ORIGINAL ARTICLE

SALIVARY UREA: A MARKER FOR CHRONIC RENAL DISEASE

Naseer Ahmed , Abid Mehmood , Narendar Dawani . Suad Roshan

ABSTRACT

Background: Salivary urea, correlates well with serum urea, can be utilized as a low-cost, easily accessible and noninvasive diagnostic tool for screening patients in early stages of kidney disease, especially for developing countries with limited resources. Saliva for diagnostic purpose, is inexpensive, non-invasive, easy to collect, use, store and transport, contain high amount of disease biomarkers and shows efficient and reliable results.

Objective: To asses and prove the salivary diagnostics as reliable alternate to serum in renal diseases.
Methods: A cross-sectional validation study of 1 year duration from June 2012 to June 2013 was conducted. Non-probability consecutive sampling technique was employed on the patients attending the Nephrology OPD or those who were admitted to Jinnah Postgraduate Medical Centre Karachi.

Results: Significant correlation (.00) was found between the levels of serum and salivary urea and creatinine. A slight increase in the level of serum urea and creatinine results in a significant increase in the level of salivary urea and creatinine. Almost 63.2% and 64.6% of changes in serum urea and creatinine can be explained by the changes in salivary urea and creatinine levels respectively.

Conclusion: Saliva can be developed as a diagnostic fluid that is an alternative to blood. It is non invasive, less expensive and collection procedure does not require technicians. The use of salivary assay for diagnostics of chronic renal failure (urea and creatinine) can be established as a cost effective test for developing countries.

KEY WORDS: Saliva, Tool, Renal Failure, Oral Pathology.

INTRODUCTION

Blood borne pathogens acquired through occupational exposure are a major professional hazard among healthcare workers. Over 20 pathogens have been transmitted to healthcare workers via needle stick injury [1] and the most important are HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV).

The ability to monitor health status, disease onset and progression and treatment outcome through non-invasive means is a highly desirable goal in healthcare management.[2]

Saliva is a unique body fluid continually bathing the mucosa of the oral cavity, oropharynx and larynx. It is a complex mixture deriving from the secretion of salivary glands, gingival fold and oral mucosa transudate, in addition to mucous of the nasal cavity and pharynx, non-adherent oral bacterial, food remainders, desquamated epithelial and blood cells, as well as traces of medications or chemical products.[3] The analysis of saliva, like blood-based analyses, has two purposes: first is to identify individuals with disease and second, to follow the progress of the affected individual under treatment.[4]

Studies from Europe, Australia, and Asia confirm the high prevalence of Chronic Kidney Disease(CKD).[5,6,7,8] In the US, 9.6% of non-institution-alized adults are estimated to have CKD.[9,10]

The annual incidence of End-Stage Kidney Disease (ESKD) in Pakistan is estimated at about 100 per million popula-tions.[11] These patients require continues monitoring of urea & creatinine level to assess the disease progress and treatment outcome. The only available option is through serum levels of analytes to monitor the disease stage, which is painful and sometimes psychologically not acceptable to patient. Moreover patient compliance is mandatory as well.

Naseer Ahmed
Assistant Professor & HOD, Department of Community Dentistry, Altamash Institute of Dental Medicines, Karachi.
Abid Mehmood
Assistant Professor, Department of Oral Surgery, Jinnah Post Graduate Medical Centre, Karachi.
Narendar Dawani
Assistant Professor & MDS Coordinator, Department of Community Dentistry, Ishrat ul Ebad Khan Institute of Oral Health Sciences, DUHS, Karachi.
Suad Roshan
BDS Student, Altamash Intitute of Dental Medicine, Karachi.
Corresponding Author
Naseer Ahmed

Keeping in view such type of hurdles there is a dire need to develop the alternatives which should be cost effective and meet the global standards of diagnostics. Salivary urea cutoff point of 20 mg/dL and a CrCl of 80 ml/min per 1.73 m(2) showed sensitivity (S) of 0.98, specificity (SP) of 0.29, pretest probability (PPT) of 0.58, positive predictive value (PPV) of 0.66, negative predictive value (NPV) of 0.92, posttest positive probability (PTPP) of 0.66 and posttest negative probability (PTNP) of 0.09. A cutoff point of 40 mg/dL and a CrCl of 80 ml/min per 1.73 m(2) showed S=0.80, SP=0.71, PPT=0.58, PPV=0.80, NPV=0.71, PTPP=0.79 and PTNP=0.28. A cutoff point of 100 mg/dL and a CrCl of 80 ml/min per 1.73 m(2) showed S=0.22, SP=1, PPT=0.58, PPV=1, NPV=0.48, PTPP=1 and PTNP=0.52. Receiver operating characteristic curve analysis showed that the best cutoff point for salivary urea was 40 mg/dL.[12] The rationale of study is to determine validation of the salivary urea test as a method to diagnose chronic kidney disease. Saliva has the capability to cater all the above said obstacles as it is easy to collect, store and transport. No special training or equipment is required for sample collection and storage. Less chances of cross-infection. The objective of the study was to find out the validity of salivary urea test for the diagnosis of chronic kidney.

METHODOLOGY

A cross-sectional validation study of was conducted from June 20012 to June 2013. Sampling done using the non-probability consecutive sampling technique from the patients attending the Nephrology OPD/Admitted patients of Jinnah Postgraduate Medical Centre Karachi. The saliva sample was collected from the study cases between 9:00am to 11:00am to prevent any bias in the concentration of saliva due to circadian rhythm. Instructions of no oral ingestion of food or drink and no oral hygiene practices to be performed 2 hours prior to the sample collection was given. To collect saliva, patients were positioned, with head and trunk inclined forwards at approximately 45 degrees. The participants were instruct-ed to hold saliva in the floor of the mouth, avoid swallow-ing it and spitting it intermittently in a collection jar for a total of 5 minutes. Venous blood was also collected from the study cases. After collection, the saliva and blood samples immediately sent to the laboratory for analysis.

For Urea level estimation, Diacetyl Monoxime method was used while Alkaline Picrate solution (Jaffe's method) was used for Creatinine estimation. SPSS Version 17 was utilized to generate descriptive statistics. Frequency and percentage was calculated for categorical variable like gender. Statistical test is used to compared variables keeping p value < 0.05 as the significance criteria.

RESULTS

There was a significant correlation between the levels of Serum and Salivary Urea and Creatinine. A linear relationship between the level of serum urea and salivary urea were found. A slight increase in the level of Serum urea would result in a significant increase in the level of Salivary Urea. Almost 63.2% of changes in Serum Urea can be explained by the changes in Salivary Urea level.

There was a linear relationship between the level of serum Creatinine and salivary Creatinine. A slight increase in the level of Serum Creatinine would result in a significant increase in the level of Salivary Creatinine. Almost 64.6% of changes in serum Creatinine can be explained by the changes in salivary Creatinine levels.

Table 1. Comparison of Characteristics between ESKD Cases and Controls (N=178)

Variables	Cases n=160(%)	Controls n=18(%)	P-value
Gender:			
Male	94(58.75%)	15(83.3%)	0.841
Female	66(41.25%)	3(16.7%)	
Age in years [Mean(SD)]	39.07(10.71)	33.8(8.3)	0.061
Serum urea [Mean(SD)]	70.38(35.25)	21.3(4.6)	<0.001
Salivary urea [Mean(SD)]	33.05(18.11)	10.9(4.6)	<0.001
Serum Creatinine [Mean(SD)]	5.64(3.03)	1.2(0.22)	<0.001
Salivary Creatinine [Mean(SD)]	2.33(1.51)	0.7(0.18)	<0.001

There is a significant difference in the values of salivary and serum levels of Creatinine and urea between ESKD cases and Controls. ESKD cases were significantly older than Controls at (Level of Significance) a = 0.01.

Table 2: Comparison of Serum and Salivary levels of Creatinine and Urea among ESKD cases (N=160) with Controls (N=18).

	ESKD cases (N=160)			Controls (N=18)		
Variables	**Serum levels**	**Salivary level**	**P-value**	**Serum levels**	**Salivary level**	**P-value**
Creatinine level [Mean(SD)]	5.64(3.03)	2.33(1.51)	<0.001	1.18(0.22)	0.68(0.18)	<0.001
Urea level [Mean(SD)]	70.38(35.25)	33.05(18.11)	<0.001	21.3(4.6)	10.9(4.6)	<0.001

The difference between levels of salivary Creatinine and salivary urea were significantly different in ESKD cases at (Level of Significance) α = 0.01.

Table 3: Comparison of Serum and Salivary Levels of Creatinine and Urea among Controls (N=18)

Variables	**Serum levels**	**Salivary level**	**P-value**
Creatinine level [Mean(SD)]	1.18(0.22)	0.68(0.18)	<0.001
Urea level [Mean(SD)]	21.3(4.6)	10.9(4.6)	<0.001

The difference between levels of Salivary Creatinine and Salivary Urea were significantly different in the case of Controls at (Level of Significance) α = 0.01.

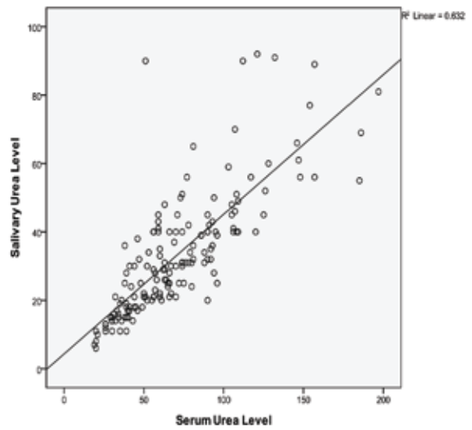
Table 4. Correlation Matrix between Age, Serum and Salivary Measurements

	Serum urea	**Salivary urea**	**Serum Creatinine**	**Salivary Creatinine**
Age in year	-0.006	0.025	0.042	0.024
Serum urea		0.795**	0.725**	0.614**
Salivary urea			0.645**	0.590**
Serum Creatinine				0.804**

**** Correlation significant at 0.01 levels**

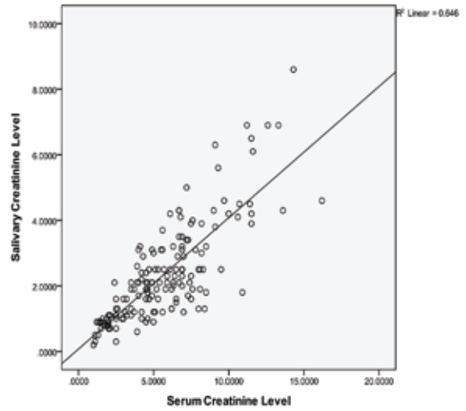
There is a significant correlation between the levels of Serum and Salivary Urea and Creatinine; however there is a very weak negative correlation between the 'Serum Urea' and 'Age in years'. There is a very strong positive correlation between the Serum and Salivary levels of Urea and Creatinine.

Figure 1. Scatter plot showing linear relationship between serum and salivary urea level



There is a linear relationship between the level of serum urea and salivary urea. A slight increase in the level of Serum urea will result in a significant increase in the level of Salivary Urea. Almost 63.2% of changes in Serum Urea can be explained by the changes in Salivary Urea level.

Figure 2. Scatter plot showing linear relationship between serum and salivary creatinine level



There is a linear relationship between the level of serum Creatinine and salivary Creatinine. A slight increase in the level of Serum Creatinine will result in a significant increase in the level of Salivary Creatinine. Almost 64.6% of changes in serum Creatinine can be explained by the changes in salivary Creatinine levels.

DISCUSSION

Study showed that saliva can be used as an alternative method to assess the urea levels which is conventionally used as Chronic Renal Failure marker in serum. There is a significant correlation between the levels of Serum and Salivary Urea. . A slight increase in the level of Serum urea resulted in a significant increase in the level of Salivary Urea. Almost 63.2% of changes in Serum Urea can be explained by the changes in Salivary Urea level. A linear relationship was found between the level of serum Creatinine and salivary Creatinine. A slight increase in the level of Serum Creatinine resulted in a significant increase in the level of Salivary Creatinine. Almost 64.6% of changes in serum Creatinine can be explained by the changes in salivary Creatinine levels.

Similar study was done by Khramov VA (1994,Russia), He took 39 patients and divide them to Group 1 i.e patients with Chronic Renal Failure Stage I-II & Group 2 which includes the End Stge Renal Failure stage III. 16 controls subjects were also included in this study and found higher correlation in salivary & blood urea concentrations. Upon correlation of salivary and blood urea concentration the proportions being 68% , 40.8% & 61% for group I , II & Controls respectively. Besides Urea & Creatinine , Potassium can also be analysed through salivary samplings to rule out End Stage Kidney Disease.

Despite of limitations, the use of saliva for diagnostic purposes is increasing day by day. Several diagnostic tests are commercially available and are currently used by patients, researchers, and clinicians. Saliva is particularly useful for qualitative (detection of the presence or absence of a marker) rather than quantitative diagnosis, which makes it an important means for the detection of viral infections (especially HIV, Hep.B & C etc.), past exposure and immunity, and the detection of illicit drug use. Saliva is also useful for the monitoring of hormone levels, especially steroids, and facilitates repeated sampling in short time intervals, which may be particularly important for hormone monitoring and avoiding compliance problems. Due to its many potential advantages, salivary diagnosis provides an attractive alternative to more invasive, time-consuming, complicated, and expensive diagnostic approaches. While many questions remain, the potential advantages of salivary analysis for the diagnosis of systemic disease suggest that further studies are warranted.

Consequently, we are likely to see the increased utilization of saliva as a diagnostic fluid. As a result, dentists will have greater involvement in the identification and monitoring of certain non-oral systemic disorders.

CONCLUSION

In conclusion, saliva is a biological fluid that offers several opportunities in diagnostics. Analysis of saliva can offer a cost-effective approach for the screening of large populations, and may represent an alternative for patients in whom blood drawing is difficult, or when compliance is a problem. The use of urea & creatinine to diagnose kidney health is an established practice that translates well into the development of a salivary assay. In the current study, it has been shown that saliva can be used as an alternate to serum to assess the kidney function. Results show a significant coorelation between serum and salivary changes in ESKD patients.

Pakistan Journal of Medicine and Dentistry 2015, Vol. 4 (02)

REFERENCES

[1]Jagger J, Hunt EH, Brand-Elnaggar J, et al. Rates of needlestick injury caused by various devices in a university hospital. N Engl J Med 1988; 319: 284-288.

[2] Castagnola M, Picciotti PM, Messana I, Fanali C, Fiorita A, Cabras T, Calò L, Pisano E, Passali GC, Lavarone F, Paludetti G, Scarano E. Potential applications of human saliva as diagnostic fluid. ACTA otorhinolaryngologica italica 2011; 31: 347-357.

[3] Humphrey SP, Williamson RT. A review of saliva: normal composition, flow, and function. J Prosthet Dent 2001; 85: 162-169.

[4] Streckfus CF, Bigler LR. Saliva as a diagnostic fluid, Oral Diseases 2002; 8: 69-76.

[5] De Zeeuw D, Hillege HL, De Jong PE. The kidney, a cardiovascular risk marker and a new target for therapy. Kidney Int Suppl 2005; 98: S25–S29.

[6] Chen J, Wildman RP, Gu D et al. Prevalence of decreased kidney function in Chinese adults aged 35 to 74 years. Kidney Int 2005; 68: 2839–2845.

[7] Hallan SI, Coresh J, Astor BC et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. J Am Soc Nephrol 2006; 17: 2275-2284.

[8] Chadban SJ, Briganti EM, Kerr PG et al. Prevalence of kidney damage in Australian adults: the Aus Diab kidney study. J Am Soc Nephrol 2003; 14(Suppl 2): S131-S138.

[9] Coresh J, Byrd-Holt D, Astor BC et al. Chronic kidney disease awareness, prevalence, and trends among US adults, 1999 to 2000. J Am Soc Nephrol 2005; 16: 180-188. [10]

Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function – measured and estimated glomerular filtration rate. N Engl J Med 2006; 354: 2473–2483.

[11] Rizvi SA, Naqvi SA. Resistance t cadaveric organ donation. Experience in a developing country in organ replacement therapy. Ethics, Justice and Commerce. (Eds) W. Lanel and JB. Dossetor. Springer-Verlag Berlin 1991; 300-302.

[12] Zúñiga ME, Estremadoyro LO, León CP, Huapaya JA, Cieza JA. Validation of the salivary urea test as a method to diagnose chronic kidney disease. J Nephrol 2012 May-Jun; 25(3): 431-436. doi: 10.5301/jn.5000022.

ORIGINAL ARTICLE

PEGYLATED INTERFERON ASSOCIATED THYROIDAL DYSFUNCTION AMONG HEPATITIS C PATIENTS

Nida Sajid , Karim Kammeruddin , Muhammad Imran

ABSTRACT

Background: Chronic hepatitis C and interferon both have their effect on thyroid gland function including clinical and subclinical thyroidal dysfunction (TD) that form major clinical manifestations of chronic hepatitis c.

Objective: To assess Pegylated interferon based therapy related thyroidal dysfunction in chronic hepatitis C patients and to compare it with those who are hepatitis C Sero positive but have not receive interferon based treatment.

Methods: A case control study in which, 203 patients of Chronic, compensated hepatitis C(130 females,73 males) were included from Baqai University Hospital Karachi Liver Clinic (b/w Jan 2010–Jun 2014). The participants were checked for thyroid dysfunction at the onset, 17 patients were found to have thyroidal dysfunction in the beginning and were excluded from the total 203 cases, then out of the remaining 186 cases, 101 patients (who were not having TD initially) opted treatment with pegylated interferon/ribavarin (Treated Group) and the rest (85 cases) were taken as control group.

Results: Thyroid dysfunction was identified in 7 patients giving a frequency of 6.9%. Out of these 7 patients only one patient was male while the rest were females. The mean age of the patients with thyroid dysfunction was 39.2 ± 7.13 years. Amongst the patients identified with the thyroid dysfunctions, 2 (28.5%) had overt hypothyroidism and 5 (71.4%) had sub-clinical hypothyroidism. The treatment with combination therapy was significant for development of thyroid dysfunction in patients with hepatitis C (p=0.013) as compared to control group in which 85 patients of chronic hepatitis C who have not developed (TD) during the study period.

Conclusion: dysfunction after pegylated interferon/ribavarin treatment in chronic hepatitis C is statistically significant with sub-clinical hypothyroidism is the predominant type in the study population.

KEY WORDS: Hepatitis C, Interferon, Thyroidal Dysfunction.

INTRODUCTION

The immensity of literature available on the subject of hepatitis C infection is not unwarranted. This specific infection is responsible for the major bulk of cirrhosis, chron-ic liver disease and hepatocellular carcinoma. Affecting 3% of the world population[1], the global nature of the disease leaves little to imagination. Preventive measures to stop the spread of the infection, early detection of the disease and prompt treatment remain the logical mainstays of management throughout the world.

Pegylated interferon alpha along with ribavarin has been considered to be the cornerstone in the management of hepatitis C infection.[2] As is with every other drug regimen this treatment is not without its side effects. The mode of action of these drugs is via modulation of the immune system and antiviral properties.[3] Side effects mentioned in the literature are varied with reported unwanted effects on the cardiac system, mental health and on the thyroid gland.[2,4,5]

Inter-relation between hepatitis C infection and thyroid dysfunction has generated a lot of debate in the research community. While interferon has been held responsible for development of thyroid dysfunction by some authors, others have implicated hepatitis C virus infection to be a cause of this clinical entity in its own right.[6] Others have implicated pegylated interferon as the culprit.[7] The former group in their study quoted the prevalence of thyroid dysfunction in untreated patients of hepatitis C to be 12.5%. Those who observed this phenomenon in patients being treated with interferon and ribavarin reported this frequency to be 18.69%.[8]

Nida Sajid
Baqai Medical University.
Karim Kammeruddin
Baqai Medical University
Muhammad Imran
Baqai Medical University
Corresponding Author
Nida Sajid