

ORIGINAL ARTICLE

*Effect of Hemodialysis on Urea Reduction Ratio, Serum Electrolytes, Calcium, Phosphorus and Bicarbonate in Chronic Kidney Disease Patients*K. Durga Sowmithri¹, M. Rasheed Khan¹, Thivyahprabha AG² and Gokul Kumar K³^{1,2} Department of Biochemistry, ³Department of Community Medicine¹Srinivasan Medical College & Hospital, Dhanalakshmi Srinivasan University, Tiruchirapalli, Tamil Nadu-621112, India.^{2,3} St. Peter's Medical College Hospital & Research Institute, Hosur, Tamil Nadu-635109, India.**Abstract:**

Background: Accumulation of fluid, toxins and electrolytes in end stage renal disease, represents the terminal stage (stage 5) of Chronic Kidney disease (CKD). Hence the toxins have to be removed by the renal replacement therapy like dialysis or kidney transplantation. **Aim and Objective:** To evaluate the effect of hemodialysis on urea reduction ratio, serum electrolytes, bicarbonate, calcium and phosphorus in CKD patients. **Material and Methods:** This cross-sectional observational study was carried out on 100 CKD patients, attending the outpatient department of nephrology for dialysis. The study participants included both males and females of age ≥ 18 years. Informed consent was obtained from the participants. Under strict aseptic precautions, 2.5 ml of venous blood was obtained immediately before and after the dialysis session in clot activator tubes. It was used for the estimation of urea, creatinine, electrolytes, bicarbonate, calcium and phosphate. **Results:** There was a significant decrease in serum urea, creatinine, potassium and phosphorus before and after hemodialysis. The value of sodium and bicarbonate were significantly increased in post dialysis sample. No significant association was observed between the sociodemographic features and the urea reduction ratio. **Conclusion:** Thus, the urea reduction ratio is the significant marker of adequacy of hemodialysis and monitoring of serum electrolytes, calcium, phosphorus and bicarbonate have an important role as prognostic markers among CKD patients on hemodialysis.

Keywords: Chronic kidney disease, Urea reduction ratio, Hemodialysis, Electrolytes.

Introduction:

Kidneys play an important role in the maintenance of

internal milieu. They carry out the excretion of metabolic waste products and are involved in the regulation of water, electrolyte and acid-base balance.^[1] In addition, they also perform a few metabolic and endocrine functions; disturbances in any of these functions can adversely affect the health of an individual. A decrease in or absence of kidney function leads to a number of maladaptive changes including retention of fluid in the extracellular compartment, anemia, increase in blood pressure, altered bone and mineral metabolism, dyslipidemia, and protein energy malnutrition.^[2] The most sensitive and specific measure of renal function is the glomerular filtration rate. Glomerular filtration rate (GFR) decreases with a decline in renal function. When the GFR falls below $60 \text{ mL/min/1.73m}^2$, signs and symptoms of kidney dysfunction will invariably be observed. When the GFR is $< 15 \text{ mL/min/1.73m}^2$ the individual is said to be suffering from kidney failure. End-stage renal disease (ESRD) is defined as an irreversible decline in kidney function, which is severe enough to be fatal in the absence of renal replacement therapy.^[3] In 2022, the global prevalence of CKD was reported to be 10% which is roughly > 800 million cases.^[4] A substantial increase was reported in age – standardized incidence of ESRD. Recent studies have estimated that the age-adjusted incidence rate of ESRD in India to be 229 million population, $>100,000$ new patients enter renal replacement therapy programs annually in India.^[5] Renal replacement therapy includes dialysis procedures and renal transplantation. While renal transplantation is the most effective form of renal replacement therapy, the most commonly used one is hemodialysis.^[6] Worldwide approximately two-thirds of people with ESRD receive hemodialysis, while one quarter have kidney transplants, and one tenth receive peritoneal dialysis.^[7] Assessment of adequacy of hemodialysis includes estimation of the clearance of small solutes urea and creatinine. In routine clinical practice an estimate of dialysis adequacy is obtained by

calculating the urea reduction ratio. It has been shown to be a significant predictor of mortality in ESRD patients.^[8] About 90% of ESRD patients are hypertensive at the start of dialysis and sodium is the major determinant of hypertension.^[9] Hyperkalemia is a serious and potentially life-threatening electrolyte imbalance among patients with ESRD under maintenance hemodialysis. Patients with end-stage renal disease also suffer from metabolic acidosis.^[10] Hyperphosphatemia is a feature of ESRD. Higher levels of serum phosphorus (P) and calcium-phosphorus (Ca x P) product have been shown to be associated with increased vascular calcification and cardiovascular mortality.^[11]

Aim and Objectives:

The aim of the study was to evaluate the adequacy of hemodialysis based on urea reduction ratio and to study the levels of serum electrolytes, calcium, bicarbonate and phosphorus in a CKD patient. The objectives were to determine the urea reduction ratio with regards to the adequacy of dialysis and to find out the difference between the pre- and post-hemodialysis serum sodium, potassium, bicarbonate, calcium and inorganic phosphate concentrations in the serum of CKD patients.

Material and Methods:

This cross-sectional prospective observational study was carried out by the Department of Biochemistry and included CKD patient attending the department of nephrology for dialysis, over a period of one year from June 2018 to May 2019. The study included both males and females of age ≥ 18 years by convenient sampling technique during the study period. These patients underwent twice weekly hemodialysis of 3 hours individual duration.—Hundred CKD patients were included in the study. The sample size was calculated using formula with relative precision as 12% of prevalence based on the study by Aniq et al.^[12] The study was approved by the Institutional ethical committee. Informed consent was obtained from the participants. After registering the patient for this study, a brief history of presence of comorbidities like diabetes, hypertension were noted. Personal history was elicited including the habit of smoking and alcohol abuse. Treatment history was also recorded. General examination and systemic examination of the cardiovascular system, respiratory system, central nervous system and abdomen was carried out. Under strict aseptic precautions, 2.5 ml of venous blood was

obtained immediately before and after the dialysis session in clot activator tubes. The samples were allowed to clot for the serum to separate out. The serum samples were used for the estimation of urea, creatinine, electrolytes, calcium and phosphate. Electrolytes were measured using the AVL 9180 electrolyte analyzer while the remaining parameters were assayed using the fully automated analyzer Cobas C311. Serum urea was analyzed by kinetic test with urease and glutamate dehydrogenase method, Serum creatinine was analysed by Compensated Jaffe's method, Serum sodium and potassium was measured by direct ISE (Ion Selective Electrode) method, serum bicarbonate by enzymatic phosphoenolpyruvate method, serum calcium was analysed by 5-nitro-5'-methyl-BAPTA (NM-BAPTA) method and serum phosphorous was analysed by molybdate UV method. Urea reduction ratio (URR) was calculated by $[(\text{Post-dialysis urea} - \text{Pre dialysis urea}) / \text{Pre dialysis urea}] \times 100 \%$.—Calcium - Phosphate product by $\text{Ca} \times \text{Pi} = \text{Serum total calcium} \times \text{Serum inorganic phosphate (mg}^2/\text{dL}^2)$ Hemodialysis was carried out using the Fresenius machine for a duration of 3 hours. The data collected was analyzed using SPSS 26 version. Paired t test was used for the comparison of variables and p value < 0.05 was considered as significant. Association among the variables was analyzed by chi-square test and p value < 0.05 was considered as significant.

Results:

This study had been carried out in 100 subjects. Table 1 explains the socio-demographic features of the study participants. The mean age of the study participants was 47.9 years. The participants included patients as young as 23 years and as old as 73 years. Table 2 provides the Mean, SD and paired sample t values obtained for the concentration of variables in the pre-dialysis and post-dialysis serum specimens. In the pre-dialysis samples the mean serum urea and creatinine concentration were high, 109.1 mg/dL and 9.557 mg/dl respectively, which was expected in CKD patients. The mean serum sodium concentration was 137.060 mmol/L. The mean serum potassium concentration was 5.170 mmol/L which was slightly above the reference interval while the serum bicarbonate concentration was 17.521 mmol/L. The mean serum calcium and inorganic phosphate were slightly low and slightly high with the mean values being 8.137 mg/dL and 4.856 mg/dL respectively. The mean serum total calcium phosphate product was 39.193

mg²/dL². The mean serum creatinine concentration was 3.969 mg/dL. The mean serum sodium concentration had undergone a slight increase after dialysis to 138.730 mmol/L. While the mean serum potassium concentration had decreased to 3.335 mmol/L, the mean serum bicarbonate concentration had increased to 25.290 mmol/L following dialysis. Dialysis did not seem to change serum calcium concentration much whereas it had decreased the serum inorganic phosphate concentration to 2.558 mg/dL which was reflected in the mean product of serum total calcium inorganic phosphate. As it is evident, the differences were statistically significant for all the variables except serum calcium. The urea reduction ratio mean and standard deviation were 65.7 % and 11.98%. 45% percentage of patients were in 61-70% URR, 15% percentage of patients were in 71-80% URR, 10% percentage of patients were in 81-90% URR, 8% percentage of patients were in 91-100% URR, 10% percentage of patients were in 41-50% URR and 20% percentage of patients were in 51-60% URR. Table 3 shows the association between the sociodemographic features and the urea reduction ratio. There was no statistical significance among the sociodemographic features of the study subjects and the urea reduction ratio.

Table 1: Sociodemographic behavior of study participants

Characteristics	Total N(%)
Gender of patients:	
Male	67(67)
Female	33 (33)
Age group(years) :	
18-30	35 (35)
31-50	47(47)
51-75	18 (18)
Educational Background:	
No formal education	3 (3)
Primary education	19 (19)
Secondary education	13 (13)
College & above	65 (65)
Smoking status:	
Non smoker	54 (54)
Former smoker	31(31)
Currently smoker	15(15)
Alcohol drinking status:	
Yes	69 (69)
No	31 (31)
History of Diabetes mellitus:	
Yes	4(4)
No	96(96)

History of Hypertension:	
Yes	19(19)
No	81(81)

Table 2: Mean and SD and Paired sample t values in the pre-dialysis and post-dialysis

Variable s	Pre-dialysis		Post-dialysis		Paired Differences		P value
	Mean	SD	Mean	SD	Mean	SD	
Urea (mg/dl)	109.1	24.6	37.09	14.0	72.0100 (67.9624-76.0576)	20.39	0.000
Creatinine (mg/dl)	9.557	2.79	3.96	1.58	5.5880 (5.1205 - 6.0555)	2.35	0.000
Sodium (mmol/L)	137.06	3.74	138.73	3.14	-1.6700 ([-2.5292]-[-0.8108])	4.33	0.000
Potassium (mmol/L)	5.170	0.87	3.33	0.50	1.8350 (1.6489 - 2.0211)	0.93	0.000
Bicarbonate(mmol/L)	17.521	3.32	25.2	2.28	-7.7690 ([-8.5107]-[7.0273])	3.73	0.000
Calcium (mg/dl)	8.137	0.89	8.33	1.0	-0.1960 ([-0.4214]-[0.0294])	1.13	0.088
Inorganic-phosphate (mg/dl)	4.856	1.49	2.55	0.9	2.2980 (0.1465-2.0073)	1.46	0.000
Total calcium phosphate product (mg ² /dL) ²	39.193	13.1	21.3	8.2	17.841 (1.257-15.346)	12.57	0.000
p-value < 0.05 is considered as statistically significant							

Table 3: Association between the sociodemographic factors with urea reduction ratio

Variable	p-value
Age	0.632
Gender	0.247
Education	0.567

Smoking	0.622
Alcohol	0.887
Diabetes mellitus	0.824
Hypertension	0.697

Discussion:

The pre-dialysis serum urea concentration of the subjects was high ranging from 46 mg/dL to 178 mg/dL with a mean value of 109 mg/dL. In a 2017 study done on patients in the southern part of the state the mean pre-dialysis serum urea concentration was reported to be 138.44 ± 49.31 mg/dl in 21 to 40 years; 133.98 ± 36.41 mg/dl in 41 to 60 years; 130.58 ± 23.11 mg/dl in 61-80 years.^[13] The variations observed between our study and these studies could well be due to differences in the frequency and duration of the hemodialysis sessions. Dietary habits of patients might also be a reason since it has been observed that green leafy vegetables and meat might lead to an increase in serum urea and creatinine level.^[14] The pre-dialysis urea (mean \pm S.D.) level was 142.3 ± 46.5 in the study of V. Sunanda et al carried out on ESRD patients on chronic hemodialysis. The size of the sample was less in this study (35 patients) and it included only those on thrice weekly hemodialysis.^[15] After dialysis, the serum urea concentration decreased in all the patients. The post dialysis urea concentration ranged from 16.0 mg/dl to 109 mg/dL with a mean of 37.090 mg/dL. The decrease was found to be statistically significant. The mean decrease in the serum urea concentration was 72 mg/dL and it ranged from 28 mg/dL to 123 mg/dL. Several studies have also reported a significant decrease in serum urea concentration after dialysis.^[16] The average urea reduction ratio in this study was 65.84%. The Kidney Disease Outcomes Quality Initiative [KDOQI] guidelines recommend that the minimally adequate dose of HD given 3 times per week to patients with Kr less than 2 mL/min/1.73 m² should be an spKt/V (excluding RKF) of 1.2 per dialysis. For treatment times less than 5 hours, an alternative minimum dose is a URR of 65%.^[17] Hence the average dose of dialysis in patients who participated in our study is hence adequate. Various studies have reported a URR of 66.3%, 66.4, 67.1% and 72%. The URR values achieved in the subjects of the present study varied from as low as 22.70% to 84.40%.^[18] A Sudanese study had reported that neither the type of permanent vascular access nor the ultrafiltration volume during HD significantly influenced the adequacy of urea clearance. However the number of weekly HD sessions, blood flow rate, dialysis hours, patients' dry weight and the presence of intra-dialytic complications statistically influenced the URR. The residual renal function of the patients also

seems to affect the URR. Adequate URR was achieved in a significantly higher percentage of patients with residual renal function and in those who underwent thrice weekly hemodialysis.^[19] URR also appears to be influenced by the dialyzer surface area with more adequate hemodialysis being seen when the surface area of the dialyzer was ≥ 1.4 m². In the current study the dose of dialysis was adequate in 57% of the patients which is higher than the percentage reported in Sudanese study and the Tanzanian study (34.3%). An Indian study had reported that out of 400 hemodialysis sessions only 112 sessions (28%) met the K DOQI guidelines. But in that study, it was not URR rather Kt/V which was used to assess the dose of dialysis. The mean pre-dialysis sodium concentration in the subjects studied was 137.1 mmol/L and it ranged from 131 mmol/L to 145 mmol/L. After dialysis the mean concentration increased slightly to 138.7mmol/L with the range being 129 mmol/L to 145 mmol/L. The mean pre-dialysis sodium concentration was 137.4 in a 2017 Canadian study.^[21] In another study, mean pre-HD Na⁺ concentration was 136.7mmol/L. During dialysis sodium gets removed from blood mostly by convection (78%) and to a lesser extent by diffusion (22%).^[22,23] The post-dialysis serum sodium concentration depends on the tonicity of the fluid removed by hemodialysis. It is also influenced by the dialysate sodium concentration. Flanigan found a positive sodium gradient from dialysate to blood in more than 3/4th of 120 patients with a predialytic natremia of 137 ± 4 mEq/L and a sodium dialysate concentration of 140 mEq/L. Flythe et.al^[24] also have reported predialytic natremia between 139 and 140 mEq/L related to a positive sodium gradient between dialysate and blood in more than 40% of the patients when dialysate sodium was 140 mEq/L and in more than 20% when the dialysate sodium was 138 mEq/L. While using a higher dialysate sodium offers the potential benefits of hemodynamic stability it is outweighed by increased thirst, higher IDWG, and higher pre-dialysis blood pressure (pre-BP).^[24] Keen and Gotch found that a 2–10 mEq rise in sodium gradient from dialysate to blood causes an increase in sodium gained from the dialysate thereby increasing the patient's sodium load. Though a dialysate with lesser sodium concentration compared to serum can increase the amount of sodium removed by diffusion and thereby have a beneficial effect with regards to blood pressure elevation and interdialytic weight gain, it carries with it an increased risk of intradialytic hypotension. The right choice of dialysate sodium concentration remains controversial.^[25] Various dialysate sodium concentrations have been used throughout the history of dialysis. Our Institution uses a standard dialysate concentration of 134 mmol/L. The

dialysate sodium concentration used by much dialysis centers around the world also seems to be a standard one for all patients; It has been reported that 57% of hemodialysis facilities use a standard dialysate sodium concentration. It is now suggested that each dialysis patient may have a unique osmolar set point for plasma sodium that requires individualization of dialysate sodium. Online measurement of plasma conductivity and using it to adjust dialysate conductivity have made individualization of dialysate sodium concentration possible.^[26] In the present study pre-dialysis serum potassium concentration had a mean of 5.170 mmol/L and ranged between 3.2 mmol/L and 7.1 mmol/L. A 2007 study had shown a similar mean pre-dialysis serum potassium concentration of 5.2 mmol/L. A pre-dialysis serum potassium of 4.6 to 5.3 mEq/L has been reported to be associated with the greatest survival in maintenance hemodialysis patients.^[27] Dialysis Outcomes and Practice Patterns Study (DOPPS) came up with the finding that the lowest risk of death among patients with pre dialysis serum potassium levels between 4 and 5.5 mEq/L. A high-normal serum K level could offer a survival advantage by being less arrhythmogenic. Hyperkalemia has been shown to be associated with higher mortality in dialysis patients.^[28] It has also been reported that hyperkalemic patients who undergo maintenance hemodialysis against lower dialysate bath may have better survival. The post dialysis mean serum potassium concentration had declined significantly to 3.3 mmol/L in the current study. Potassium removal during hemodialysis occurs both via diffusive (85%) and convective (15%) clearance. The potassium removed is from the extracellular fluid compartment, which contains only 2% of total body potassium. A typical dialysis treatment removes 70–100 mEq of potassium. The amount of potassium removed is largely a function of the serum-dialysate potassium gradient with the highest rate of potassium decline occurring in the first hour. The gradient is largest during this period. This is followed by a more gradual decline over next 2 hours. During the final hour, serum potassium levels remain steady despite diffusive clearance still occurring which indicates an equilibrium between the rates of potassium removal and the rate of re-equilibration from intracellular space.^[29] Increases in serum bicarbonate levels during a dialysis treatment can further lower serum potassium levels during HD by causing an intracellular shift of potassium.^[30] Haemodialysis is currently the main way to provide bicarbonate and control acidosis in ESRD patients. In our study the mean pre-dialysis serum bicarbonate concentration was 17.5 mmol/L. Many studies have reported a higher

bicarbonate concentration before dialysis. The target serum bicarbonate recommended by the KDOQI51 is at least 22 mEq/L immediately before a haemodialysis session. It does not specify if the number refers to the first dialysis session of the week or a midweek one.^[31] From 2001 to 2006 at one large dialysis provider, 40% of patients receiving haemodialysis had a time-averaged pre dialysis serum bicarbonate less than 22 mEq/L.^[32] In our study it was greater with only 13 patients having a serum bicarbonate concentration of at least 22 mmol/L. This is lesser than the percentage reported in Filiopoulos et.al study.^[33] Serum bicarbonate levels are lower with higher interdialytic weight gain and longer dialytic interval. Phosphate binders containing alkali precursors increase serum bicarbonate while the use of sevelamer hydrochloride reduces serum bicarbonate.^[33] The predialysis bicarbonate concentration may be associated with survival. A recent review had reported best survival with bicarbonate before the mid-week session between 18 and 21 mEq/L. In general, patients being dialyzed against a high-bicarbonate bath do have higher predialysis bicarbonate levels. The dialysate bicarbonate concentration varies widely between countries with values ranging from 32.2 ± 2.3 mEq/L in Germany to 37.0 ± 2.6 mEq/L in the United States.^[34] In our study the dialysate bicarbonate concentration was 30 mmol/L. The best concentration of dialysis bath bicarbonate is yet to be established. Ideally the dialysate bicarbonate concentration should be individualized.^[35] As shown in a study by Noh et.al.^[36]—the mean serum bicarbonate concentration increased significantly after dialysis and it was 25.3 mmol/L. The change in serum bicarbonate during hemodialysis correlates with the dialysate–serum bicarbonate gradient and relates inversely to the predialysis so patients with the highest levels at the initiation of treatment experience modest increases.^[36] In the present study the mean Ca x P was $39.1 \text{ mg}^2/\text{dL}^2$ before dialysis and $21.3 \text{ mg}^2/\text{dL}^2$ after dialysis. K DOQI guidelines recommend that the serum calcium-phosphorus product should be maintained at $<55 \text{ mg}^2/\text{dL}^2$. Only 11 patients in our study had a C x P value of $55 \text{ mg}^2/\text{dL}^2$ or more.^[37] This is lower than the percentage quoted by other studies. DOPPS I and DOPPS II had mentioned that 43.3% and 38.6 of patients respectively had higher Ca x P values. A Korean study had reported a percentage of 29.3 while it was 41.1 in J-DOPPS. In an Italian study 35.5% of patients' Ca x P values did not meet the guidelines. It has been suggested that high levels of Ca x P product can cause vascular calcification.^[38] There is no statistical significance in the current study among the diabetics and urea reduction ratio but in a study by Yu.et.al there were more female diabetic patients diagnosed with CKD due to the

imbalanced sex hormones in females.^[39] Good blood sugar control and HbA1c control have association with the adequacy of hemodialysis.^[40]

Conclusion:

The average URR was found to be 66% reflecting an adequacy of the hemodialysis as per the guidelines of NFK-KDOQI. URR being a simple test to be done periodically to know the adequacy of hemodialysis on all patients. The interpretation of abnormal values of

calcium, phosphorus and electrolytes on routine analysis may be useful in initiating important clinical interventions and have prognostic significance in end stage renal disease. It is important to consider pre-dialytic electrolytes and dialysate to be altered according to the electrolytes for every patient to prevent

Sources of supports: Nil

Conflicts of Interest: Nil

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