http://www.banglajol.info/index.php/JNINB

Original Article

DOI: https://doi.org/10.3329/jninb.v10i1.75455

Journal of National Institute of Neurosciences Bangladesh,
January 2024, Vol. 10, No. 1, pp. 44-51

ISSN (Online) 2518-6612
ISSN (Print) 2410-8030

Net Urinary Acid Excretion and its Association with Kidney Disease Progression in Different Stages of Chronic Kidney Disease

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Abstract

Background: Chronic kidney disease as an important public health issue. Previous studies suggest that higher urinary acid excretion is associated with progression of chronic kidney disease, but such relationship is not universally proven. **Objective:** To further assess such relationship between urine net acid excretion and renal outcomes in patients with chronic kidney disease, present study was designed to measure net acid excretion and to compare it with the changing stages of chronic kidney disease. **Methodology:** This was a cross sectional study conducted in the Department of Nephrology and Department of Biochemistry of National Institute of Kidney Diseases and Urology, Dhaka, from July 2020 to August 2021, among chronic kidney disease stage 1 to stage 5 patients who had not received dialysis as case and age and sex matched control. Patients of both gender with chronic kidney disease (stages 1-5) with urine output at least 500ml/day and age ≥ 18 years old, were enrolled in the study. Data collection sheet consisted of patient's demographics, clinical examination and investigation result sheet. Anthropometric parameters like height and weight were measured. Systolic and diastolic BP of each patient was recorded at the time of data collection. Blood and urine samples were taken for biochemical analysis. **Results:** As per the selection criteria, 46 case were enrolled in the study, along with 13 age and sex matched control. Mean age of the case and control group were 51.24 ± 12.80 years and 39.38 ± 10.28 years respectively ($p < 0.05$). No statistically significant difference regarding net acid excretion was noticed between the case and control groups ($p = 0.67$). Also, no statistically significant association was found between net urinary acid excretion and different stages of chronic kidney disease. NAE was found to have statistically significant ($p<0.05$) positive correlation with serum phosphorus and total cholesterol. NAE had statistically significant ($p<0.05$) negative correlation with urine pH. Although NAE had positive correlation with serum creatinine, this was not statistically significant ($p=0.30$). **Conclusion:** In conclusion there is no statistically significant relation between net urinary acid excretion and stages of chronic kidney disease. *[Journal of National Institute of Neurosciences Bangladesh, January 2024;10(1):44-51]*

Keywords: Urinary Acid Excretion;

Introduction

Chronic kidney disease (CKD) is recognized as an important public health issue. CKD is a progressive condition that affects more than 10.0% of the general population worldwide, amounting to more than 800 million individuals[1]. The overall pooled prevalence of

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CKD among Bangladeshi adults is 17.3% cases[2]. Metabolic acidosis is defined as a low arterial pH as well as reduction in serum bicarbonate (HCO3-) concentration, where the plasma bicarbonate concentration falls below 20 mmol/L[3] which is a risk factor for progression of CKD[4-6]. Treatment of CKD patients showed slowed disease progression by increasing the systemic pH or by lowering the amount of acid that must be excreted in the urine, also known as the urinary acid excretion[7-9]. Previous studies suggest that higher urinary acid excretion is associated with progression of CKD; where urinary acid excretion data were measured from dietary data rather than direct measurements[10-12]. Excreting the nonvolatile acids (i.e., H+) generated during metabolism through urine is maintained by the kidneys[13-15]. Alkali may be ingested in the form of alkali supplements or metabolizable organic anion salts found abundantly in fruits and vegetables, both of which may buffer nonvolatile acids[10,16-17]. Thus, the total load of urinary acid excretion equals the difference between acids produced and alkali consumed in foods or supplements.

The kidney excretes the nonvolatile acid load as ammonium (NH4+) or as titratable acid bound to anionic urinary buffers such as phosphate and creatinine[18-20]. Regulation of urinary acid excretion maintains acid-base homeostasis in response to dietary changes or systemic acid-base balance[21-22]. Net Acid Excretion is the sum of urinary NH4+ and titratable acid excretion. In the steady state, NH4+ accounts for 60% of total acid excretion. NAE factors in any bicarbonate excretion that may occur (NAE = NH4+ + titratable acid – HCO3−, all units in mEq/d)[23]. Due to the fact that the daily net acid excretion approximates the daily nonvolatile acid load, direct measurement of urinary net acid excretion is the reference standard for measuring acid load[16,24]. Many factors contribute to the development of Metabolic Acidosis in patients with CKD including the accumulation of organic or inorganic acids due to the reduced capacity of the diseased kidney to generate ammonia (NH3+) and excrete Hydrogen Ion (H+), lack of bicarbonate production and of tubulo-interstitial damage through ammonium retention and complement deposition[25].

Prior study showed a potential association between urine net acid excretion and renal outcomes in patients with CKD[26] but such relationship is not universally proven. To further assess such relationship between urine net acid excretion and renal outcomes in patients with CKD among Bangladeshi population, present study directly measured net acid excretion among participants of the study and compared it with the changing stages of CKD.

Methodology

Study Settings and Population: This was a cross sectional study which was conducted in the Department of Nephrology and Department of Biochemistry at National Institute of Kidney Diseases and Urology, Dhaka, Bangladesh from July 2020 to August 2021, among chronic kidney disease stage 1 to stage 5 patients who had not received dialysis as case and age and sex matched control. Patients of both gender with chronic kidney disease (stages 1-5) with urine output at least 500ml/day and age ≥18 years old, were enrolled in the study. Chronic kidney disease patients on dialysis, renal allograft recipients, presence of active infection, acute MI in last three months, complete heart block, atrial fibrillation, abdominal aorta aneurysm, the presence of aortic and/or femoral artery prosthesis, patients with glomerulonephritis currently on immunosuppression, acute renal failure, chronic liver disease and urine pH value > 7.4 or < 4.0 were excluded from the study.

Study Procedure: As per the selection criteria, 46 case were enrolled in the study, along with 13 age and sex matched control. Purposive sampling technique was used. A pre-tested data collection sheet and a hand-held pH meter was used as research instrument. Data collection sheet consisted of patient's demographics, clinical examination and investigation result sheet. Anthropometric parameters like height and weight were measured. Systolic and diastolic BP of each patient was recorded at the time of data collection. Blood and urine samples were taken for biochemical analysis and results were recorded in data collection sheet.

Statistical analysis: Statistical analysis was performed using Windows® based software program Statistical Packages for Social Sciences 25 (SPSS-25) (Chicago, IL, USA). After collection, all the data were checked and cleaned. Quantitative data were expressed as percentage, mean and standard deviation and qualitative data were expressed as frequency distribution and percentage. To determine statistical significance, chi square test, independent sample t test, one-way ANOVA and Pearson correlation were considered according to applicability. P value of < 0.05 was considered statistically significant.

Ethical Consideration: All procedures of the present study were carried out in accordance with the principles for human investigations (i.e., Helsinki Declaration 2013) and also with the ethical guidelines of the Institutional research ethics. Formal ethics approval was

granted by the local ethics committee. Participants in the study were informed about the procedure and purpose of the study and confidentiality of information provided. Risks and benefits were also made clear. All participants consented willingly to be a part of the study during the data collection periods. All data were collected anonymously and were analyzed using the coding system.

Results

The mean age of the study population was 48.63±13.17 years. Among the case group, 45.7% of the respondents were from the age group of 51 to 60 years, followed by 30.8% from the age group of 20 to 30 years and 23.1% from 31 to 40 years of age group. Mean age of the case group was 51.24 ± 12.80 years and control group was 39.38 ± 10.28 years. This difference in mean age of the case and control group was statistically significant ($p<0.05$). The difference in age group between case and control group was also statistically significant ($p<0.05$). CKD patients were male predominant (60.9% male) and rural in origin (54.3%). Over half (54.3% of case and 53.8% of control) of the respondents had monthly income between BDT 7,501/- and 15,000 (Table 1).

Table 1: Descriptive Statistics of the Study Population (n = 59)

Variables	Case Group (n = 46)	Control Group (n = 13)	P Value
Mean ±SD Age (years)	51.24 ± 12.80	39.38 ± 10.28	<0.05[a]
Age Group			
• 20 to 30 Years	4 (8.7%)	4 (30.8%)	
• 31 to 40 Years	9(19.6%)	3 (23.1%)	<0.05b
• 41 to 50 Years	3(6.5%)	5 (38.5%)	
• 51 to 60 Years	21(45.7%)	1 (7.7%)	
• 61 to 70 Years	9(19.6%)	0(0.0%)	
Gender			
• Male	28(60.9%)	4 (30.8%)	0.06[b]
• Female	18(39.1%)	9 (69.2%)	
Residence			
• Rural	31(54.3%)	6 (46.2%)	0.76[b]
• Urban	21(45.7%)	7 (53.8%)	
Level of education			
• No formal education	6 (13.0%)	2 (15.4%)	
• Primary	11 (23.9%)	5 (38.5%)	
• Secondary	11 (23.9%)	2 (15.4%)	0.81[b]
• Higher secondary	11 (23.9%)	3 (23.1%)	
• Graduate and above	7 (15.2%)	1 (7.7%)	
Occupation			
• Housewife	11 (23.9%)	5 (38.5%)	
• Service	8 (17.4%)	2 (15.4%)	
• Business	8 (17.4%)	3 (23.1%)	0.31[b]
• Others	7 (15.2%)	3 (23.1%)	
• Retires	12 (26.1%)	0	
Monthly income (BDT)			
• < 7500	12 (26.1%)	5 (38.5%)	
• 7501 – 15000	25 (54.3%)	7 (53.8%)	0.50[b]
• ≥ 15001	9 (19.6%)	1 (7.7%)	

Data are presented as n (%) or mean ± SD; [a] Independent Sample T-test was done and p values < 0.05 was considered statistically significant; [b] Chi-square test was done and p values < 0.05 was considered statistically significant.

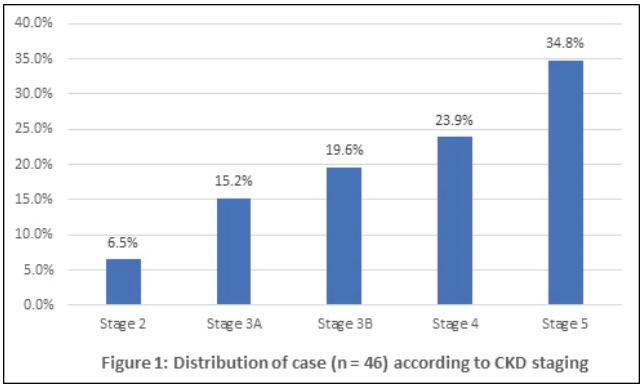

Figure 1: Distribution of case (n = 46) according to CKD staging

Among the 46 CKD patients, 34.8% had CKD Stage 5, followed by 23.9% with CKD Stage 4, 19.6% with CKD Stage 3B, 15.2% with CKD Stage 3A and 6.5% with CKD Stage 2 (Figure I).

Anthropometric and biochemical parameters of the study population were evaluated. Among the study population 65.2% case and 61.5% control were healthy. The distribution of the study population by BMI category was statistically significance between the two groups ($p <0.05$). Mean systolic and diastolic blood pressure was significantly ($p < 0.05$) higher among the cases compared to the control group. According to laboratory investigation, fasting blood sugar was significantly higher in cases compared to the control group ($p < 0.05$). Both groups were statistically similar regarding serum total protein, serum albumin and serum calcium concentration ($p > 0.05$). Moreover, Serum uric acid, serum phosphorus, serum potassium, and serum chloride levels were significantly higher in cases compared to the control group ($p < 0.05$). The serum sodium levels were lower among the cases than the control. There was no statistically significant difference regarding total cholesterol, triglycerides, and high-density lipoprotein concentration ($p > 0.05$) among the case and the apparently healthy population group. According to urine parameters, serum creatinine and serum urea were significantly higher in cases compared to the control group ($p < 0.05$). There was no statistically significant difference between the case and

control groups regarding 24 hours urine total volume, urine pH, and urea nitrogen appearance (g/day). Urinary ammonium and urinary phosphorus were significantly lower in cases compared to the control group ($p < 0.05$). There was no statistically significant difference regarding urinary creatinine. No statistically significant difference was found regarding dietary protein intake between case and control groups in this study ($p = 0.50$). No statistically significant difference regarding net acid excretion was noticed between the case and control groups ($p = 0.67$) (Table 2).

There was no statistically significant association between net urinary acid excretion and different stages of chronic kidney disease. No statistically significant association was also found between net urinary acid excretion and BMI category, sex and diabetic status (Table 3).

Table 2: Anthropometric and Biochemical Parameters of the Study Population (n = 59)

Variables	Case Group (n = 46)	Control Group (n = 13)	P value
BMI category			< 0.05[b]
• Underweight (< 18.5 kg/m2)	2 (4.3%)	3 (23.1%)	
• Healthy (18.5 – 24.9 kg/m2)	30 (65.2%)	8 (61.5%)	
• Overweight (> 25.0 – 29.9 kg/m2)	12 (26.1%)	0(0.0%)	
• Obese (≥ 30.0 kg/m2)	2 (4.3%)	2 (15.4%)	
Blood Pressure Levels			< 0.05[a]
• Systolic BP (mmHg)	127.2±22.4	107.7± 13	< 0.05[a]
• Diastolic BP (mmHg)	80.0±11.7	71.2 ± 9.2	
Biomedical Parameters			< 0.05[a]
• Fasting Blood sugar (mmol/L)	5.7 ± 2.72	4.3 ± 0.66	0.50a
• S. Total protein (g/dL)	7.7 ± 0.96	7.9 ± 0.34	0.30[a]
• S. Albumin (g/dL)	4.2 ± 0.55	4.5 ± 0.42	< 0.05[a]
• S. Uric Acid (mg/dL)	6.8 ± 2.52	4.6 ± 1.1	0.30[a]
• S. Calcium (mg/dL)	9.2 ± 1.22	9.4 ± 0.72	< 0.05[a]
• S. Phosphorus (mg/dL)	4.5 ±1.34	3.8 ± 0.4	< 0.05[a]
• S. Sodium (mEq/L)	139.2 ± 8.7	140.0 ± 3.9	< 0.05[a]
• S. Potassium (mmol/L)	5.94 ± 0.5	4.04 ± 0.3	< 0.05[a]
• S. Chloride (mmol/L)	115.0 ± 6.2	102.0 ± 3.2	0.08
• 24-hour urine total volume (ml)	2102 ± 509	2485 ± 672	0.10
• Urine pH	5.8 ± 0.4	6.0 ± 0.4	< 0.05[a]
• S. Creatinine (mg/dL)	3.86 ± 3.13	0.85 ± 0.15	< 0.05[a]
• S. Urea (mg/dL)	46.1 ± 15.1	22.7 ± 3.2	0.05
• Urea nitrogen appearance (g/day)	3.9 ± 1.9	5.9 ± 5.8	0.34
• U. Ammonium (µmol/day)	104.1 ± 151.7	148.4 ± 124.6	< 0.05[a]
• U. Phosphorus (mmol/day)	8.1 ± 6.0	16.7 ± 15.3	0.72
• U. Creatinine (mg/dl)	37.9 ± 22.7	35.0 ± 34.5	
Lipid profiles			0.60
• Total cholesterol (mg/dl)	174 ± 45	180 ± 42	0.05
• Triglycerides (mg/dl)	209 ± 113	190 ± 124	0.50
• HDL-C (mg/dl)	41 ± 11	42 ± 6	
Estimated dietary protein intake			0.50
• DPI (g/day)	36.4 ± 12	47 ± 37	
Net urinary acid excretion			0.67
• NAE (mmol/day)	132.0 ± 172.2	110.4 ± 112.1	

Data are presented as n (%) or mean ± SD; [a] Independent Sample T-test was done and p values < 0.05 was considered statistically significant; [b] Chi-square test was done and p values < 0.05 was considered statistically significant.

Table 3: Net Urinary Acid Excretion in Different Stages of CKD

Variables	NAE (mmol/day)	P value
CKD stage		
• Stage 2	166.7 ± 189.3	
• Stage 3A	108.1 ± 151.9	
• Stage 3B	109.8 ± 135.3	0.94[c]
• Stage 4	166.1 ± 161.9	
• Stage 5	125.1 ± 214.5	
BMI category		
• Underweight (< 18.5 kg/m2)	133.4 ± 104.0	
• Healthy (18.5 – 24.9 kg/m2)	114.9 ± 133.8	0.59[c]
• Overweight (> 25.0 – 29.9 kg/m2)	180.6 ± 257.4	
• Obese (≥ 30.0 kg/m2)	77.1 ± 43.3	
Gender		
• Male	143.2 ± 189.7	0.41[a]
• Female	108.4 ± 117.2	
Diabetic status		
• Present	99.1 ± 108.0	0.22[a]
• Absent	162.2 ± 213.0	

Data are presented as n (%) or mean ± SD; [a] Independent Sample T-test was done and p values < 0.05 was considered statistically significant; [c] One-way ANOVA was done and p values < 0.05 was considered statistically significant.

Table 4: Correlation with Net Urinary Acid Excretion and Biochemical Parameters of the CKD Patients (n = 46)

Variables	r value	P value
Serum Creatinine (mg/dL)	0.133	0.38
Fasting Blood sugar (mmol/L)	0.031	0.84
Serum Total protein (g/dL)	-0.026	0.86
Serum Albumin (g/dL)	-0.131	0.39
Serum Uric Acid (mg/dL)	0.215	0.15
Serum Calcium (mg/dL)	0.148	0.33
Serum Phosphorus (mg/dL)	0.353	< 0.05[d]
Serum Sodium (mEq/L)	0.210	0.16
Serum Potassium (mmol/L)	0.052	0.73
Serum Chloride (mmol/L)	0.076	0.61
Urine pH	-0.721	< 0.05[d]
S. Urea (mg/dL)	-0.205	0.17
Urea nitrogen appearance (g/day)	0.105	0.49
U. Ammonium (µmol/day)	0.184	0.22
U. Phosphorus (mmol/day)	0.019	0.90
U. Creatinine (mg/dl)	0.059	0.70
Total cholesterol (mg/dl)	0.293	< 0.05[d]
Triglycerides (mg/dl)	0.151	0.32
HDL-C (mg/dl)	0.059	0.70
Dietary protein intake (g/day)	0.108	0.48
eGFR (mL/min/1.73m2)	-0.051	0.74

[d] Pearson Correlation was done and p values < 0.05 was considered statistically significant.

Association between net urinary acid excretion and biochemical parameters of the CKD patients were assessed. NAE was found to have statistically significant ($p < 0.05$) positive correlation with serum phosphorus and total cholesterol. NAE had statistically significant ($p < 0.05$) negative correlation with urine pH. Although NAE had positive correlation with serum creatinine, this was not statistically significant ($p = 0.30$) (Table 4).

Discussion

Metabolic acidosis is a known complication of chronic kidney disease (CKD) resulting from an imbalance of acid load and excretion that may ultimately contribute to disease progression[4,9]. In previous studies, higher acid load has been hypothesized as the mechanism which links metabolic acidosis with poor kidney outcomes, in part due to associations of higher diet-derived acid load and faster chronic kidney disease progression[11,12,27-28]. Net acid excretion is considered as the gold standard measure of acid load. This study aimed to assess the pattern of net urinary acid excretion in patients with chronic kidney disease.

The kidneys excrete the endogenous non-volatile acid load as ammonium and titratable acidity. Previous studies demonstrated that the central biologic response to nonvolatile acids increases ammonia excretion[23,29]. This process also facilitates bicarbonate generation and thus helps to maintain normal systemic bicarbonate and pH. But this enhanced NH4+ excretion to maintain normal systemic bicarbonate and pH may result in further kidney fibrosis, and some chronic kidney disease patients with clinically normal acid-base status might still have kidney injury because of higher ammonia production. Raphael et al[29] study showed the mean ammonium excretion to be 1.27 ± 0.72 mEq/h in chronic kidney disease populations which is much higher than the mean urine ammonium of 104.1 ± 151.7 µmol/d found in present study.

The NAE is calculated in this study as the sum of urine ammonium and titratable acidity in 24-hour urines from patients with chronic kidney disease and a healthy control group in a cross-sectional study design. The mean net acid excretion was 132.0 ± 172.2 mmol/d for the individuals with chronic kidney disease, which was higher than the control group, with mean value of 110.4 ± 112.1 mmol/d. Both are higher than previous study findings showing net acid excretion to be between 30 to 50 mEq/d for chronic kidney disease patients[30].

Patients with chronic kidney disease are at high risk for the adverse effects of high BP. Present study showed significant ($p < 0.05$) difference in both systolic and diastolic blood pressure between case and control group, which is consistent with prior study showing similar difference[31]. Present study showed the mean NAE for male to be 143.2 ± 189.7 mmol/d, which is higher than the mean NAE for female of 108.4 ± 117.2 mmol/d. Scialla and Anderson[27] showed higher NAE among male than in female which is consistent with present study findings. Endogenous acid production is hypothesized to be increased in diabetes mellitus due to altered energy metabolism. Present study found mean NAE to be 99.1 ± 108.0 mmol/d for chronic kidney disease patients with DM, which is lower than the mean NAE of 162.2 ± 213.0 mmol/d for chronic kidney disease patients without DM. While this difference is not statistically significant, it coincides with the findings of Crews et al[32] study. In the present study, the mean score of dietary protein intake was 36.4 ± 12 (g/day) among chronic kidney disease patients. In a prior study, greater dietary acid load, quantified by estimated NAE, was associated with albuminuria and low eGFR, markers of chronic kidney disease[33].

Present study used urinary nitrogen appearance to calculate the dietary protein intake. In this study population, the net urinary acid excretion showed no statistically significant variation with protein intake. It is important to note that the net endogenous acid production considers the balance of protein and potassium intake in the diet and was more strongly associated with GFR decline than either protein or potassium intake alone. Current clinical guidelines recommend restricted protein intake in chronic kidney disease[34]. This finding was consistent with the previous study concluding diet as a minor predictor of NAE[32]. Other factors like dietary potassium load may influence NAE than protein intake alone.

BMI is an independent risk factor for chronic kidney disease[35–37]. Present study found negative correlation between NAE and BMI, which contradicts prior study findings showing higher NAE being associated with greater BMI[38] which could be due to the smaller sample size and demography of the study population. Adequate blood pressure control is widely recognized as an essential factor in slowing the progression of chronic kidney disease[39-40]. These findings hypothesized with the present study as hypertension and diabetes mellitus were the most common etiological factors associated with chronic kidney disease patients.

The net urinary acid excretion usually increases with progression of chronic kidney disease. A previous study demonstrated the higher NAE in advanced stages of chronic kidney disease[16]. In present study NAE showed no statistically significant variation with different stages of chronic kidney disease. The mean value of NAE was highest in stage IV chronic kidney disease 166.1±161.9 mmol/day. From present study we can say that NAE is not dependent on stages of chronic kidney disease alone, rather the wide variation showed here may be a reflection of numbers of residual nephrons, degree of tubular dysfunction, high endogenous acid production which may vary greatly from person to person despite of having similar category of eGFR.

Close monitoring to adherence to dietary recommendations and frequent evaluation of nutritional status is fundamental in the management of patients with chronic kidney disease since it can affect important health outcomes, including chronic kidney disease progression, quality of life, morbidity, and mortality. Additional nutritional measures to delay chronic kidney disease progression, some of them considered experimental, may include the limitation of phosphate and calorie intake, the increase of fiber intake, and the promotion of healthy dietary patterns.

Conclusions

Present study showed that there was no statistically significant relation between net urinary acid excretion and stages of chronic kidney disease, but statistically significant correlation with serum phosphorus, total cholesterol and urine pH. It also did not demonstrate any significant association with sex, BMI, dietary protein intake or the presence of diabetes mellitus. Further studies with larger population from multiple centers are needed to clarify the changes of these factors.

Acknowledgements
None.

Conflict of interest: Other than technical and logistic support from the scientific partner the investigators did not have any conflict of interest in any means.

Financial Disclosure
This research project was not funded by any organization.

Contribution to authors: Sutapa Das: from protocol preparation upto manuscript writing; Md. Abdus Sabur Khan: Data Collection, Protocol writing; Md. Abdus Sukur: Data Collection; Md. Raquib Morshed, Sumon Das, Dilip Kumar Debnath, Md. Zakir Hussain and Sheikh Mohammad Ershad: Protocol writing;

Ayesha Alom Mita: Data Collection; Ayub Ali Chowdhury, Kazi Shahnoor Alam and Babrul Alam: Co-guide; Md. Zahid Hasan: Data analysis and interpretation. All authors read and approved the final manuscript.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Ethical approval for the study was obtained from the Institutional Review Board. As this was a prospective study the written informed consent was obtained from all study participants. All methods were performed in accordance with the relevant guidelines and regulations.

How to cite this article: Das S, Khan MAS, Sukur MA, Morshed MR, Das S, Debnath DK, Hussain MZ, Ershad SM, Mita AA, Chowdhury AA, Alam KS, Alam B. Net Urinary Acid Excretion and its Association with Kidney Disease Progression in Different Stages of Chronic Kidney Disease. J Natl Inst Neurosci Bangladesh, 2024;10(1):44-51

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Article Info
Received on: 7 April 2023
Accepted on: 24 May 2023
Published on: 1 January 2024

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