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The Value of Plasma Copeptin Level in Children with Chronic Kidney Disease

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Abstract

Copeptin is cleared by the kidney. In patients with chronic kidney disease, plasma levels of copeptin and Arginine Vasopressin (AVP) are inversely correlated with the estimated glomerular filtration rate. To assess plasma copeptin level in children with renal impairment as a marker of diagnosis and to assess its value as an indicator of disease progression. The present study was a case control study which conducted during the period from February up to November 2020 and carried out at the pediatric nephrology unit of the pediatric department of AL-Zahraa University Hospital on 90 children who were divided into three groups, Group (1) Thirty children suffering from chronic kidney disease on conservative treatment (case group), Group (2) Thirty children suffering from chronic kidney disease on dialysis (case group), Group (3) Thirty children apparently healthy age and sex matched (control group) and Assay of serum Copeptin using enzyme-linked immunosorbent assay (ELISA) and kidney function profile was done. There was highly statistically significant increase between patient groups (I & II) and control group (I) as regard Urea, Creatinine, highly statistically significant increase between patient groups and control groups as regard plasma Copeptin and there was statistically significant negative correlation between plasma Copeptin and GRF in patients groups when compared with control group. Copeptin was highly increased in patients with chronic kidney diseases and its level increased as serum Creatinine increased and as GFR decreased. Plasma Copeptin was increased as the stage of kidney disease progressed.

Keywords: Chronic Kidney Disease, Copeptin, Arginine Vasopressin.

1. Introduction

Chronic kidney disease (CKD) is a serious and common disease, and it eventuates in multiple complications, including premature mortality and end-stage kidney disease (ESKD). An estimated 1 in 7 to 10 adults worldwide have CKD, with only

approximately 10% surviving ESKD and only half of survivors receiving dialysis or a kidney transplant because of lack of access or high costs. From 1990 to 2016, the prevalence of CKD increased by 90%, and related deaths, mainly due to cardiovascular diseases and infections, nearly doubled in the United States and globally. In high-income countries, 2% to 3% of annual health care costs are devoted to the 0.03%of the population with ESKD [1]. Management of CKD requires a clear understanding of its definition as proposed by the National Kidney Foundation (NKF). An informed interpretation of the estimated glomerular filtration rate (eGFR) is required, since the GFR is still considered the best overall index of kidney function in stable, non-hospitalized patients. Kidney damage is defined by any one of the following findings: Pathologic kidney abnormalities, persistent proteinuria, other urine abnormalities, e.g., renal hematuria, imaging abnormalities and eGFR <60 mL/min/1.73 m2 on two occasions separated by >90 days and that is not associated with a transient, reversible condition such as volume depletion [2].

Arginine vasopressin (AVP or antidiuretic hormone) is one of the key hormones in the human body responsible for a variety of cardiovascular and renal functions. It has so far escaped introduction into the routine clinical laboratory due to technical difficulties and preanalytical errors. Copeptin, the C-terminal part of the AVP precursor peptide, was found to be a stable and sensitive surrogate marker for AVP release. Copeptin behaves similarly to mature AVP in circulation, with respect to osmotic stimuli and hypotension [3]. Arginine Vasopressin (AVP) and Copeptin derive from the same precursor peptide Pre-Pro-Vasopressin. While both peptides are stimulated by similar physiological processes, such as osmotic stimulation, hypovolemia or stress, the physiological function of AVP is homeostasis of fluid balance, vascular tonus and regulation of the endocrine stress response [4].

Copeptin can be measured from blood samples and is demonstrated to be a reliable marker of vasopressin [5]. At normal concentrations, the role of AVP is to regulate the plasma osmolality by eliminating free water in the kidney. Like mature AVP, copeptin is regulated within a certain normal range but may fluctuate according to individual physiologic conditions. Copeptin increases to upper normal values during fasting and shows a rapid decline in vivo to low normal values after oral water load [6]. Dehydration and a modest elevation of plasma osmolality are major stimuli for vasopressin (or antidiuretic hormone) secretion by neurohypophysis. Vasopressin is cosecreted into the blood in an equimolar amount with copeptin, the C-terminal portion of the pre-pro-vasopressin peptide. Copeptin is easier to assay and is an adequate surrogate of vasopressin [5].

2. Patient and Methods

2.1 Study design

This case-control study was conducted during the period from February up to November 2020.

2.2 Study site

The study was carried out at the pediatric nephrology unit of the pediatric department of AL-Zahraa University Hospital, Al-Azhar University.

2.3 Study population

The study was conducted on 90 children aged from 5 to 18 years, males and females. They were divided into three groups: Group I: Included 30 children suffering from chronic kidney disease on conservative treatment. Group II: Included 30 children suffering from chronic kidney disease on dialysis. Group III: Included 30 children apparently healthy age and sex matched. The Patient selection was based on criteria of inclusion and exclusion criteria.

2.4. Inclusion criteria

Children with chronic kidney disease according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative [7] and children aged from 5-18 years of both sexes.

2.5 Exclusion criteria

Full Children below 5 years, any condition associated with abnormal copeptin level other than renal diseases as patients with respiratory disease e.g. pneumonia, patients with cardiovascular diseases & heart failure, patients with diabetes mellitus & metabolic syndromes, patients with diabetes insipidus, patients with sepsis and patients with primary hypertension.

2.6 Ethical consideration

An oral informed consent to participate in this study was obtained from each patient after an explanation of the objectives and benefits of the study. All Studied Groups were submitted as shown below.

2.7 History

Full history taking including age, sex and duration of the disease. Treatment was taken and for how long.

2.8 Clinical examination

Thorough anthropometric measurement which included height, weight and body mass index (BMI). Assessment of vital signs especially systolic and diastolic blood pressure. Systemic examination. Estimation of GFR: bedside SCHWARTZ equation eGFR = 0.413 x (Height/Scr), height is expressed in centimetres [8].

2.9 Laboratory investigation

2.9.1 Routine investigation

Hemoglobin count (HB), kidney function profile (urea, creatinine, sodium, and potassium), calcium level and serum Albumin.

2.9.2 Special investigations

Assay of serum Copeptin using enzyme-linked immunosorbent assay (ELISA).

2.10 Statistics analysis

Statistical presentation and analysis of the present study were conducted, using the mean, standard deviation, student t-test, Chi-square, Linear Correlation Coefficient and Analysis of variance [ANOVA] tests by SPSS V20. The unpaired Student T-test was used to compare between two groups in quantitative data. Chi-square the hypothesis that the row and column variables are independent, without indicating strength or direction of the relationship. Pearson chi-square and likelihood-ratio chi-square. Linear Correlation coefficient was used for detection of correlation between two quantitative variables in one group. Analysis of variance [ANOVA] tests. According to the computer program SPSS for Windows. The ANOVA test was used for comparison among different times in the same group in quantitative data. P-value > 0.05 Non-significant, ‑ P-value ≤ 0.05 Significant, P-value < 0.01 Highly Significant.

3. Result

As shown in Table 1. there was no statistically significant difference between patients and control as regards age and sex (P-value > 0.05). As shown in Table .2. there was highly statistically significant decrease between patient groups and control groups as regard weight, Height and BMI (P-value < 0.001). As shown in Table .3. there was a highly statistically significant increase between patient groups in comparison to control group as regard Systolic and Diastolic Blood Pressure (P-value < 0.001). As shown in Table .4. there

was a highly statistically significant decrease between patient groups (I&II) in comparison to control group (III) as regard haemoglobin and GFR, highly statistically significant increase between patient groups (I&II) in comparison to the control group (III) as regards urea and creatinine, highly statistically significant increase between patient groups II and I as regard urea and Creatinine and highly statistically significant decrease between patient groups II and I as regard GFR (P-value < 0.001). As shown in Table .5 there was a highly statistically significant decrease between patient groups (I&II) in comparison to the control group (III) as regards Albumin and calcium (P-value < 0.001) and a statistically insignificant difference between patient groups and control groups as regards sodium and potassium (P-value > 0.05). As shown in Table .6. there was a highly statistically significant increase between patient groups (I&II) in comparison to the control group (III) as regards copeptin (P-value < 0.001). As shown in Table .7. there was a statistically insignificant relation between copeptin level and sex in all studied groups (P-value > 0.05). As shown in table .8. there was a statistically significant positive correlation between copeptin and creatinine and statistically significant negative correlation between copeptin and GFR and a statistically insignificant negative correlation between copeptin, albumin and calcium.

Table (1): Comparison between patient groups (I&II) and control group (III) as regards age and sex.

		Groups						**ANOVA**	
		Group I		**Group II**		**Group III**		**F**	**P-value**
Age (years)	Mean ± SD	11.30±3.62		11.40±3.90		11.33±3.44		0.006	0.994
	Range	5-18		5-18		5-18			
		N	%	N	%	N	%	Chi-Square	
								X^2	P-value
Sex (%)	Male	18	60.00	19	63.33	12	40.00	3.853	0.146
	Female	12	40.00	11	36.67	18	60.00		

P-value > 0.05 Non-significant, P-value ≤ 0.05 Significant, P-value < 0.01 Highly Significant, Chi square test, ANOVA test.

Table (2): Comparison between patient groups (I&II) and control group (III) as regard Weight, Height and BMI.

		Groups			ANOVA		TUKEY'S Test		
		Group I	Group II	Group III	F	P-value	I&II	I&III	II&III
Weight (kg)	Mean ± SD	25.73±9.92	26.23±10.43	35.16±9.78	8.366	<0.001*	0.980	0.001*	0.003*
	Range	11-50	11-46	20-60					
Height (cm)	Mean ± SD	123.03±16.86	125.60±18.53	133.20±17.46	2.696	<0.001*	0.973	0.001*	0.002*
	Range	95-150	96-155	105-185					
BMI (kg/m2)	Mean ± SD	16.35±2.94	16.09±2.34	19.58±2.92	14.951	<0.001*	0.929	<0.001*	<0.001*
	Range	12-25.51	11.94-20.93	16.46-28.7					

Table (3): Comparison between patient groups (I&II) and control group (III) as regards Systolic and Diastolic Blood Pressure.

		Groups			ANOVA		TUKEY'S Test		
		Group I	Group II	Group III	F	P-value	I&II	I&III	II&III
Systolic BP (mmHg)	Mean ±SD	114.93±14.79	113.83±13.04	98.66±8.80	15.941	<0.001*	0.938	<0.001*	<0.001*
	Range	130-155	160-175	90-119					
Diastolic BP (mmHg)	Mean ±SD	78.43±10.09	77.33±11.57	67.00±7.38	12.329	<0.001*	0.902	<0.001*	<0.001*
	Range	90-95	100-109	50-80					

Table (4): Comparison between patient groups (I&II) and control group (III) as regards HB, Urea, Create and GFR.

		Groups			ANOVA		TUKEY'S Test		
		Group I	Group II	Group III	F	P-value	I&II	I&III	II&III
HB (g/dL)	Mean ±SD	10.69±1.43	9.95±1.43	12.56±1.25	28.721	<0.001*	0.096	<0.001*	<0.001*
	Range	7.7-12	7-11	10-14					
Urea (mg/dl)	Mean ±SD	24.83±5.30	43.90±7.85	12.50±4.09	211.366	<0.001*	<0.001*	<0.001*	<0.001*
	Range	37-55	30-70	12-35					
Create (mg/dl)	Mean ± SD	1.21±0.31	8.64±2.99	0.40±0.15	203.659	<0.001*	<0.001*	0.175	<0.001*
	Range	2-5	5-10	0.2-0.9					
GFR (ml /min/ 1.73m2)	Mean ± SD	44.56±13.47	6.78±2.71	102.45±11.66	643.078	<0.001*	<0.001*	<0.001*	<0.001*
	Range	30-60	14-55	89-126					

Table (5): Comparison between patient groups (I&II) and control group (III) as regard Albumin, Calcium, Sodium and Potassium.

		Groups			ANOVA		TUKEY'S Test		
		Group I	Group II	Group III	F	P-value	I&II	I&III	II&III
Albumin (g/dl)	Mean ± SD	2.38±0.52	2.07±0.41	2.88±0.35	25.866	<0.001*	0.021*	<0.001*	<0.001*
	Range	2.2-3.5	1.7-3.2	3.5-5.5					
Calcium (mg/dl)	Mean ± SD	8.09±0.58	7.86±0.43	9.44±0.84	52.776	<0.001*	0.344	<0.001*	<0.001*
	Range	7.5-10	7.1-9.5	8.5-10.5					
Sodium (mEq/L).	Mean ± SD	135.63±7.16	134.83±8.50	140.10±3.79	5.253	0.007*	0.891	0.033*	0.010*
	Range	130-145	128-146	135-145					
Potassium (mmol/L)	Mean ± SD	4.73±0.76	4.81±0.81	4.20±0.54	6.412	0.003*	0.909	0.014*	0.004*
	Range	3.4-5.8	3.4-5.9	3.5-5.5					

Table (6): Comparison between patient groups (I&II) and control group (III) as regard Copeptin level.

Copeptin (pmol/l)	**Groups**			**ANOVA**		**TUKEY'S Test**		
	Group I	**Group II**	**Group III**	**F**	**P-value**	**I & II**	**I & III**	**II & III**
Mean ± SD	47.09±22.72	70.92±24.38	10.85±6.14	71.670	<0.001*	<0.001*	<0.001*	<0.001*
Range	50-120	50-180	1-16					

Table (7): Relation between Copeptin and sex in all studied groups.

Sex	Copeptin (pmol/l)		T-Test	
	N	Mean±SD	t	P-value
Male	37	58.346±28.376	-0.246	0.806
Female	23	60.078±23.078		

Table (8): Correlations between Copeptin and All studied parameters in groups (I, II, III).

Correlations		
	Copeptin (pmol/l)	
	r	**P-value**
Age (years)	-0.176	0.179
Weight (kg)	-0.203	0.120
Height (cm)	-0.194	0.137
BMI (kg/m2)	-0.160	0.223
Systolic BP (mmhg)	-0.197	0.132
Diastolic BP (mmhg)	-0.085	0.520
HB (g/dl)	-0.120	0.362
Urea (mg/dl)	0.165	0.207
Creat (mg/dl)	0.524	<0.001*
GFR (ml/min/1.73m2)	-0.603	<0.001*
Albumin (g/dl)	-0.389	0.002*
Calcium (mg/dl)	-0.264	0.042*
Sodium (mEq/l)	-0.194	0.137
Potassium (mmol/l)	0.014	0.915

4. Discussion

This study aimed to assess plasma copeptin level by ELISA in children with renal impairment as a marker of diagnosis and to assess its value as an indicator of disease progression.

The present study was a case-control study, conducted during the period from February up to November 2020, on 90 children aged from 5 to 18 years, males and females, age and sex-matched.

They were divided into three groups: Group I: Included 30 children suffering from chronic kidney disease on conservative treatment. Group II: Included 30 children suffering from chronic kidney disease on dialysis. Group III: Included 30 children of healthy age and sex. In our study, the incidence of CKD was greater in males than females, Mean±SD11.30±3.62, 11.40±3.90 in Group I, Group II respectively as with P value 0.994.Male percent was 60% while female was 40% which came in agreement with [9] who found that the incidence and prevalence of CKD was greater in males than females because of the higher frequency of congenital abnormalities of the kidney and urinary tract in males.

In Our Study Weight, Height and subsequently BMI were highly affected in diseased children comparable with those healthy ones and also affected between the group on conservative treatment and the other group on dialysis. Mean ± SD was 16.35±2.94, 16.09±2.34, and 19.58±2.92 in Group I, Group II, and Group III

respectively as regard BMI with P value <0.001*. Growths impairment was a common and perhaps the most visible complication of CKD in children. The degree of growth impairment increased as GFR declined, even though a significant decrease in growth was seen at all levels of kidney function. We also believe our study highlights the need for greater attention to weight status and nutrition during CKD progression.

This came in agreement with the study of [10] who found that intensified weight loss (reflected by BMI changes) began earlier specifically after eGFR fell below 35 mL/min/1.73 m2. That weight loss was, in particular, more pronounced among children and adolescents who had glomerular causes of CKD and was associated with a higher risk of ESRD.

Hypertension was highly noticeable in our study as about 60% of diseased children suffered from hypertension either systolic or diastolic, with Mean ± SD 114.93±14.79,113.83±13.04, 98.66±8.80 in Group I, Group II, and Group III respectively as regard systolic blood pressure with P value <0.001* and Mean ± SD 78.43±10.09 77.33±11.57 67.00±7.38 in Group I, Group II, and Group III respectively as regard diastolic blood pressure with P value<0.001*, which came in agreement with Becherucci et al. (2016) [9]. who said that unlike many of the complications of CKD, hypertension could be present from the earliest stages of the disease and its prevalence increased as GFR progressively declined and that 54% of the children had high blood pressure levels despite the use of antihypertensive medications.

We found that as the kidney disease progressed, the percentage of patients with hypertension increased and plasma copeptin level increased which agreed with the study of Afsar [11] who showed a positive association with copeptin and hypertension and said that recent evidence suggested that elevated blood pressure was associated with increased copeptin levels.

In our study GFR was highly significantly decreased in children with CKD as kidney disease progressed, group I on conservative treatment GFR ranged from 30-60 ml/min/ 1.73 m2 and in group II on dialysis GFR ranged from 14-55 ml/min/ 1.73 m2 which came in agreement with [12] which stated that GFR is generally accepted as the best overall index of kidney function. And they referred to a GFR less than 60 ml/min/ 1.73 m2 as decreased GFR and a GFR less than 15 ml/min/ 1.73 m2 as kidney failure with Mean ± SD 44.56±13.47,6.78±2.71, 102.45±11.66 in Group I, Group II, and Group III respectively as regard GFR with P value <0.001*. Our findings also were in agreement with [13] who found that chronic kidney disease had evolved over time and the international guidelines defined that condition as decreased kidney function shown by glomerular filtration rate (GFR) of less than 60 mL/min per 1·73 m^2, or markers of kidney damage, or both, of at least 3 months duration, regardless of the underlying cause.

In our study all diseased children whether on treatment or dialysis suffered from anaemia, mean ± SD 10.69±1.43,9.95±1.43,12.56±1.25 in Group I, Group II, and GroupIII respectively as regards Hemoglobin level with P value <0.001* and there was a significant decrease in haemoglobin level in group I and II in comparison to control group III. This agreed with Atkinson and [14] who reported that in children with CKD who did not take iron supplements, iron deficiency was associated with younger age, lower haemoglobin, and lower ferritin levels. Anemia and iron deficiency are important complications in pediatric patients with CKD.

And with [15] who stated that anemia was an important risk factor for the development and progression of cardiovascular disease. In addition, anemia negatively affected the quality of life of patients with CKD and their caregivers.

In our study groups, I and II who were on treatment or on dialysis showed a

significant increase in potassium levels when compared with the control group III which required regular monitoring of potassium to avoid cardiac complications, which came in agreement with [16] who said that advanced CKD frequently led to inadequate renal potassium (K) excretion owing to loss of nephron mass, and thus a decrease in the number of collecting ducts to secrete K. Hyperkalemia is a well-recognized risk factor for arrhythmias and cardiac arrest and it predictably leads to higher mortality.

Also [17] found that hyperkalemia was one of the most common and life-threatening electrolyte disorders in CKD and ESRD, and that it became increasingly prevalent as CKD advanced.

Our results showed that there was statistically significant decrease in patient groups when compared with control group as regard albumin level and that decrease was more in patients who were on dialysis. This came in agreement with the study done by [18]. who reported that hypoalbuminemia was associated with excess mortality in patients with kidney disease. Albumin was an important oxidant scavenger and an abundant carrier protein for numerous endogenous and exogenous compounds. And found that chronic kidney disease affected all these determinants and might result in altered pharmacokinetics and increased risk of toxicity.

In our study patient groups showed a wide range of sodium level (128 mEq-146 mEq) this came in agreement with the study of [19] who said that children with CKD might experience a spectrum of dysnatremias, ranging from deficit to excess. Children with obstructive uropathies and/or renal dysplasia might experience excessive urine sodium loss, requiring sodium supplementation. Some peritoneal dialysis patients had excessive sodium loss with ultrafiltration, which might also need to be replaced. It had been suggested that, without adequate repletion, chronic total body sodium deficit might contribute to growth impairment.

We found that plasma copeptin was normal among healthy individuals. The range of plasma copeptin concentration was between 1 and 16 pmol/L which came in agreement with the study of [20] who found that the range of plasma copeptin concentration was between 1 and 13.8 pmol/L. Similarly, copeptin concentrations in healthy volunteers of a population of 5000 individuals ranged between 1 and 13 pmol/L (upper 97.5 percentile).

In our study we found that there was insignificant difference between males and females as regard copeptin level. Our results were disagreed with [21] who found that males consistently show slightly higher values than females, but the difference in median values was only about 1 pmol/L. Also, we disagreed with Afsar (2017) [11] who found that the baseline plasma copeptin concentration was positively associated with male sex. In Our Study, we found that plasma copeptin level increased as the stage of CKD increased as it was higher in the patients group who were on dialysis (group II) when compared with those on conservative treatment (group I) and there was a significant increase in plasma copeptin level in patient groups when compared with control group and this was in agreement with the study of [22]. who said that the close association between copeptin and renal failure in ICU patients was not surprising, given the important role of vasopressin in water and sodium resorption, vascular tone of renal vessels and kidney perfusion. So, these data indicated that copeptin contributes to hemodynamic alterations resulting in tissue hypoperfusion.

Our study agreed also with [15] who found that increased copeptin was associated with decreased GFR and increased CKD stage and there were two suggested mechanisms, first, as copeptin was cleared by kidney excretion, copeptin levels would tend to increase as kidney function decreased. Second, in patients with lower kidney function, more copeptin was released, because the AVP system was activated due

impaired urine concentrating capacity to maintain water homeostasis.

In our study we found that Copeptin concentrations increased in parallel with decreased kidney function. Mean copeptin concentration was 10.85±6.14 pmol/L in healthy individuals with GFR more than 90 mL/min/1.73 m2, mean copeptin concentration was 47.09±22.72 pmol/L in patients with eGFR 30-60 mL/min/1.73 m2 and mean copeptin concentration was 70.92±24.38 pmol/L in patients with eGFR 14-55 mL/min/1.73 m2 which came in agreement with the study of Krane et al. (2017)[23] who showed the following in their study, mean copeptin concentrations were 5.6 pmol/L, 6.7 pmol/L, 13.4 pmol/L, 17.05 pmol/L, 25.3 pmol/L, and 119.15 pmol/L in patients with eGFR more than 90 mL/min/1.73 m2,, eGFR 60–89 mL/min/1.73 m2,, eGFR 45–59 mL/min/ 1.73 m2, eGFR 30–44 mL/min/1.73 m2, eGFR 15–29 mL/min/1.73 m2, and eGFR less than 15 mL/min/1.73 m2, respectively and said that copeptin level was increasing with decreasing eGFR, but copeptin was increasing much faster than AVP, suggesting that the peptide clearances differed when renal function was impaired.

Our findings showed that as plasma copeptin level increased, more kidney impairment was developed Mean ±SD47.09±22.72 70.92±24.38 10.85±6.14 in Group I, Group II, and GroupIII respectively as regards Copeptin level with P value <0.001*, which came in agreement with the study of [23] who found that plasma copeptin concentrations were associated with adverse outcomes in patients with impaired renal function and evaluated the association of copeptin with cause-specific mortality among patients with the whole spectrum of renal function (CKD 0–5D). Also, Roussel et al. (2014) demonstrated that copeptin content increased with progressing CKD, which might suggest a causal relationship of the two. And that copeptin content was proportional to both disease progression and kidney size.

And agreed with [24] and [25] who showed that copeptin content increased with CKD progression, they also found that Patients who were in need to start dialysis therapy had a greater higher copeptin content than those with no need to be dialyzed, despite similar creatinine clearance and concluded that the assessment of copeptin content was a predictor of CKD development. We found that plasma copeptin concentrations showed a positive correlation with creatinine ($p < 0.001$) as in the study of [26] who reported that high copeptin level at baseline was associated with a decline in kidney function.

5. Conclusion

Plasma Copeptin was highly significantly increased in patients with chronic kidney diseases and its level was increased as serum Creatinine increased and eGFR decreased. Plasma Copeptin was increased as the stage of kidney disease progressed.

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