to severely decreased
G 4	15-29	Severely decreased
G 5	<15	Kidney failure

CKD is associated with accumulation of metabolic waste products and multi-organ dysfunction. These changes usually manifest as elevated blood urea and serum creatinine as well as other haematological, electrolyte, endocrine and skeletal disturbances.[9,10] Normal level of blood urea is 20-40 mg/dl and that of serum creatinine is 0.6-1.2 mg/dl.[7]Human saliva is a unique fluid secreted by major and minor salivary glands. Whole saliva is composed of components that originate from salivary glandular and non salivary glandular sources.[10] CKD

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is one of the systemic diseases that affect the contents of salivary secretions.[11] Normal level of salivary urea is 12-70mg/dl[11] and that of salivary creatinine is 0.05-0.2mg/dl.[12] Various studies have been done world over to assess the correlation of salivary urea and creatinine with blood urea and serum creatinine in patients with CKD. Many of these studies have shown positive correlation between blood urea and serum creatinine with salivary urea and creatinine.[13,14,15,16,17,18,19,20,21] This suggests that saliva is a fluid of interest that can be used as a sample, alternative to blood in clinical practice. This can prevent process of periodic withdrawal of blood in patients with CKD who are already anaemic.

When the patients with CKD undergo dialysis, fall in blood urea and serum creatinine is expected. There have been few studies to assess the affect of dialysis on salivary urea and creatinine. Our study was aimed to assess the correlation of salivary urea and creatinine with blood urea and serum creatinine in patients with CKD and to assess the change in salivary urea and creatinine with blood urea and serum creatinine in patients with CKD undergoing dialysis, so that estimation of salivary urea and creatinine can be considered to be used as an alternative to blood urea and serum creatinine to assess renal function in patients with CKD.

MATERIALS AND METHODS

The present cross- sectional study was carried out in 60 patients with chronic kidney disease admitted in various wards of Medicine department or those undergoing haemodialysis in Guru Nanak Dev Hospital attached to Government Medical College, Amritsar. After recording various parameters, GFR was estimated using Cockroft and Gault formula and patients were classified into various stages of CKD on the basis of KDIGO guidelines. The patients were grouped in two groups of 30 each according to indications for dialysis at the time of examination and those with presence of indications were subjected to it. The patients included in group A had no indication for dialysis and were studied to assess the correlation of salivary urea and creatinine with blood urea and serum creatinine and patients in group B who had indications for dialysis were studied to assess the change in pre and post dialysis blood urea and serum creatinine and their correlation with the change in salivary urea and creatinine.

Inclusion criteria

- Patients with CKD with age more than 25 years (diagnosed on the basis of history of raised blood urea and serum creatinine for more than 3 months, estimated GFR less than 60 ml/min/1.73m^2, ultrasonographic findings of deranged renal parameters).

Exclusion criteria

- Patients with history of intake of any nephrotoxic drug
- Patients who were known to have any salivary gland or oral cavity disease.
- Patients who were active smoker or tobacco chewer
- Pregnant women

Each patient was assessed as follows

Routine investigations

Blood urea and serum creatinine in group A

Blood urea and serum creatinine in group B (both pre and post dialysis in patients undergoing haemodialysis)

Special investigations

Salivary urea and creatinine in group A

Salivary urea and creatinine in group B (both pre and post dialysis in patients undergoing haemodialysis)

Creatinine clearance using Cockroft and Gault formula

Statistical analysis

The results thus obtained were tabulated and analysed using SPSS version 23.0 statistical package for windows. The results were presented as mean ± SD. Pearson coefficient of correlation analysis was performed to assess the relationship between salivary and serum urea and creatinine. Statistical significance was taken as a value of $p < 0.05$. Paired t test was used to compare the results of pre and post dialysis salivary and serum urea and creatinine.

RESULTS

The various observations of the study were

Table 1 Distribution of patients according to CKD stage and GFR (ml/min/1.73m^2) in group A and group B

CKD stage	Group A		Group B			
			Pre-dialysis		Post-dialysis	
	No.	Mean GFR	No.	Mean GFR	No.	Mean GFR
3a	0		0		1	58.99±0.00
3b	3	36.90±5.38	1	34.58±0.00	4	37.62±6.53
4	16	18.41±3.42	4	20.56±4.38	12	20.14±3.70
5	11	10.51±2.29	25	9.39±2.67	13	12.15±2.12
Total	30	17.36±8.23	30	11.72±6.43	30	20.41±11.58

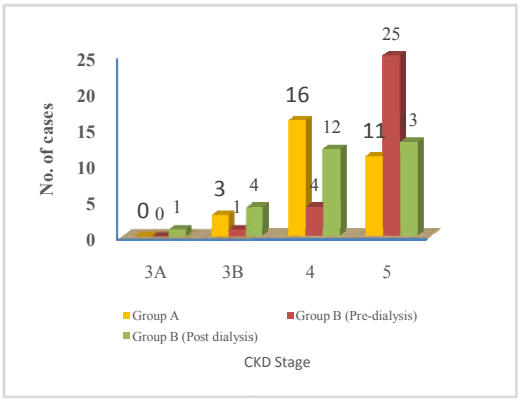

Fig. 1 Distribution according to CKD stage

Table 2 Distribution of blood urea (mg/dl) in group a and group b

CKD stage	Group A		Group B			
			Pre-dialysis		Post-dialysis	
	No.	Mean blood urea	No.	Mean blood urea	No.	Mean blood urea
3a	0		0		1	160.00±0.00
3b	3	84.00±17.52	1	260.00±0.00	4	82.00±32.29
4	16	124.14±56.10	4	139.50±35.75	12	79.75±34.31
5	11	153.00±43.71	25	185.54±59.14	13	130.53±45.01
Total	30	130.71±52.40	30	179.42±58.98	30	104.73±46.11

Table 3 distribution of serum creatinine (mg/dl) in group a and group b

CKD stage	Group A		Group B			
			Pre-dialysis		Post-dialysis	
	No.	Mean	No.	Mean	No.	Mean
3a	0		0		1	1.70±0.00
3b	3	2.16±0.50	1	2.90±0.00	4	2.40±0.355
4	16	4.11±1.11	4	4.87±0.66	12	4.32±0.76
5	11	7.26±2.15	25	9.36±2.91	13	6.92±1.40
Total	30	5.07±2.33	30	8.55±3.25	30	5.10±2.04

Table 4 Distribution of salivary urea (mg/dl) in group a and group b

CKD Stage	Group A		Group B			
			Pre-dialysis		Post-dialysis	
	No.	Mean	No.	Mean	No.	Mean
3a	0		0		1	225.00±0.00
3b	3	197.33±6.50	1	490.00±0.00	4	159.25±104.98
4	16	240.94±109.08	4	290.25±151.17	12	173.66±83.06
5	11	249.91±54.36	25	368.36±147.07	13	227.07±92.51
Total	30	239.87±86.04	30	362.00±146.88	30	196.60±90.29

Table 5 Distribution of salivary creatinine (mg/dl) in group a and group b

CKD stage	Group A		Group B			
			Pre-dialysis		Post-dialysis	
	No.	Mean salivary creatinine	No.	Mean salivary creatinine	No.	Mean salivary creatinine
3a	0		0		1	1.90±0.00
3b	3	2.20±0.91	1	2.90±0.00	4	2.77±0.78
4	16	3.41±0.90	4	3.72±1.55	12	3.25±1.71
5	11	5.08±1.68	25	6.63±1.83	13	3.06±0.99
Total	30	3.90±1.55	30	6.12±2.10	30	3.06±1.29

Table 6 Correlation of salivary urea (mg/dl) with blood urea (mg/dl) in patients with chronic kidney disease

	Group A (n=30)		Group B (Predialysis) (n=30)	
	Blood urea	Salivary urea	Blood urea	Salivary urea
Mean	130.71 ± 52.40	239.87 ± 86.04	179.42 ± 58.98	362.00 ± 146.88
Pearson correlation coefficient (r)	0.758		0.448	
p-value	0.001		0.013	

**p value <0.05; statistically significant

In group A, the mean blood and salivary urea were 130.71±52.40 mg/dl and 239.87±86.04 mg/dl, respectively. The correlation coefficient for salivary and blood urea was r = 0.758 and a statistically significant positive correlation was found between blood and salivary urea (p = 0.001). Similarly in predialysis group B, the mean blood and salivary urea were 179.42±58.98 mg/dl and 362±146.88 mg/dl, respectively. The correlation coefficient for salivary and blood urea was r = 0.448 and a statistically significant positive correlation was found between blood and salivary urea (p = 0.013) in this group also.

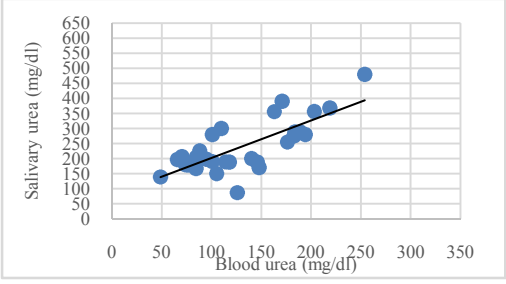

Fig. 2 Correlation of salivary urea with blood urea in Group A

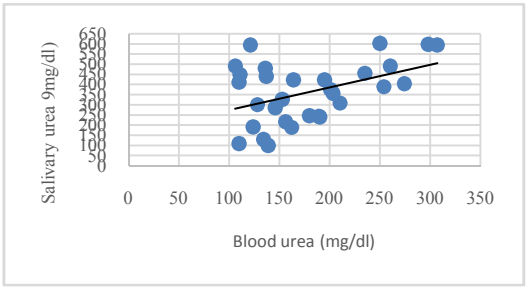

Fig. 3 Correlation of salivary urea with blood urea in Group B (Predialysis)

Table 7 Correlation of salivary creatinine (mg/dl) with serum creatinine (mg/dl) in patients with chronic kidney disease

	Group A (n=30)		Group B (Predialysis) (n=30)	
	Serum creatinine	Salivary creatinine	Serum creatinine	Salivary creatinine
Mean	5.07 ± 2.33	3.90 ± 1.55	8.55 ± 3.25	6.12 ± 2.10
Pearson correlation coefficient (r)	0.780		0.374	
p-value	0.001		0.04	

**p value <0.05; statistically significant

In group A, the mean serum and salivary creatinine was 5.07±2.33 mg/dl and 3.90±1.55 mg/dl, respectively. The correlation coefficient for salivary and serum creatinine was r = 0.780 and a statistically significant positive correlation was found between serum and salivary creatinine

(p = 0.001).Similarly in predialysis group B, the mean serum and salivary creatinine was 8.55±3.25 mg/dl and 6.12±2.10 mg/dl, respectively. The correlation coefficient was r = 0.374 and a statistically significant positive correlation was also found between serum and salivary creatinine (p = 0.04) in this group.

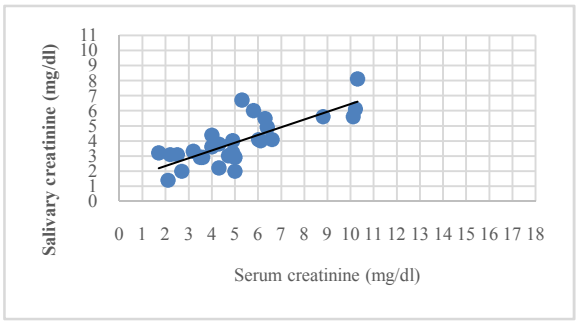

Fig. 4 Correlation of salivary creatinine with serum creatinine in Group A

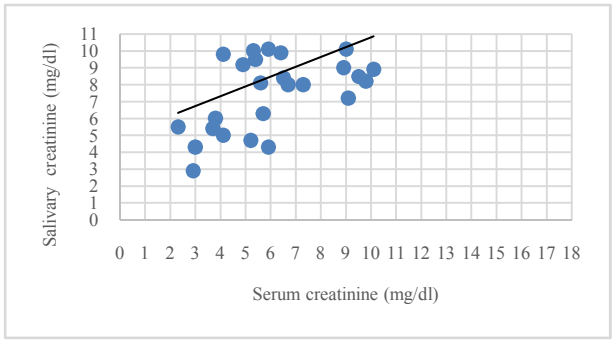

Fig. 5 Correlation of salivary creatinine with serum creatinine in Group B (Predialysis)

To assess the change in pre and postdialysis blood urea and serum creatinine and their correlation with the change in salivary urea and creatinine

Table 8 Change in pre and post dialysis blood urea, salivary urea, serum and salivary creatinine (mg/dl)

CKD Stage	Pre-dialysis	Post-dialysis	Change	t-value	p-value	Mean %age of change
Blood urea	179.42±58.98	104.73±46.11	74.68±43.83	9.333	0.001	41.62%
Salivary urea	362.00±146.88	196.60±90.29	165.40±124.48	7.277	0.001	45.69%
Serum creatinine	8.55±3.25	5.10±2.04	3.44±1.99	9.443	0.001	40.23%
Salivary creatinine	6.12±2.10	3.06±1.29	3.06±0.81	8.065	0.001	50.0%

The mean change in blood and salivary urea in group B after dialysis was 74.68±43.83 mg/dl and 165.40±124.48 mg/dl, respectively. The data was analyzed using Pearson coefficient of correlation and a statistically significant positive correlation of change was found between the change in blood and salivary urea in the dialysis group (r = 0.388, p-value = 0.034).

Table 10 Correlation of the change in pre and postdialysis serum creatinine (mg/dl) with the change in salivary creatinine (mg/dl)

	Serum creatinine	Salivary creatinine
Mean	3.44±1.99	3.06±0.81
Pearson correlation coefficient (r)	0.196	
p-value	0.299	

The mean change in serum and salivary creatinine in group B after dialysis was 3.44±1.99 mg/dl and 3.06±0.81 mg/dl, respectively. The data was analyzed using Pearson coefficient of correlation and a statistically negative correlation of change was found between the change in blood and salivary creatinine in the dialysis group (r = 0.196, p-value = 0.299).

DISCUSSION

Normal range of blood urea is 20-40mg/dl and salivary urea is 12-70 mg/dl. The normal range of serum creatinine is 0.6-1.2 mg/dl and salivary creatinine is 0.05-0.2 mg/dl.

We observed a higher urea and creatinine level both in serum and saliva of patients with CKD than the normal reference range (Table 6, 7). When salivary level of urea was correlated with blood, we obtained a statistically significant positive correlation in both group A (r = 0.758, p = 0.001, Table 6) and predialysis group B (r = 0.448, P = 0.013, Table 6).

Similarly, when salivary level of creatinine was correlated with serum creatinine, a statistically significant positive correlation in both group A (r = 0.780, p = 0.001, Table 7) and predialysis group B (r = 0.374, p = 0.04, Table 7) was obtained. As per above mentioned findings in our study, salivary levels of urea and creatinine showed corresponding increase with their serum counterpart. These correlations showing increased levels in saliva substantiate similar findings in the previous studies. The increased concentration in saliva may be because of increased serum concentration which creates a concentration gradient which in turn increases the diffusion of urea and creatinine from serum to saliva in patients with CKD. It is also possible that high level of urea and creatinine in saliva may be an alternative route of excretion in compromised renal function state.[12]

The change in the levels of urea and creatinine both in blood and saliva was also assessed in pre and postdialysis group. The study showed fall in the levels of blood urea, serum creatinine, salivary urea and creatinine after dialysis. The mean percentage of the change observed was 41.62%, 40.23%, 45.69% and 50% respectively in all these parameters (Table 8, 9, 10, 11). These findings were in accordance to previous studies done to assess efficacy of dialysis by using salivary urea and creatinine.[20,22,23]

In our study, the correlation of the change in salivary urea and creatinine with the change in blood urea and serum creatinine after dialysis was also assessed. A positive correlation was observed between the change in salivary and blood urea (p=0.034, r=0.388, Table 12). When we studied the correlation of the change in salivary creatinine with the change in serum creatinine after dialysis, a negative correlation was observed (p=0.299, r=0.196, Table 13). The moleculer weight and size of urea being 60.03 D and 0.26 nm respectively, is lower in comparison with that of creatinine having molecular weight of 113 D and size of 0.3 nm.[20] Urea being smaller and lesser in weight, is possibly filtered more compared to creatinine.

The study supported the fact that adds to the existing data that whenever there is increase in blood urea and serum creatinine, there will be concomitant increase in salivary urea and creatinine also.

CONCLUSION

From the results of our study, following conclusions were drawn

- Blood and salivary urea and serum and salivary creatinine are significantly higher in patients with CKD than normal reference range.
- There is significant positive correlation between salivary urea and salivary creatinine with blood urea and serum creatinine in patients with CKD.
- There is significant positive correlation of change between the change in blood and salivary urea after dialysis.
- There is negative correlation of change between the change in serum creatinine and salivary creatinine after dialysis.

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