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Original Research Article

Assessment of Blood Urea Nitrogen (BUN) and Creatinine As Biochemical Markers in Chronic Kidney Disease and End Stage Renal Disease Patients Undergoing Hemodialysis

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Abstract

Chronic Kidney Disease (CKD) is a progressive diminution in renal function especially in normal excretory and regulatory functions of the kidney. Kidney function is assessed in clinical practice to screen for kidney diseases. It is of prime importance to evaluate kidney function as accurately as possible due to different clinical presentations during the cource of the disease which are often asymptomatic. Evaluation of biochemical markers like serum BUN, creatinine, BUN:Cr ratio and ALP could play an important role in accurate diagnosis and in assessing risk of renal failure that could assists in adopting therapeutic strategies to minimize the mortality rates associated with renal failure. Keeping in view, one hundred patients with varying degree of renal disease categorized as mild, moderate and End stage renal disease (ESRD) were enrolled in the present study. Serum levels of BUN, creatinine, uric acid and ALP were measured and analysed statistically by SPSS software. Males had higher levels of BUN, Creatinine, uric acid compared to females. Serum levels of these markers were found to increase significantly ($P<0.05$) from mild to moderate CKD to ESRD patients. Thus, indicating role of BUN:Cr ratio as efficient prognostic marker in diagnosis of renal failure. Also pre-dialysis and post-dialysis evaluation of these markers done in ESRD patients resulted in significant decrease in these markers following dialysis. Hence, confirming dialysis as an efficient renal replacement therapy in patients with ESRD.

Keywords: Blood Urea Nitrogen (BUN), Creatinine, Chronic kidney disease (CKD), End stage renal disease (ESRD), Dialysis.

INTRODUCTION

Chronic kidney disease (CKD) is emerging as a serious health problem globally. CKD is characterized by an irreversible damage of kidney function that gradually progresses to end-stage renal disease (ESRD) which then requires a renal replacement therapy in the form of dialysis or a kidney transplant [1,2]. Kidneys are the main organ responsible for removal of metabolic wastes and excess water from the body. Abnormal functioning of kidney leads to serious complications like CKD or the renal failure. It is the systemic disease with slow loss of kidney function and progressively gets worsened over time. The symptoms of kidney damage are inconspicuous and sometimes even leads to direct kidney failure. It has become a serious public health problem. CKD is defined as decrease in kidney function with a glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m2 and/or kidney damage for 3 or more. Kidney damage is evaluated based on diagnoses of biopsy, alterations in urinary sediment or proteinuria (proteinuria/creatinuria > 200 mg/g, albuminuria/creatinuria > 30 mg/g) [3]. CKD in contrast to acute renal failure, occurs gradually over a period of weeks, months or years and as the kidneys slowly stop working, leading to an end-stage renal disease (ESRD) [4]. At this stage, the kidneys are no longer able to remove enough wastes and excess fluids from the body. Patients with ESRD require renal replacement therapy in the form of dialysis either hemo- or peritoneal dialysis. Under adverse conditions, kidney transplantation is the only therapy [2]. The incidence and prevalence of ESRD are increasing worldwide. In Saudi Arabia, the incidence and prevalence of ESRD have increased in the last three decades inevitably due to rapid changes in lifestyle, urbanization, and increase in population size. The prevalence of CKD in the young Saudi population is around 5.7% [5]. Treatment of around 15,782 dialysis patients in 187 dialysis centers had been reported in the Kingdom of Saudi Arabia. Among which 513 were cases of end stage renal failure per million population [6].There are numerous causes underlying CKD. One of the main cause is the high blood pressure. In addition to these, many other factors are responsible that results in loss of normal excretory functions which can be due to infections, autoimmune diseases, diabetes,

hypertension, cancer and toxic chemicals, other endocrine dysfunction, autoimmune disorders like systemic lupus erythrematosus, congenital defects and certain malignancies [2].

Chronic renal failure occurs progressively slow and asymptomatically and patient requires a long treatment in the form of renal replacement therapy. Haemodialysis is one of the renal replacement therapy. In this technique body waste product like urea, creatinine and free water are removed from the blood, when the kidneys are impaired. The principle of hemodialysis is the diffusion of solutes through a semi permeable membrane [7]. It is important to assess kidney function as accurately as possible as renal disease has different clinical presentations and as patients are often asymptomatic. The progression of kidney damage is marked by the rise in two important chemical substances in the blood -creatinine and urea whose evaluation in serum helps to assess Glomerular Filtration Rate (GFR).GFR is a useful index and the most important marker to assess the kidney function [8]. Unfortunately GFR cannot be easily measured in most clinical or research settings. Creatinine, urea and uric acid are non-protein nitrogenous metabolites that are cleared from the body by the kidney following glomerular filtration [9]. Measurements of plasma or serum concentration of these metabolites are commonly used as indicators of kidney function and other conditions. Therefore, analysis of these serum markers reflects the status of kidney function and assist in evaluating these as efficient biomarkers in patients with CKD and ESRD patients undergoing hemodialysis.

One of the major metabolic product of protein is the creatinine. It is formed in muscles and later is expelled out with other waste products through kidneys. Kidney as a result is involved in maintenance of the levels of various metabolites like urea, creatinine, uric acid, etc. In the blood approximately 2% of the body's creatine is converted into creatinine per day, resulting in the daily generation of creatinine at a fairly constant rate (male: 20 to 25 mg/kg/day; female 15 to 20 mg/kg/day) [10]. The levels of creatinine in serum depends on their generation, glomerular filtration and tubular secretion of serum creatinine [11]. Another important determinant of kidney function is urea, an organic compound and waste product from metabolism of proteins and is also filtered into urine by the kidneys and plays a vital role in the metabolism of nitrogen-containing compounds. Blood Urea Nitrogen (BUN) is a normal waste nitrogen product found in blood that comes from the breakdown of protein from foods. Healthy kidneys remove urea nitrogen from blood, but the level of urea in blood rises in kidney failure [12]. A recent data published in Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommended evaluation of alkaline phosphatase (ALP) in CKD stages 4 and 5 [13]. Fewer studies had examined the associations of ALP with mortality, its relationship with progression of kidney disease is unclear. We hypothesized that higher ALP levels are associated with an increased risk for ESRD.

The present study was undertaken to speculate changes in the biochemical parameters such as BUN, creatinine, uric acid and ALP in serum of patients with mild CKD, moderate CKD and ESRD which could help in early diagnosis of CKD. An attempt has been made to evaluate the levels of these markers in ESRD patients during pre and post hemodialysis to ascertain the role of BUN:Cr ratio and ALP as an index of renal damage.

MATERIALS AND METHODS

This cross sectional study was conducted from October 2014 to January 2015, in Department of Clinical Laboratory Sciences, King Saud University in collaboration with King Fahad Kidney Centre, King Saud Medical City Hospital, Riyadh. The study was approved by hospital's ethics committee. Informed consent was obtained from patients before blood sampling. Depending upon the baseline parameters and physician diagnosis 150 subjects were selected and divided into three groups-Mild CKD (n=25), Moderate CKD (n=25) and Severe CKD/ESRD (n=50).Subjects were screened and patients with diabetes females with pregnancy, cardiovascular damage, cancer, liver disease, history of chronic alcohol abuse or organ transplantation specially kidney were excluded from the study.

Sample Collection and Laboratory Investigations

On admission, five milliliter of blood was drawn from each subject participated in the study in metal free sterile vacutainers. Blood samples obtained were then kept at room temperature for 30 min and centrifuged at 3000 rpm for 15 min to extract the serum for further biochemical investigations. The serum samples were transferred in eppendorf tubes and stored at -80 ºC until analysis. The blood samples were collected from ESRD patients before and after hemodialysis. All the biochemical parameters were determined in the biochemical analyzer, COBAS INTEGRA Autoanalyzer 800 (Roche, Germany). Serum Uric acid was measured by enzymatic colorimetric test ver., 2. Creatinine concentration was determined based on Jaffes reaction. Blood urea nitrogen (BUN) was measured using Urease test.Alkaline phosphatase (ALP) was measured using IFCC liquid ver., 2.

Statistical Analysis

The results were expressed as Mean ± S.D. Statistical analyses were performed using SPSS software. Comparison of clinical characteristics and biochemical parameters among the groups was performed by one - way ANOVA. The correlation between BUN:Cr ratio and ALP was performed by Pearson's correlation coefficient. $P < 0.05$ was considered to be statistically significant.

RESULTS

A total of 100 patients based on diagnosis and level of the severity of CKD, were grouped into 3 groups- mild CKD, moderate CKD and severe CKD / ESRD with 25 participants each in mild and moderate CKD group and 50 in ESRD group respectively. There were 53 males and 47 females in the age group of 21 to 85 years. Mean values of serum FBG, BUN, Creatinine and ALP in mild CKD, moderate CKD and severe CKD or the ESRD group are shown in Table 1 and 2. The levels of SBP (systolic blood pressure) and DBP (diastolic blood pressure) increased significantly from mild to ESRD. Values with same superscript are significant at p<0.001 and * at p < 0.05. Serum levels of creatinine was found to increase significantly in moderate and ESRD group compared to mild CKD (p<0.001). Like serum creatinine, serum levels of BUN and BUN:Cr ratio were found to increase significantly in moderate and ESRD group compared to mild CKD at P<0.001 level of significance (Figure-1). One way ANOVA showed overall significance at p<0.001 in changes in serum creatinine, BUN and BUN:Cr ratio among the cases. Additionally, serum levels of uric acid was found to increase significantly in moderate and ESRD group compared to mild CKD at P<0.05.To evaluate the status of these serum markers in ESRD patients, these patients were subjected to biochemical analysis before and after dialysis. The data obtained is represented in Table-3. There was marked change in the levels of serum creatinine and BUN in ESRD patients following dialysis (P<0.001). On contrary, there was no significant change in level of serum ALP following dialysis. Furthermore, status of biochemical markers studied in ESRD group in both gender before and after dialysis are shown in Table-4. It was found that males had higher levels of these markers compared to females in ESRD. Similar pattern of result was obtained after dialysis in both genders. To evaluate the correlation between BUN:Cr and ALP in ESRD, Pearsons correlation "r" was performed. It was found that BUN:Cr was positively correlated with ALP (before dialysis r=-0.08,p=0.56;after dialysis r=0.14, p=0.32). However, there was no significant correlation in the levels of ALP before and after dialysis with BUN:Cr in ESRD patients.

Table-1: Baseline Characteristics and Biochemical Investigations in Study Population

	Mild CKD (n=25)	Moderate CKD (n=25)	End stage renal disease-ESRD (n=50)	p value
Age(years)	25-85	26-82	21-72	
SBP(mmHg)	114.66 ±10.83	120.7 ±18.21	169. 0 ±25.53	<0.001
DBP(mmHg)	69.86 ±9.38	84.45 ±18.15	99.50 ±10.28	<0.001
FBG(mmol/L)	5.64±2.15	6.83±2.92	7.93±3.5	<0.05
Serum Creatinine(µmol/l)	231.83 ± 100.2	613.35 ± 230.4	897.94 ± 227.73	<0.001
BUN (mmol/L)	15.83 ± 7.29	25.49 ± 9.87	23.64 ± 6.13	<0.001
BUN:Cr ratio	26.99± 9.66	42.74 ± 22.3	62.92± 23.7	<0.001
Serum ALP(U/L)	105.27±30.96	140.12±45.94	400.18±58.9	<0.05
Serum Uric acid	421.25±105.82	446.17±99.94	489.05±68.3	<0.05

Mean±SD values of each group, at P value <0.0001, <0.05

Table-2: Comparison of the Clinical Characteristics between the three groups

	Mild with Moderate CKD		Moderate CKD with ESRD		Mild CKD with ESRD	
	t	p	t	p	t	p
FBG	1.36	0.17	1.44	0.28	3.01	< 0.01*
Creatinine	6.5	<0.001[a]	5.68	< 0.001[a]	13.29	< 0.001[a]
BUN	4.54	< 0.001[a]	1.00	0.31	4.24	< 0.001[a]
BUN:Cr	4.05	< 0.001[a]	3.65	< 0.001[a]	8.33	< 0.001[a]
ALP	0.29	0.77	2.52	0.026*	2.86	0.015*
Uric acid	2.00	0.09	1.01	0.31	3.17	0.006*

Values with same superscript are significant at p<0.001 and * at p < 0.05

Table-3: Comparison of Biochemical Parameters before and after Dialysis in ESRD group

	Before Dialysis	After Dialysis	t	p value
Creatinine	897 ± 227.73	341 ± 115.1	15.43	<0.001
BUN	22.89 ± 6.4	7.52 ± 3.18	15.25	<0.001
BUN:Cr ratio	26.99± 9.66	20.86± 8.00	3.45	<0.001
Serum ALP(U/L)	398.14±59.8	270.90±18.3	0.15	NS

Table-4: Status of Biochemical Parameters in both genders

	Before Dialysis		After Dialysis	
	Male	Female	Male	Female
Creatinine	980.98 ± 226.68*	814.90 ± 200*	397.89 ± 100.03[a]	284.32±98.62[a]
BUN	23.68 ± 5.6[a]	22.11 ± 7.26[a]	7.52 ± 2.45[a]	6.98±3.8[a]
BUN:Cr ratio	30.55± 9.49 [a]	23.42 ± 8.6 [a]	22.72± 8.27 [a]	19.00±7.41 [a]
Serum ALP(U/L)	461.88±62.53	334.0±71	282±227.4	258.96±130.0

Values with same superscript are significant at p<0.001 and * at p < 0.05

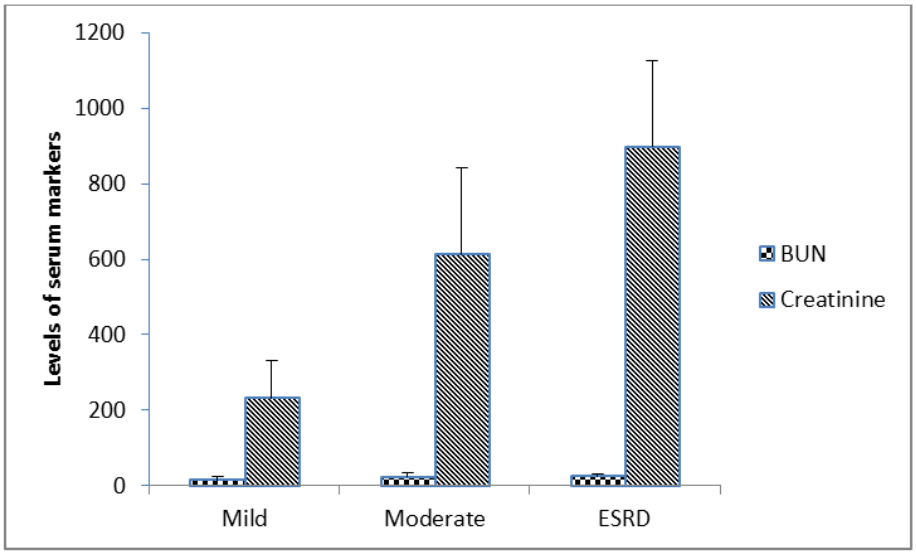

Fig-1: Serum levels of BUN and Creatinine in three groups

DISCUSSION

The main hallmarks of the present study were elevated levels of serum BUN, creatinine, BUN:Cr, uric acid and ALP. Increased levels of BUN, creatinine, uric acid observed in the present study could be due to impaired kidney function or damage. There are numerous causes reasoned for the malfunctioning of kidney like acute or chronic kidney disease, congestive heart failure or dehydration. Raised levels of BUN could also be due to excessive catabolism of protein, increased dietary intake of protein, or gastrointestinal bleeding. In the present study, three groups varying in severity of CKD were included to speculate the changes in the levels of the serum biomarkers like BUN, Creatinine and ALP. It was found that serum markers exhibited significant increase in the levels in ESRD patients compared to mild and moderate CKD group. Patients with CKD has higher serum biomarkers studied due to impairement in kidney function or complete renal failure. Thus, a comparative study involving these three group was undertaken to observe the changes in levels of these markers during the cource of renal failure. An attempt had been made to evaluate the role of BUN:Cr and ALP as probable markers in diagnosis of the renal failure so that assessment of these markers at initial stages would help to control the progression and also effective treatment strategies could be planned. Increased levels of BUN and creatinine observed in the present study are similar to that reported by earlier studies [14, 15].

As mentioned earlier, BUN is a major nitrogenous end product of protein and amino acid catabolism and creatinine is a breakdown product of creatine phosphate in muscle which are excreted by kidneys. BUN is an indirect measurement of renal function that measures the amount of urea nitrogen in blood and is directly related to excretory function of kidney. Increased levels of BUN, creatinine and uric acid in serum of these patients are reflective of kidney damage. Furthermore, hyperuricemia might have a pathogenic role in the development and progression of CKD, rather than solely reflecting decreased renal uric acid excretion. Indeed, several prospective studies recently have shown a significant association between hyperuricemia and adverse renal outcomes in both the general population and other nondiabetic high-risk patient populations [16, 17]. In Saudi Arabia, the incidence and prevalence of ESRD have increased in the last three decades probably due to factors such as an increase in life expectancy, rapid changes in lifestyle, urbanization, and high population growth [18]. Nevertheless, an important factor apart from the serum biomarkers that need to be monitored is the blood pressure. Raised levels of blood pressure may also accounts for the renal failure.

In the present study, confounding results was obtained with respect to ALP. Levels of ALP was observed to increase significantly in CKD and ESRD group. Patients with CKD are known to be at high risk of cardiovascular disease too. Patients with CKD have higher ALP due to disturbances in the bone mineral

disease which may contribute to the higher cardiovascular burden in this population. Previous studies have reported that an elevated ALP is associated with increased risk of coronary artery calcification and mortality in maintenance hemodialysis patients [19, 20]. ALP is formed from various tissue but mostly found in liver, biliary ducts, bone, and placenta. Under conditions such as hypertension, aging, diabetes and CKD, vascular cells undergo osteoblastic differentiation, and express several bone associated proteins like alkaline phosphatase. Subsequently, this leads to mineralization of the endothelium, arterial stiffening and vascular calcification thereby contributing to the cardiovascular disease and mortality in CKD [21]. ALP has been shown to be associated with arterial calcification in the coronary, carotid, and aorta, and superficial femoral artery and therefore ALP has been suggested as a surrogate for arterial stiffening [22]. ALP was found to increase from mild-mod-ESRD in the present investigation, indicating its role in renal damage and associated blood pressure. We observed an independent association between higher ALP levels in CKD and ESRD. However, there were no significant correlation between ALP and BUN: Cr ratio. Our results are in compliance with earlier study by Beddhu *et al*., [23]. Hence, ALP is also a potent risk factor and contributes to the progression of kidney disease from mild CKD to ESRD. Approximately 17% risk of death for every 50 U/L increase in ALP with CKD stages 1–5 has been reported in a study on veteran population [24].Additionally, affirmative results were obtained in ESRD after dialysis. There was marked reduction in levels of these markers in post-dialysis ESRD patients. Hence, role of dialysis as an effective treatment in ESRD has been manifested.

CONCLUSION

Our finding finally support that hyperuricemia and high BUN: Cr ratio correlate to severe CKD/ESRD and increased BUN: Cr ratio in mild CKD above normal value (20:1) is an alarm for an effective prophylactic treatment to prevent the onset of renal damage. The index may be noteworthy in understanding the pathological stage of renal damage and helps in development of strategies for prevention and early diagnosis of renal failure. Precautionary, blood pressure need to monitored on regular basis to diagnose the disease at its inception.

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