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Salivary Urea Creatinine and GFR Estimation in Patients with Chronic Kidney Disease

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Abstract
Chronic kidney disease (CKD) is a type of kidney disease in which there is gradual loss of kidney function over a period of months or years. Causes of chronic kidney disease include Diabetes Mellitus, Systemic Hypertension, Glomerulonephritis, and Polycystic Kidney Disease with family history of Chronic kidney Disease. Blood urea and serum creatinine is important in normal functioning of the kidney and estimation of both blood urea and serum creatinine helps in diagnosis of CHRONIC KIDNEY DISEASE. Serum analysis is an invasive and painful procedure. It would be highly beneficial if a noninvasive alternative process to serum analysis were identified1. Saliva can be collected noninvasively, repeatedly, and without the use of healthcare personnel. In this study we compare serum and salivary urea and creatinine levels in patients with CHRONIC KIDNEY DISEASE and AGE AND SEX matched healthy controls, and to determine if salivary creatinine and urea levels can be used to diagnose CHRONIC KIDNEY DISEASE.

Keywords: *Chronic Kidney Disease, Blood urea and creatinine, Salivary urea and creatinine.*

Introduction

CHRONIC KIDNEY DISEASE is a progressive reduction in renal function. The prevalence and incidence are increasing worldwide with DIABETES and HYPERTENSION as the leading cause .the condition requires frequent serum analysis to diagnose and monitor therapeutic outcomes and to ascertain prognosis. Creatinine, a waste product of muscle metabolism, is primarily excreted by kidney and its level in serum is used as an index to renal function. Collection of blood for serum analysis is an invasive procedure causing anxiety and discomfort for the patient. Certain amount of blood loss is associated with each dialysis procedure in CKD patients which amounts to about 4 to 20ml, with additional loss which results from frequent blood sampling ,also the patient undergoing dialysis are at greater risk of developing Hepatitis B and C potentially increasing the risk of health care personal to blood borne diseases[1]. Thus, a simple diagnostic test that provide reliable evaluation of disease status and stages would be of value of both the clinicians and patient. Saliva, a multi constituent biological fluid secreted by salivary gland, is the major contributor to oral health .it has got a cutting edge over serum because saliva collection is a non-invasive, simple and economic procedure that can be performed by the patient with minimum involvement from the medical personnel. when

required, a repeat sample can be easily obtained and is suitable for all age groups. It also provides a cost effective approach for the screening of large population. Saliva is a diagnostic medium will also be a boon to patients suffering from clotting disorders like Hemophilia and in patients with compromised venous access. There is minimal risk of contacting infection, such as obtaining samples from children or handicapped or anxious patients, in whom blood sampling could be a difficult to perform. In this study we compare serum and salivary urea and creatinine levels in patients with CHRONIC KIDNEY DISEASE and AGE AND SEX matched healthy controls, and to determine if salivary creatinine and urea levels can be used to diagnose CHRONIC KIDNEY DISEASE.

Aim and Objectives

1. To correlate serum and salivary urea and creatinine and GFR calculation using both serum and salivary creatinine.
2. To evaluate the role of saliva as annon invasive alternative to serum creatinine estimation in Chronic Kidney Disease.
3. To assess AGE and SEX distribution among CHRONIC KIDNEY DISEASE patients.

Materials and Methods

Setting: Hospital based

Study Design: Case- control study which was conducted in chronic kidney disease patients with age and sex matched health controls admitted in south Indian rural based hospital.

Study Participants: Patients with established chronic kidney disease who is either on medical management or dialysis, with age and sex matched healthy controls were included in the study.

Study Duration: 6 months

Sample Size: 130 (90 Cases and 40 age and sex matched controls)

Inclusion Criteria: Patients with well documented Chronic kidney Disease (GFR estimation through COCKCROFT GAULT formula) and its complications who is either under medical management or Hemodialysis were included in the study.

Exclusion Criteria: Patients with chronic kidney Disease stage 1 is excluded (GFR estimation through COCKCROFT GAULT formula)

After obtaining a written informed consent, a clinical examination was performed and the case details were recorded on a special proforma. GFR CALCULATION was done on both patients and controls using both SERUM CREATININE and SALIVARY CREATININE using COCKCROFT GAULT formula both for MEN and WOMEN respectively.

$$\text{MALES} - \frac{(140 - \text{AGE IN YEARS}) \times \text{WEIGHT (KG)}}{\text{SERUM CREATININE (MG/DL)} \times 72}$$

$$\text{FEMALES} - \frac{(140 - \text{AGE IN YEARS}) \times \text{WEIGHT (KG)} \times 0.85}{\text{SERUM CREATININE (MG/DL)} \times 72}$$

Sample Collection

All the samples were collected between 9:00 and 11:00 a.m. to minimize the effect of diurnal variation. In patients undergoing hemodialysis, the sample was collected prior to dialysis. Two mL of blood was drawn from anterior cubital vein with minimal trauma under aseptic condition. Two mL of whole saliva was obtained under restful conditions, in a sterile graduated container by spitting method. The participants were instructed to refrain from eating and drinking at least 90 min before collection and thoroughly rinse mouth with deionized/distilled water prior to the collection to void the mouth of saliva. They were asked to sit in a comfortable position with eyes open and head tilted slightly forward and to avoid swallowing

and oral movements during collection and to pool the saliva in the floor of the mouth and spit every 60 seconds or when they experience an urge to swallow the fluid accumulated. This was done until 2 mL of whole saliva was obtained.

All collected samples were centrifuged at 3000 RPM for 10 minutes Salivary supernatant and serum were separated. The samples were assayed immediately in automatic analyzer (EM360 chemistry analyzer with ISE module) using creatinine estimation kit.

Data Entry and Analysis: Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test** was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. **Independent t test** was used as test of significance to identify the mean difference between two quantitative variables and qualitative variables respectively. **Paired t test** was the test of significance for paired data such as before and after surgery for quantitative and qualitative data respectively.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs such as bar diagram, Pie diagram and Scatter plots.

Pearson correlation or Spearman's correlation was done to find the correlation between two quantitative variables and qualitative variables respectively.

Correlation coefficient (r)	Interpretation
0 - 0.3	Positive Weak correlation
0.3-0.6	Positive Moderate correlation
0.6-1.0	Positive Strong correlation
0 to (-0.3)	Negative Weak correlation
(-0.3) to (-0.6)	Negative Moderate Correlation
(-0.6) to – (1)	Negative Strong Correlation

p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

The Cockcroft and Gault formula was used to estimate eGFR among cases and controls using Serum and Salivary Creatinine values

C_{Cr}= {((l 40–age) x weight) /(72xS_{Cr})}x 0.85 (if female)

Abbreviations/ Units

C_{Cr} (Creatinine clearance) = mL/minute

Age = years

Weight = kg

SCr (Serum Creatinine) = mg/dL

Statistical Software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

Results

In this hospital based case – control study totally 130 patients were taken after ethical committee approval and participation consent from all study population. Patients with chronic kidney diseases blood urea creatinine and salivary urea creatine was collected from cases and healthy controls with age and sex matched. .The study population is sub-divided based on age grouping age of < 30 years (s – 2 , c -7) 31-40 years (s-16 ,c-22) 41-50 years (s-20 , c-25) 51- 60 years (s-26, c-19) 61 – 70 years (s-20 c-10)> 70 years of age (s-6 c-7).

Table 1: Profile of subject's comparison between cases and controls

		Group				P value
		Cases		Controls		
		Count	%	Count	%	
Age	<30 Years	2	2.2%	7	7.8%	0.118
	31 to 40 Years	16	17.8%	22	24.4%	
	41 to 50 Years	20	22.2%	25	27.8%	
	51 to 60 Years	26	28.9%	19	21.1%	
	61 to 70 Years	20	22.2%	10	11.1%	
	>70 Years	6	6.7%	7	7.8%	
Sex	Female	27	30.0%	28	31.1%	0.871
	Male	63	70.0%	62	68.9%	

*p<0.05 statistically significant, p>0.05 Non significant, NS

Among cases majority of subjects were in the age group 51 to 60 years (28.9%) and among controls majority of subjects were in the age group 41 to 50 years (27.8%). There was no significant difference in age distribution between two groups. Hence age matching was attained.

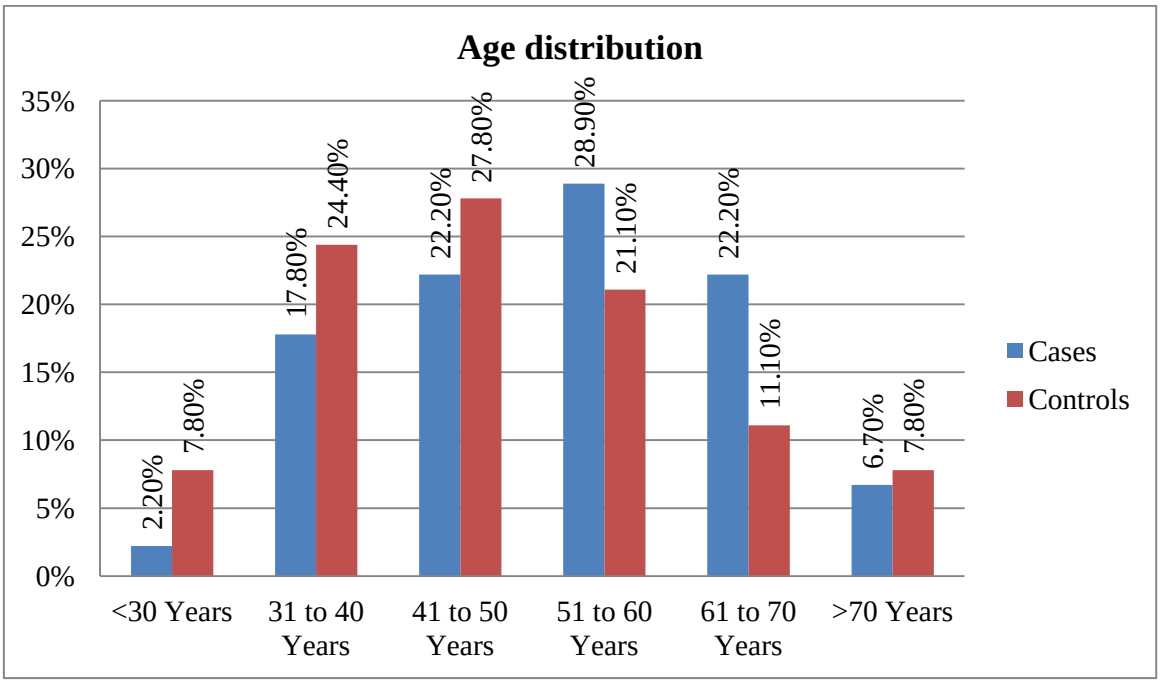

Figure 1: Bar diagram showing Age distribution of subjects between cases and controls

Among cases 70% were males and 30% were females and among controls 68.9% were males and 31.1% were females. There was no significant difference in gender distribution between two groups.

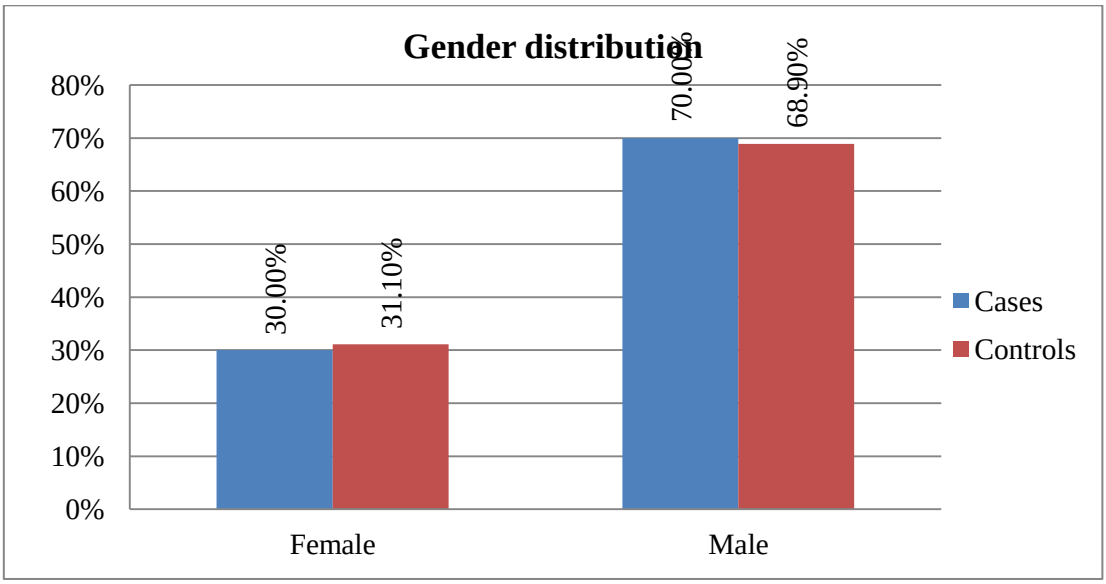

Figure 2: Bar diagram showing gender distribution of subjects between cases and controls

Table 2: Salivary Urea, Creatinine and Serum Urea and Creatinine comparison between cases and controls

	Serum (Mean ± SD)				Saliva (Mean ± SD)				P value
	Cases		Controls		Cases		Controls		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Urea	105.9	34.7	22.2	7.6	81.4	43.1	25.6	17.8	<0.001*
Creatinine	6.9	1.8	0.3	0.2	1.2	1.5	0.3	0.4	<0.001*
eGFR	11.2	4.4	412.5	252.2	219.5	247.7	349.5	285.3	<0.001*

In the study among cases mean Salivary Urea was 81.42 ± 43.11, mean Salivary Creatinine was 1.22 ± 1.52, mean Blood Urea was 105.86 ± 34.7, mean Serum Creatinine was 6.87 ± 1.79, Mean serum eGFR was 11.2 ± 4.4 and mean salivary eGFR was 219.5 ± 247.7. Among controls mean Salivary Urea was 25.61 ± 17.85, mean Salivary Creatinine was 0.34 ± 0.35, mean Blood Urea was 22.19 ± 7.64, mean Serum Creatinine was 0.27 ± 0.21, mean serum eGFR was 412.5 ± 252.2 and mean salivary eGFR was 349.5 ± 285.3. There was significant difference in mean Salivary Urea, Salivary Creatinine, Blood Urea, Serum Creatinine Serum eGFR and Salivary eGFR between cases and controls.

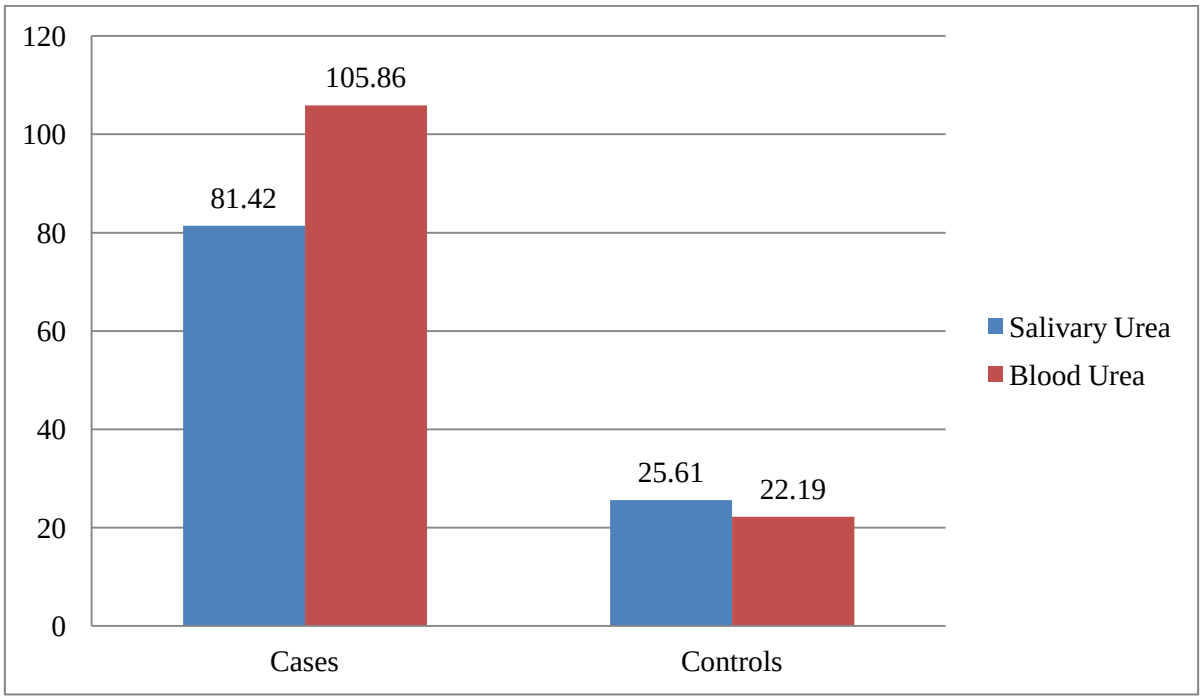

Figure 2: Bar diagram showing Salivary Urea and Blood Urea comparison between cases and controls

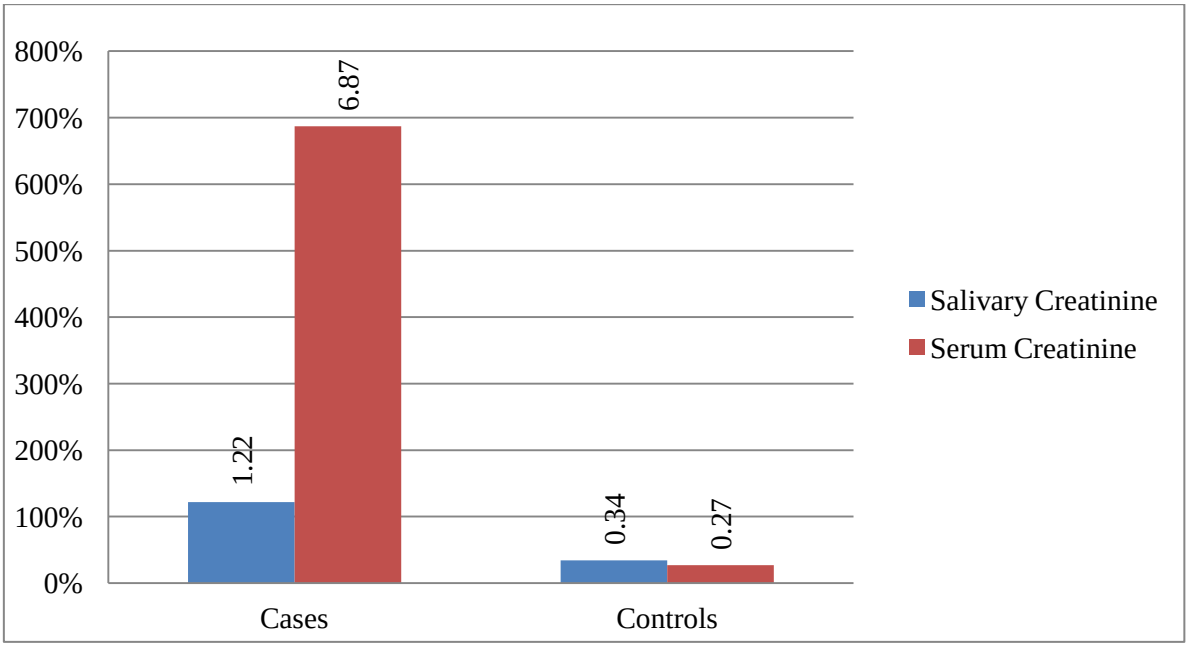

Figure 3: Bar diagram showing Salivary Creatinine and Serum Creatinine comparison between cases and controls

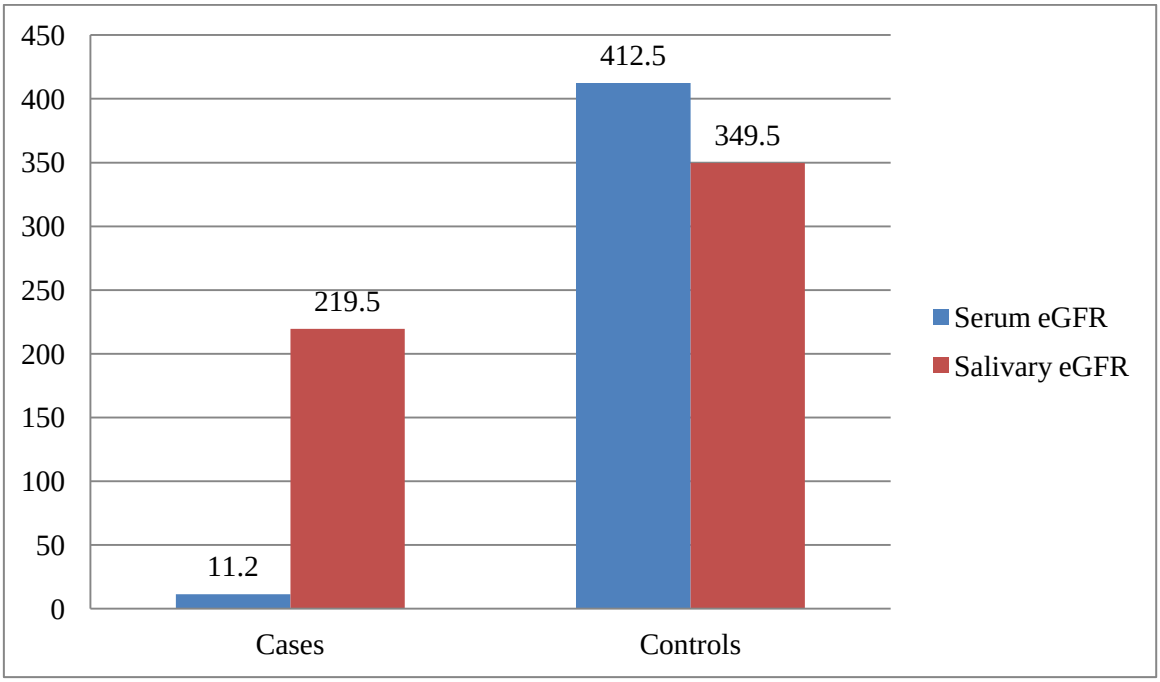

Figure 4: Bar diagram showing Salivarye GFR and Serum eGFR comparison between cases and controls

Table 4: Salivary Urea and Salivary Creatinine comparison between cases and controls

	Cases				P value	Controls				P value
	Serum		Saliva			Serum		Saliva		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Urea	105.9	34.7	81.4	43.1	<0.001*	22.2	7.6	25.6	17.8	0.014*
Creatinine	6.9	1.8	1.2	1.5	<0.001*	0.3	0.2	0.3	0.4	0.012*
eGFR	11.2	4.4	219.5	247.7	<0.001*	412.5	252.2	349.5	285.3	0.08

In the study among cases mean Blood Urea was 105.86 ± 34.7 and mean Salivary Urea was 81.42 ± 43.11. This difference in serum and salivary urea was statistically significant. Mean Salivary Creatinine was 1.22 ± 1.52 and mean Serum Creatinine was 6.87 ± 1.79. This difference was in serum and salivary Creatinine was statistically significant.

Among controls mean Blood Urea was 22.19 ± 7.64 and mean Salivary Urea was 25.61 ± 17.85, this difference in serum and saliva urea was statistically significant. Similarly mean Serum Creatinine was 0.27 ± 0.21 and Mean Salivary Creatinine was 0.34 ± 0.35. This difference in mean serum and salivary Creatinine was statistically significant.

Table 5: Correlation between Serum and salivary eGFR

Correlations			
		eGFR by Serum Creatinine	eGFR by Salivary Creatinine
eGFR by Serum Creatinine	Pearson Correlation	1	0.284**
	P value		<0.001*
	N	180	180

In the study there was significant positive correlation between Serum and Salivary eGFR, i.e. with increase in Serum eGFR there was increase in Salivary Creatinine and vice versa.

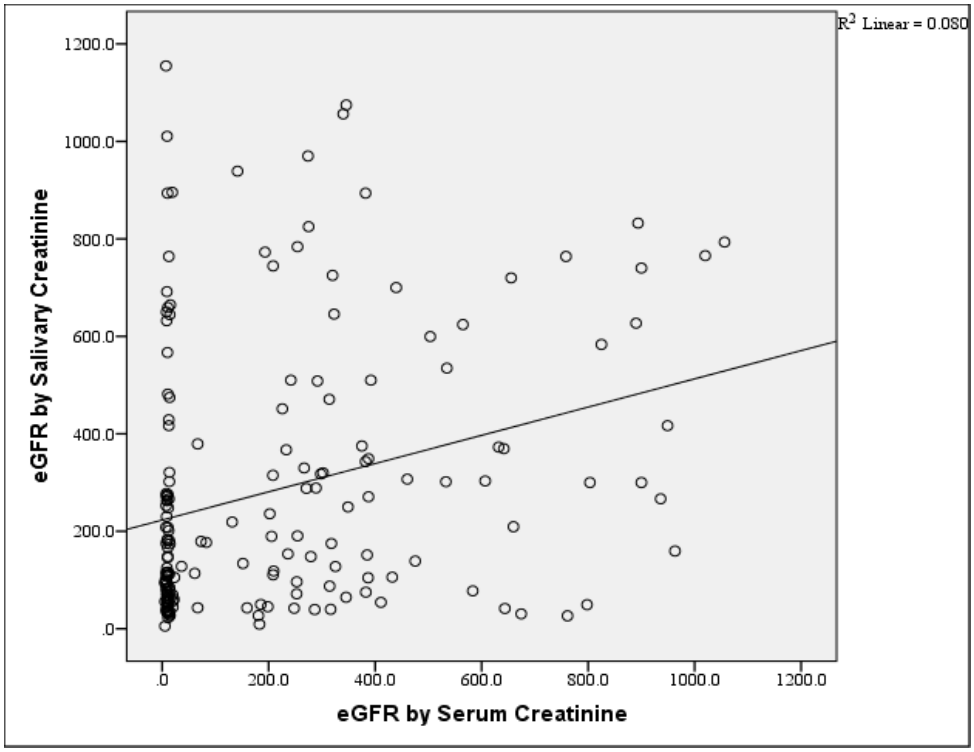

Figure 5: Scatter plot showing Correlation between Serum and salivary eGFR

Discussion

Creatinine is a waste product of metabolism primarily excreted by the kidneys. All creatinine is excreted without reabsorption; as such, its levels in blood are used as an index of kidney function. Due to an increase in serum creatinine and urea in CKD, the salivary creatinine and urea levels also increase because when there is renal failure the kidneys cannot excrete creatinine and its blood level increases. Elevated salivary creatinine and urea causes dry mouth, uremic breath, tongue coating, and other oral complications of CKD[2]. A high concentration of urea and creatinine in saliva might be due to elevated serum creatinine and urea levels, which produce and elevated level gradient which in turn increases the diffusion of creatinine as well as urea consistent with previous reports. Creatinine is a large molecule with a high molecular weight that exhibits low lipid solubility. In healthy individuals, it is unable to diffuse across the cells and the tight junction of the salivary gland, but in CKD patients serum creatinine increases, a concentration gradient occurs, and creatinine diffusion increases from serum to saliva[3]. In the present study among cases majority of subjects were in the age group 51 to 60 years (28.9%) and among controls majority of subjects were in the age group 41 to 50 years (27.8%). There was no significant difference in age distribution between two groups. Hence age matching was attained.

Among cases 70% were males and 30% were females and among controls 68.9% were males and 31.1% were females. There was no significant difference in gender distribution between two groups. In the study among cases mean Salivary Urea was 81.42 ± 43.11, mean Salivary Creatinine was 1.22 ± 1.52, mean Blood Urea was 105.86 ± 34.7, mean Serum Creatinine was 6.87 ± 1.79, Mean serum eGFR was 11.2 ± 4.4 and mean salivary eGFR was 219.5 ± 247.7. Among controls mean Salivary Urea was 25.61 ± 17.85, mean Salivary Creatinine was 0.34 ± 0.35, mean Blood Urea was 22.19 ± 7.64, mean Serum Creatinine was 0.27 ± 0.21, mean serum eGFR was 412.5 ± 252.2 and mean salivary eGFR was 349.5 ± 285.3. There was significant difference in mean Salivary Urea, Salivary Creatinine, Blood Urea, Serum Creatinine Serum eGFR and Salivary eGFR between cases and controls.

When Salivary Urea and Salivary Creatinine comparison between cases and controls were done

in the study among cases mean Blood Urea was 105.86 ± 34.7 and mean Salivary Urea was 81.42 ± 43.11. This difference in serum and salivary urea was statistically significant. Mean Salivary Creatinine was 1.22 ± 1.52 and mean Serum Creatinine was 6.87 ± 1.79. This difference was in serum and salivary Creatinine was statistically significant.

Among controls mean Blood Urea was 22.19 ± 7.64 and mean Salivary Urea was 25.61 ± 17.85, this difference in serum and saliva urea was statistically significant. Similarly mean Serum Creatinine was 0.27 ± 0.21 and Mean Salivary Creatinine was 0.34 ± 0.35. This difference in mean serum and salivary Creatinine was statistically significant. oncewheather ant significant positive correlation between Serum and Salivary eGFR was assessed th study results revealed that a positive correlation exsits between serum and salivary e GFR, i.e. with increase in Serum eGFR there was increase in Salivary Creatinine and vice versa[4].

The present findings suggest that saliva can be used as an alternative bio fluid for estimating serum creatinine in patients with CKD.

Conclusion

In the study there was significant positive correlation between Serum and Salivary eGFR, i.e. with increase in Serum eGFR there was increase in Salivary Creatinine and vice versa with significant p value. Based on these findings, we think that salivary creatinine can be used as an alternative to serum creatinine in calculating eGFR and staging of CKD[5]. Also saliva could be an alternative to blood for diagnosis and monitoring patients with CKD. Saliva collection is a noninvasive method for obtaining diagnostic fluid in patients with CKD, and can reduce the anxiety and discomfort associated with blood collection, can be taken to allow frequent that will increase the monitor these patients general health over time to diagnose morbidities in the early stages[6]. The most important finding in the present study is that saliva can be used as a noninvasive diagnostic tool for estimating the serum creatinine level in patients with CKD. Additional larger scale controlled studies in patients with CKD are needed to further understand the role of saliva analysis in the diagnosis and treatment.

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