RA Publications
JMST Journal of Medical Science & Technology

Original research **Open Access**

Reference Intervals For Serum Creatinine In Nepal.

Sushil Kumar[1], Roshan Takhelmayum[2], Athokpam Rajendra Singh[3], Jitendra Narayan Sinha[4]

Lecturer[1, 2], Associate professor[3], Professor & HOD[4] of Biochemistry, College Of Medical Sciences & Teaching Hospital, Nepal

ABSTRACT

Objective- *The aim of the study is to find reference intervals of serum creatinine (Scr) in central region of Nepal.*

Material and methods- *In present study, after excluding patients with possible disease a final group of 903 healthy subjects (420 males and 483 females) at the age 21 to 80 years (mean age 48±16 yrs) from laboratory based data were taken as reference population. Creatinine in serum was measured in Auto analyzer Roche 902 (Hitachi) by Jaffe's Kinetic method (rate blanked and compensated).*

Results and conclusions- *The calculated serum creatinine in male and female were 0.60- 1.3 mg/dl and 0.45- 1.12 mg /dl respectively (p value<0.0001). Significant differences were observed in each age group between males and females.*

Key words- *Serum creatinine, Reference intervals, Reference population, Standard value, Creatinine clearance.*

Introduction

Creatinine (Molecular weight-113.3D, radius-30nm, water soluble) is one of the urinary nitrogenous excretory products synthesized from muscle creatine and Phosphocreatine, and is released in body fluids at a constant rate and its plasma levels are maintained within normal limits [1].It is present in all body fluids and secretions and is freely filtered by the glomerulus. Although creatinine is not reabsorbed from tubules to any great extent (absorption is increased in patient with low urine flow [1], there is a small but significant amount of creatinine secretion that increases with increasing levels of Scr [2].

***Corresponding author:** Sushil Kumar, Department of Biochemistry, *College Of Medical Sciences & Teaching Hospital.* E-mail: kumarsshl@yahoo.com
Received: Dec 26, 2011; Accepted Jan 5, 2012; Published January 20, 2012

Actual measurement of creatinine clearance is decreasing in clinical practice and also National Kidney Disease Education Program is giving more focus on the measurement of Scr [3]. Scr can be measured more accurately and reproducibly and, despite of many confounding factors, can be used to predict the creatinine clearance using one of the several algorithms for measuring GFR for assessing as an indicator of renal function [2]. Therefore inter laboratory agreement of Scr results has become an important international priority [4].

Scr concentration varies with age, sex, race, diet and muscle mass of the individual and also varies with methodology adopted, therefore, it is necessary to estimate scientifically sound reference intervals in particular reference population which represents a defined group of individuals [3].

Reference ranges used in the clinics in Nepal are usually taken from textbooks or values indicated by Kit manufacturer. In order to improve the diagnostic accuracy, it is necessary to establish reference intervals for Scr in population of Nepal. Direct selection of reference individuals is the only method that agrees

Name of control	Lot no of controls	Range mg/dl	Mean mg/dl	Obtained mean mg/dl ± SD	CV%
Precinorm-U	172101	1.04-1.52	1.28	1.29±0.018	1.39
Precipath-U	181948	3.20-4.64	3.92	3.93±0.075	1.92

Table-3: Showing comparison of the mean value of quality controls with obtained mean values in laboratory and day to day coefficient of variation during study period

with the concept of reference values as recommended by IFCC [5]. However hospital data when combined with the information of clinical database and or exclusion criteria can be used for the establishment of reference values [6, 7]. In light of these facts we have selected individuals from hospital data and estimated the reference intervals of Scr in different sex and age groups.

Materials and Methods

It was laboratory based retrospective study among adult individuals of central Nepal which comprise of population from Tarai, hill and surrounding areas, who had been sent to Clinical biochemistry department of College of Medical sciences and Teaching Hospital, Bharatpur, Chitwan for biochemical investigations from March to August 2011. A total of 1241 person's data were analyzed out of which 338 were excluded based on the exclusion criteria given in Table 1 and 2.

Table 1: *Exclusion criteria for defining reference individuals [8]

History of	Risk factors
Diabetes mellitus	Pregnancies,
Liver dysfunction	Strenuous exercise,
Hypertension or other cardiovascular abnormalities	Alcohol consumption and
Tuberculosis	Smoking
Acute inflammatory conditions	

*From National Committee For Laboratory Standards: how to define, determine and utilize reference intervals in the clinical laboratory; proposed guidelines (2000) 2nd edition, NCCLS document, Villanova PA, NCCLS

Table 2: Other exclusion criteria for defining reference individuals [1, 9]

Disease	Drugs that alter the creatinine
Muscular disorders	Nephrotoxic drugs
Autoimmune disorders	Drugs that alter systemic hemodynamics
Renal disorders	Drugs that alter Intrarenal hemodynamics
Cerebral vascular disorder	Drugs that interfere with tubular secretion of creatinine
Any obvious pathology	Drugs effect on creatinine measurement (Jaffe's method)

Age group (Years)	Sex	No	Min mg/dl	Max mg/dl	Mean± SD mg/dl	Obtained range mg/dl	P value
21-40	Male	140	0.5	1.4	0.926 ±0.172	0.58-1.26	<0.0001
	Female	193	0.3	1.2	0.763±0.161	0.45-1.07	
41-60	Male	182	0.6	1.6	0.960±0.178	0.61-1.30	<0.0001
	Female	174	0.4	1.3	0.804±0.167	0.47-1.13	
61-80	Male	98	0.5	1.6	0.951±0.186	0.59-1.32	<0.0001
	Female	116	0.4	1.4	0.795±0.197	0.41-1.18	
21-80	Male	420	0.5	1.6	0.946±0.178	0.60-1.30	<0.0001
	Female	483	0.3	1.4	0.785±0.173	0.45-1.12	

Table 4: Showing the reference range of Scr for male and female in different age groups

On the basis of physical examination, biochemical analysis and hematological profile of the patient, mentioned in patient's data records, the remaining 903 adults (21-80years) were considered as healthy subjects and this group was allocated into male and female for

calculation of reference intervals. The sample collection, serum separation and estimation of parameters were done under supervision of department of biochemistry. Creatinine in serum of all samples were estimated on Auto analyzer 902 (Roche/ Hitachi) by Jaffe's, rate blanked and compensated method by using same single batch/lot of reagent. All the kits, calibrators, and controls were supplied by COBAS-Roche/Hitachi Ltd, Mannheim, Germany. The machine was calibrated to assay creatinine in serum as manufacturer instructions with the Calibrator For Automated Systems (CFAS-universal). To ensure the accuracy and precision, commercially available controls precipath-U and precinorm-U were run every day in the morning as a part of routine checkup. The standard deviation and coefficient of variation were calculated accordingly in Table 3.

The reference intervals were derived from calculation of the 2.5^{th} – 97.5^{th} percentiles of the measured Scr concentrations as recommended in NCCLS guidelines [10]. The 97.5^{th} percentiles denoted upper reference limit and 2.5^{th} percentile denoted lower reference limit of the study population.

Reference range was calculated in age group 21-40, 41-60, and 61- 80 years for each sex separately. In order to see significance of the differences 'p value' were calculated by using Student 't' test in SPSS-16 package.

Table 5

Showing comparison between measured reference values and standard values of Scr for total male and female

Gender	Measured value (mg/dl)	Standard value (mg/dl)*
Male	0.60-1.30	0.70-1.20
Female	0.45-1.12	0.50-0.90

Results

Of the 903 selected patients, 420 were males and 483 were females. Table 4 shows the reference values of Scr in male and female in different age groups. The mean values of Scr were found to be less in females than males in all age groups which was statistically

significant (p value <0.0001). The difference between mean value of Scr in total males and total females was also significant (<0.0001). In both sexes, mean values were not showing increasing or decreasing trend with age.

Table 5 shows the comparison between observed values and standard values (*as per kit manufacturer recommendation Hitachi/ Roche Diagnostics, Mannheim, Germany) of Scr in male and female. The measured reference values in both males and females differed from standard values. The lower limit was 0.05-0.1 units less than standard limits and upper limit was 0.1-0.2 more than standard limits.

Discussion

Creatinine is produced non-enzymatically from creatine and phosphocreatine in skeletal muscles. Its excretion depends mostly on glomerular filtration, much less on tubular secretion. In this study we have taken Scr values from laboratory data for evaluating the reference range acceptable to our study population. The calculated reference intervals in male and female are 0.6-1.30 mg/dl and 0.45-1.12 mg/dl respectively. The lower limit for female and male are found to be respectively 0.05 and 0.1 units less than standard range while the upper limit were 0.1 and 0.2 units more than standard range for male and female respectively. Junge et al reported 0.72-1.16mg/dl for male and 0.55-0.96 mg/dl for female as calculated reference intervals by same Jaffe's compensated method [11]. A multicentre study performed in Spain gave similar results using Jaffe's compensated method [3]. Scr concentration varies in different population because of the fact that creatinine concentration is altered by its renal handling, its metabolism, analytical interferences in its measurement [1].

This rate blanked and compensated Jaffe's method in Hitachi system yields on average15% lower and 12% higher creatinine concentrations in normal serum and urine samples respectively. These effects result in significantly higher creatinine clearances than clearances measured by other conventional Jaffe's method [12]. In age group 41-60 years the calculated reference values are found to be highest for both male and female. We do not get increasing trend with age in both sexes as observed by other authors. Morgan et al quoted after reviewing many articles that in healthy population there was little increase in the average Scr with age. However, the frequency of renal disease increased with age so that, in unselected patients in hospital, the average Scr increased with age. There was progressive reduction in Glomerular function with age even in the patients without having clear-cut evidence of renal disease whose Scr didn't increased with age. The constancy of Scr in the face of a fall in Glomerular function was explained by a fall in creatinine production which was proportionally similar to the fall in Glomerular function [13, 1].

Statistically significant lower value is observed in female as compared to male in all the age groups. It is due to less muscle mass in female.

Conclusion

From our study we can conclude that there is slight variation in the calculated reference intervals of Scr as compare to the standard range. Female have lower reference interval than male and effect of aging on Scr level is not seen in both the sex.

As our study was based on hospital data, we are unable to show relation of other factors that influence the result, like diurnal variation [14], racial, socioeconomic, dietary habits, drugs and any hidden pathological conditions. Therefore, a wider population base study is required to make the study more significant.

Acknowledgement

The Author would like to thank Mr. D.K Singh and Mr. K.P.Mandal; senior laboratory technicians who had help them in running the tests during the course of study. Author would also like to thank Mr. N. Manandhar, Assistance Professor in Community Medicine of College of Medical Sciences for his help in statistical analysis.

References

1. Perrone R D, Madias NE, Levy AS. Serum creatinine as an index of renal function: new insight into old concepts. *Clin Chem* 1992; **38**: 1933-53,
2. Newman DJ, Christopher PP. Renal function and nitrogen metabolites. Burtis CA and Ashwood ER. Tietz Textbook of clinical chemistry. 3rd edition 1999 Philadelphia USA. W B Saunders Company, 1204-70.
3. Ceriotti F, Boyd JC, Klein G et al. Reference intervals for serum creatinine concentrations. Assessment of Available Data for Global Application. *Clin Chem* 2008; **54** :(3) 559-66.
4. Micheal Peake, Malcolm Whiting. Measurement of serum creatinine- current status and future goals. *Clinical Biochem Rev* 2006; **27**: 173-84.
5. International Federation of Clinical Chemistry, Expert Panel on Theory of reference values: Approved recommendation

on theory of reference values. Part 1. The concept of reference values. *J. Clin. Chem. Clin. Biochem* 1987; **25**: 337-42. Part 2. Selection of individuals for the production of reference values. *J. Clin. Chem. Clin. Biochem* 1987; **25**: 639-44.

6. Kouri T, Kairisto V, Virtanen A et al. Reference intervals developed from data for hospitalized patients: Computerized method based on combination of laboratory and diagnostic data. *Clin. Chem* 1994; **40**: 2209-15.
7. Solberg H E. Using a hospitalized population to establish reference intervals: Pros and cons. *Clin Chem* 1994; **40**: 2205-6.
8. Verma M, Khadapkar R, Sahu PS et al. Comparing Age-wise reference intervals for serum creatinine concentration in a reality check of the recommended cut-off. *IJCB* 2006; **21**: (2) 90-4.
9. Lory .J. Sokoll, Russel RM, Sadowski JA et al. Establishment of creatinine clearance reference values for older women. *Clin Chem* 1994; **40**: (12) 2276-81.
10. National committee for clinical laboratory standards: how to define, determine and utilize reference intervals in the clinical laboratory: proposed guidelines. NCCLS document C 28-A2. 2nd edn 2000 Villanova PA, NCCLS.
11. Junge W, Wilke B, Halabi A et al. Determination of reference intervals for serum creatinine, creatinine excretion and creatinine clearance with an enzymatic and a modified Jaffe method. *Clin Chim Acta* 2004; **344**: 137–48.
12. Mazzachi BC, Peake MJ, Ehrhardt V. Reference range and method comparison studies for enzymatic and Jaffe creatinine assays in plasma and serum and early morning urine. *Clin Lab* 2000; **46**: 53-5.
13. Morgan DB, Payne RB, Dillon S. The assessment of Glomerular function creatinine clearance or plasma creatinine. *Post Graduate Medical Journal* 1978; **54**: 302-10.
14. Doolan PD, Alpen EL, Theil GB. A clinical appraisal of plasma concentration and endogenous clearance of creatinine. *Am J Med* 1962; **32**: 65-79.