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Association between Urea levels and Gradual Renal Function Decline in Children Afflicted with Chronic Kidney Diseases

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Abstract: Chronic kidney disease (CKD) poses a significant health challenge in the paediatric population, leading to enduring adverse effects on affected individuals' well-being. The heightened mortality and morbidity rates associated with CKD. Accumulation of urea as a result of impaired renal function may induce kidney damage and accelerate CKD progression. Therefore, we measured the concentration of creatinine and urea to study the correlation between the progressive decline in renal function and urea levels in blood samples within our study cohort of 5 groups of paediatric CKD patients (stages 1 to 5) in order to understand the relation between uremia and compromised renal function and improve the quality of life for children grappling with CKD. Our findings indicated a significant positive correlation between creatinine and urea levels in our study group of children with CKD.

Keywords: Chronic kidney disease, CKD, creatinine, urea, CKD in children.

Introduction

Chronic kidney disease (CKD) constitutes a significant public health challenge on a global scale, impacting nearly 13.4% of the world's population. [1, 2]. CKD represents a progressive pathological condition marked by the gradual loss of functional renal mass. It is delineated by enduring abnormalities in kidney structure or function, persisting for a minimum duration of three months or longer. [3]. Chronic kidney disease (CKD) predominantly impacts adults, with a lifelong incidence rate reaching up to 60% within the general population.[4]. In the adult population, chronic kidney disease (CKD) predominantly manifests as a complication arising from hypertension and diabetes mellitus.[5]. Conversely, the prevalence of chronic kidney disease (CKD) in children is significantly lower than that observed in adults, with the primary attribution often directed towards congenital abnormalities of the kidneys and urinary tract (CAKUT). [6]. However, pediatric individuals affected by chronic kidney disease (CKD) face a heightened susceptibility to consequential complications, including neurocognitive degeneration, growth impairment, cardiovascular diseases, anemia, bone fractures, and deformities. This elevated risk contributes to increased rates of morbidity and mortality, ultimately resulting in a diminished overall quality of life.[7].

Chronic kidney disease (CKD) is characterized by a progressive deterioration in the kidneys' capacity to effectively eliminate waste products from the bloodstream. Elevated levels of creatinine in the blood serve as a prominent indicator of CKD. Creatinine, a byproduct of muscle metabolism, undergoes filtration by the kidneys. With the impairment and diminishing function of the kidneys, there is a concurrent rise in creatinine levels within the bloodstream. [8]

In assessing renal function, healthcare professionals frequently employ the estimated glomerular filtration rate (eGFR), a metric reflecting the kidneys' efficiency in filtering waste products from the bloodstream. The

eGFR is determined through a formula incorporating variables such as age, sex, race, and serum creatinine levels. [9]. Additionally, progressive impairment of renal function leads to accumulation of uremic toxins, especially urea in CKD patients [10].

Various serum biomarkers, including but not limited to serum creatinine, urea, and blood urea nitrogen (BUN, reflecting the nitrogen content of urea), are standard tools employed in clinical settings for the assessment of kidney function. Urea, the principal metabolite originating from dietary proteins and tissue protein turnover, is predominantly excreted by the kidneys in urine following filtration in the glomerulus and partial reabsorption from the filtrate. Although multiple non-renal factors can influence serum urea concentration [11], the primary determinant of elevated serum urea levels is the diminished urinary elimination of urea, notably attributed to chronic kidney disease (CKD).

Urea is commonly utilized as an indicator for assessing the severity of chronic kidney disease (CKD) and the adequacy of dialysis in clinical contexts. Traditionally regarded as a relatively inert and non-toxic molecule, recent studies have revealed urea to be both a direct and indirect uraemic toxin [12]. While the precise mechanisms underlying urea's direct toxicity necessitate further exploration, in vitro and in vivo investigations have demonstrated that uraemia influences the phenotype of smooth muscle cells and prompts the expression of pro-apoptotic BCL-2 family genes. This phenomenon may elucidate the heightened apoptosis rate observed in the arterial walls of uraemic patients [13, 14]. Additionally, elevated urea concentrations in cultures of endothelial cell progenitors have been linked to increased senescence and the generation of free radicals [15].

In this context aimed to investigate the association between serum creatinine and serum urea levels in our study group of children with CKD.

Subjects and methods

Study population

The current study was authorized by the Medical Research Ethics Committee, Institutional Review Board, Faculty of Medicine, Mansoura University, code number MS.21.09.1664. All patients signed a written informed agreement before the inclusion in the study.

This study included 100 children with CKD, 52.7% of the study population were males and while 47.3% were females, in addition to 50 healthy control subjects of matched age and gender.

Sample collection

Whole blood samples (3mL) were collected from CKD patients and control subjects in plain vacuum tubes and let to clot in room temperature, then the tubes were centrifuged at 2000 rpm for 5 minutes, serum was obtained from samples, and Creatinine and urea levels were measured soon after sample collection.

Biochemical analysis:

Serum creatinine was measured by commercially available kinetic method kit (Agappe Diagnostics LTD, ‘Agappe Hills’, Dist. Ernakulam, Kerala, India-683 562). [16]

Blood urea was measured by a commercially available fixed time UV method kit (Agappe Diagnostics LTD, ‘Agappe Hills’, Dist. Ernakulam, Kerala, India-683 562). [17,18]

Statistical analysis

Obtained data was analyzed by the Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.), A probable value (p value) is considered significant if $p<0.05$ at confidence interval 95%.

Results and Discussion

Table 1. Comparison of demographic data among patients and control group.

	Control N = 50		**CKD N = 100**		**Test (p)**
	№	**%**	**№**	**%**	
Gender					
Male	27	54.0	53	53.	X^2=0.013 p=0.908
Female	23	46.0	47	47.	
Age(years)					
Mean ±SE.	8.46 ± 0.58		8.83 ± 0.46		U=2592.0 p=0.713
Median (Range)	8.0 (2.0 – 18.0)		8.0 (1.0 – 17.5)		

SE. Standard error, Range: Min. – Max; X2, Chi-Square; U, Mann Whitney test. *: P value Significant <0.05.

The current study was conducted on 100 CKD cases. Their median age was 8.8 years, ranged from 1 to 17.5 years. They were 53% males and 47% females. In addition to 50 healthy control subjects of matched age and gender.. There were no significant statistical differences between CKD patients and control subjects in terms of age and gender (P>0.05).

Table 2. Comparison of Creatinine and phosphate levels among patients and control group.

	Control N = 50	CKD N = 100	Test (p)
Creatinine (mg/dl)			
Mean ± SE.	0.50 ± 0.01	1.96 ± 0.20	U=4194.0 p-value<0.001*
Median (Range)	0.50 (0.32 – 0.72)	1.15 (0.30 – 10.50)	
Urea (mg/dl)			
Mean ± SD.	24.50 ± 0.79	73.73 ± 4.92	U=4715.5 p-value<0.001*
Median (Range)	24.0 (15.0 – 37.1)	64.2 (22.2 – 241.1)	

SE. Standard error, Range: Min. – Max; U, Mann Whitney test.

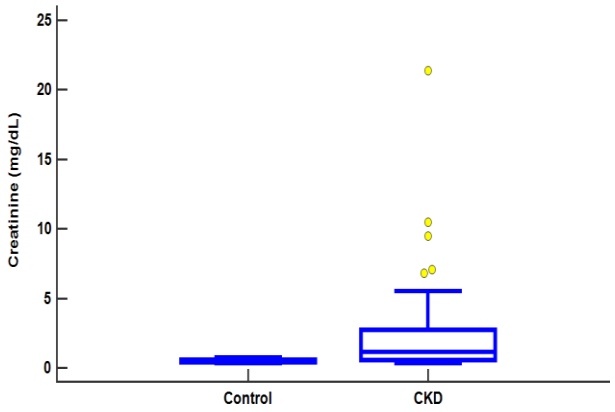

Figure 1 Boxplot for comparison of creatinine among patients and control group.

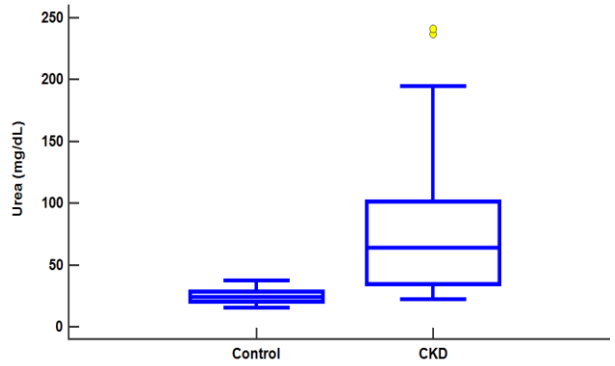

Figure 2 Boxplot for comparison of urea among patients and control *group.*

Comparisons of phosphate levels between CKD patients and controls.

The results illustrated in Table 2, Figure 1, and figure 2 demonstrate that Creatinine levels has significantly increased in CKD patients compared to control subjects (p<0.001). Additionally, serum urea levels in CKD patients showed significant increase compared to control group (p<0.001).

Table 3. Correlation between Creatinine and Urea levels among CKD patients

CKD N=100	**Urea (mg/dl)**	
	r	**p-value**
Phosphate (mg/dl)	0.814	<0.001*

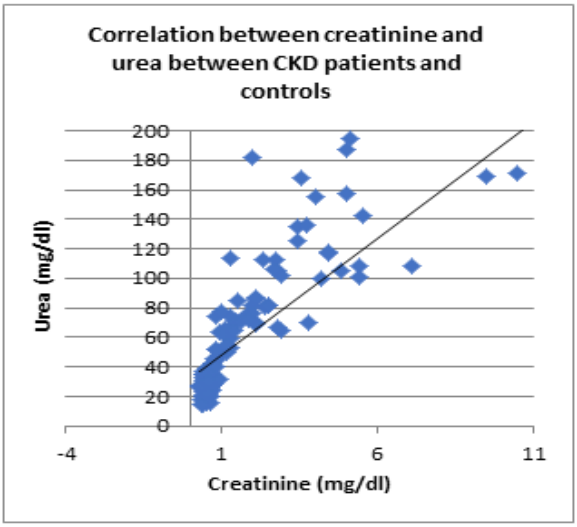

Figure 3 Significant Correlation between creatinine and urea between CKD patients and **controls**

Our findings shown in Table 3 and Figure 3 indicated a significant positive correlation between Creatinine and urea levels in our study group of children with CKD (p< 0.05) indicating that higher levels of urea may indicate more advanced stages of the disease. These results highlight the potential utility of measuring serum urea levels in clinical practise for the early detection and monitoring of CKD

Conclusion and recommendations

Chronic Kidney Disease (CKD) in children is indeed a serious health condition that can have profound effects on a child's well-being. Unlike acute kidney injury, CKD involves the gradual loss of kidney function over an extended period. This can result in various complications and impact different systems in the body. CKD involves the gradual decline in the kidneys' ability to filter waste and excess

fluids from the blood. This can lead to the accumulation of harmful substances in the body. Uremic toxins, including urea and creatinine, accumulate in the blood as kidney function declines. These toxins can have systemic effects and contribute to the progression of CKD. We recommend that, managing uremia is crucial in slowing CKD progression and improving the quality of life for children with CKD.

References

1 Vos T, Lim SS, Abbafati C, et al (2020) Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet **396**:1204–1222

2 Lv J-C, Zhang L-X (2019) Prevalence and Disease Burden of Chronic Kidney Disease. Adv Exp Med Biol 1165:3–15

3 Levin A, Stevens PE, Bilous RW, et al (2013) Kidney disease: Improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl (2011) **3**:1–150

4 Grams ME, Chow EKH, Segev DL, Coresh J (2013) Lifetime Incidence of CKD Stages 3-5 in the United States. *American Journal of Kidney Diseases* **62**:245–252

5 Vos T, Allen C, Arora M, et al (2016) Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet **388**:1545–1602

6 Chevalier RL (2023) CAKUT: A Pediatric and Evolutionary Perspective on the Leading Cause of CKD in Childhood. Pediatr Rep **15**:143–153

7 Beng-Ongey H, Robinson JS, Moxey-Mims M (2022) Chronic kidney disease emerging trends in children and what to do about it. *J Natl Med Assoc* **114**:S50–S55

8 National Kidney Foundation. (2021). About chronic kidney disease. Retrieved from https://www.kidney.org/atoz/content/about-chronic-kidney-disease

9 Stevens, L. A., & Levey, A. S. (2013). Measured GFR as a confirmatory test for estimated GFR. *Journal of the American Society of Nephrology*, **24(11)**, 1715-1720

10 Czaya B, Heitman K, Campos I, et al (2022) Hyperphosphatemia increases inflammation to exacerbate anemia and skeletal muscle wasting independently of FGF23-FGFR4 signaling. Elife. https://doi.org/10.7554/eLife.74782

11 Luke RG. (1981) Uremia and the BUN. N *Engl J Med*; **305**: 1213–1215

12 Massy ZA, Pietrement C, Touré F. (2016) Reconsidering the lack of urea toxicity in dialysis patients. Semin Dial; **29:** 333–337

13 Trécherel E, Godin C, Louandre C et al. (2012) Upregulation of BAD, a pro-apoptotic protein of the BCL2 family, in vascular smooth muscle cells exposed to uremic conditions. Biochem Biophys Res Commun; **417**: 479–483

14. Shroff RC, McNair R, Figg N et al. (2008) Dialysis accelerates medial vascular calcification in part by triggering smooth muscle cell apoptosis. Circulation; **118**: 1748–1757

15. D'Apolito M, Colia AL, Lasalvia M et al (2017). Urea-induced ROS accelerate senescence in endothelial progenitor cells. Atherosclerosis; **263**: 127–136

16. Burtis, C.A. and Ashwood, E.R. (1999) Tietz Textbook of Clinical Chemistry. 3rd Edition, W. B. Saunders Co., Philadelphia, 29-150.

17. Talke h, schubert ge. (1965). Enzymatische harnstoffbestimmung in blut und serum im optischen test nach warburg [enzymatic urea determination in the blood and serum in the warburg optical test]. Klin wochenschr. **1;43**:174-5.

18. Kassirer JP. (1971). Clinical evaluation of kidney function--glomerular function. N *Engl J Med*. **285(7):**385-9.