Original Article

Comprehensive Assessment of Correlation of Copeptin with Some Electrolytes in Adult Patients with Chronic Kidney Disease in Babylon Governorate

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Abstract

Background: Chronic kidney disease (CKD) is a rapidly expanding public health problem typified by either an increased excretion of albumin in the urine, a reduced glomerular filtration rate, or both. Copeptin is formed by the breakdown of arginine vasopressin precursor (AVP), produced in the hypothalamus in an equimolar ratio and processed during axonal transport. AVP is an unstable peptide with a short half-life of five to twenty minutes. Compared to AVP, copeptin is a stable molecule that is simple to test. **Objective:** This study aims to determine whether plasma copeptin is a helpful biomarker for predicting chronic renal disease and the relationship between copeptin and certain electrolytes. **Materials and Methods:** This research involved a case–control study involving 88 participants, 44 individuals diagnosed with CKD, and 44 apparently healthy individuals serving as the control group. Blood samples were collected to measure copeptin, calcium, potassium, and sodium. Other variables, including age and body mass index (BMI), were also assessed. BMI was calculated by dividing weight in kilograms by height in meters squared. Statistical analyses, including Pearson correlation and receiver operating characteristic curve analysis, were conducted to evaluate the diagnostic accuracy of copeptin. **Results:** This study found that the copeptin concentration in the patient group increased significantly ($p < 0.05$) compared to the control group, and the area under the curve for copeptin was 0.994. **Conclusion:** The results emphasize that copeptin plays a crucial role in CKD.

Keywords: Chronic kidney disease, copeptin, sodium

Introduction

Chronic kidney disease (CKD) is characterized by decreased glomerular filtration rate, increased excretion of albumin in the urine, or both, which is a growing public health concern. Damaged kidney structure detected by imaging investigations or renal biopsy that lasts longer than three months. One of the main causes of illness and mortality in the globe is CKD.[1]

Increased cardiovascular diseases, acute renal injury, anemia, mineral and bone disorders, and fractures are among the complications.[2] Globally, the prevalence is estimated to be between 8% and 16%.[3] Furthermore, it has become a serious public health issue in Babylon city. In Iraq, CKD is among the top five life-threatening diseases. It was responsible for approximately 7000 deaths attributed to renal failure in 2015, as reported by the Iraqi Ministry of Health.[4] It is recognized as a devastating condition that has reached epidemic proportions due to the rising prevalence of its associated risk factors.[5,6]

Copeptin is a 39-amino acid glycopeptide produced in the hypothalamus with a short half-life of 5–20 min. It is formed from the cleavage of the precursor of arginine vasopressin (AVP).[7] AVP is an unstable peptide with serious technical issues with quantification. Copeptin is a chemical that is easily measurable and stable.[8] Copeptin

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is produced in an equimolar ratio for AVP, and because of this, circulating copeptin is currently employed in a variety of clinical circumstances, such as renal disorders, as a substitute for AVP.[9]

The kidneys are largely responsible for managing bodily fluids, electrolytes, and acid–base balance. Multiple derangements, such as hyperkalemia, metabolic acidosis, and hyperphosphatemia, are expected to be brought on by CKD and end stage renal disease. These derangements can lead to significant consequences, such as muscle wasting, bone mineral problems, vascular calcification, and death.[10] Patients with CKD frequently experience electrolyte abnormalities and acid–base imbalances.[11]

Potassium (K) is one of the most abundant intracellular cations, accounting for over 98% of the body's intracellular content and less than 2% extracellular. The energy-dependent formation of the transcellular K gradient (Na-K-ATPase) is essential for many cellular activities, including the maintenance of cell membrane potential.[12]

The kidneys are the organs primarily responsible for maintaining K homeostasis because they eliminate 98% of the daily K intake in response to increasing blood K, aldosterone, distal renal tubular sodium (Na) supply, and tubular fluid flow.[13]

In medicine, sodium abnormalities are the most prevalent electrolyte problems. These problems are common in patients with CKD. As a result, there may be a significant chance of death. As chronic renal disease progresses, both hypernatremia and hyponatremia can occur, even with appropriate water intake. This is mainly because of the kidney's limited capacity for diluting and concentrating.[14,15]

The chemical element calcium (Ca^{2+}) is an alkaline earth metal that, when exposed to air, forms a reactive metal that develops a dark oxide-nitride layer.[16] The mineral calcium is the most prevalent in the human body in terms of quantity. Serum-ionized calcium is regulated within a small range through hormone control of the three-tissue axis consisting of the gut, kidney, and bone. Para thyroid hormone (PTH) and 1,25D are the two main hormones at play.[17]

Materials and Methods

This study was a case-control study and included a total of 88 subjects, 44 of whom suffered from CKD (19 females and 25 males) and 44 apparently healthy control subjects (19 females and 25 males). All samples were collected during the period between October and November 2023. Samples were collected from dialysis units at Marjan and Imam Al-Sadiq teaching hospitals in Babylon city, Iraq. The study included patients aged ranged between 18 and 63 years. Many pieces of information were gathered, such as age, sex, weight, height, and medical history of the patients. Nephrologists selected the patient groups based on selection criteria and exclusion criteria, which included smokers and subjects with metabolic syndrome, diabetes, hypertension, pregnancy, liver disease, cardiovascular disease, obesity, and autoimmune diseases.

A blood sample was collected from the vein of each participant. The patient's sample was taken at prehemodialysis time. Blood was pushed slowly into a gel tube and allowed to clot at room temperature for 10–15 min, then centrifuged at 3000 × g for 10 min. The serum was obtained, transferred into Eppendorf tubes and then used to determine copeptin, potassium, calcium, and sodium levels.

Determination of study parameters

Determination of human serum (Copeptin) concentration by ELISA

Serum copeptin levels were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions (Bioassay Technology Laboratory). Copeptin levels ranged from 0.05 to 20 ng/ml.

Determination of serum calcium ion

The serum calcium (ionized) levels were determined using an electrolyte analyzer instrumentation. This method is based on the ion selective electrode principle. The electrolyte analyzer (Fuji-Dry Chem), Europe, was used to test this parameter using the Ca kite from Fuji Xerox Co., China.

Determination of potassium ion

The serum potassium (K^+) levels were calculated using the Genx Smart-150 Chemistry Analyzer. This device uses a potassium measurement kit from Giesse Diagnostics, which relies on the utilization of potassium-dependent pyruvate kinase and an enzymatic colorimetric technique (PDPK). In this method, the pyruvate produced is converted to lactate, together with the transformation of an nicotinamide adenine dinucleotide hydrogen analog to an Nicotinamide adenine dinucleotide analog. The potassium concentration in the serum is proportionate to the corresponding decrease in optical density at 380 nm (23).

Determination of sodium

The current method is based on the reaction of sodium with a selective chromogen, which produces a chromophore whose absorbance varies directly with the concentration of sodium in the test specimen. The spectrophotometer (Jenway) from Italy was utilized to test this parameter using the Na kit manufactured by CHEMPAK, India.

Ethics approval

Before collecting samples, all study participants were informed and allowed to consent verbally. A local college and hospital ethics committee examined and approved the study protocol, subject information, and permission form under the document number [IRB: 5-25, 8/8/2023].

Statistical analysis

The results of the current comparative study of the patient and control groups were calculated statistically using the *t*-test to determine the mean difference between the control and patient groups, with a significant level set at *P*-value ≤ 0.05, and the correlation between studied parameters was done by using Pearson correlation. The receiver operating characteristic (ROC) curve analysis for copeptin levels was performed by using the IBM Statistical Package for the Social Sciences (SPSS V. 26).

Results

The demographic characteristics of the study participants

The results of the current comparative study of the patient and control groups were calculated statistically using the *t*-test to determine the difference in mean between the control and CKD groups and the correlation between the different parameters of all patients. The total number of study groups was 88 adults divided into two control groups (44). The results of the 44 patients and their ages, which ranged between 18 and 63 years, from demographic data are shown in Table 1.

BMI

The data in Table 1 showed that body mass index (BMI) was significantly higher in control ($P \leq 0.05$); the mean and SD were 26.90 ± 2.08 compared to patients with CKD; the mean and SD were 24.81 ± 1.45.

Discussion

As indicated in Table 2, we found a significant difference ($P < 0.05$) in the mean levels of copeptin between the patient and control groups in the current investigation. When comparing the patient group to the control group, serum copeptin levels were higher in the former.

CKD is associated with diminished kidney function, leading to increased copeptin levels. In response to osmotic shifts and stress, the body releases copeptin, a stable consequence of the prohormone vasopressin.[18] The kidneys may have difficulty in removing waste from the body and maintaining fluid balance in people with CKD. Because the kidneys cannot adequately remove copeptin from the body, this might result in a buildup of copeptin in the bloodstream.[19]

Copeptin levels are elevated in CKD due to changes in vasopressin activity and the body's reaction to preserving electrolyte and water balance. Copeptin levels may increase further in individuals with CKD when kidney function fails, which could lead to problems such as electrolyte imbalances and fluid retention.[20]

Table 2 displays the distribution of electrolytes among the groups under investigation. In comparison to the control group, the serum potassium levels were considerably higher ($P < 0.05$). When compared to the control group, the serum sodium (Na^+) levels in the patients were considerably lower ($P < 0.05$), which is summarized in Table 3. This study supports the findings of Molla, Degef, Bekele, *et al*.[21] that aberrant serum electrolyte levels, specifically Na^+ and K^+, may be associated with the occurrence and severity of renal injury.

The study also revealed a substantial decrease in calcium in CKD patients compared to controls. Decreased activation of vitamin D, diminished renal function in converting vitamin D to its active form, decreased intestinal absorption of calcium, and increased urinary calcium loss can all contribute to low calcium levels. Low calcium levels can also be exacerbated by an imbalance in the blood phosphorus levels.[22] The findings of the current study concur with those of Keung and Perwad,[23] DiMeglio and Imel,[24] and Barreto *et al*.,[25] who discovered that plasma calcium levels of CKD patients were considerably lower than those of healthy controls.

In comparison to CKD patients, the BMI of the control group was much higher. Cachexia, or muscle wasting, is a common occurrence in CKD patients and can lower BMI. Due to reduced renal function, the body breaks down muscle tissue for energy, which causes muscle wasting. In addition, individuals may lose their appetite for a variety

Table 1: Demographic characteristics of the study groups

Variable	Patients (Mean ± SD)	Control (Mean ± SD)	*P* value
Age (years)	49.66 ± 9.06	49.08 ± 8.52	0.781 NS
BMI(kg/m²)	24.81 ± 1.45	26.90 ± 2.08	0.001*
Number	44	44	

BMI: body mass index, NS: Nonsignificant, * ($P \leq 0.05$)

Table 2: Comparison of copeptin, potassium, calcium, and sodium levels between study participants

Variable	*N*	Patients (Mean ± SD)	Control (Mean ± SD)	*P* value
Copeptin (ng/ml)	44	3.28 ± 0.50	1.70 ± 0.42	0.001*
Potassium (mmol/l)	44	4.83 ± 0.97	3.85 ± 0.62	0.01*
Calcium(mg/dl)	44	4.12 ± 0.24	8.41 ± 0.62	0.001*
Sodium(mmol/l)	44	128.89 ± 4.27	140.60 ± 3.31	0.001*

* ($P \leq 0.05$)

Table 3: Pearson correlation between the study variables in the patients group

Study variables		BMI	Copeptin	Potassium	Calcium	Sodium
BMI	R	—	−.167	−.21	.175	.066
	P value	—	.279	.890	.255	.669
Copeptin	R	−.167	—	−.106	.323*	.069
	P value	.279	—	.493	.033	.655
Potassium	R	−.021	−.106	—	−.146	.188
	P value	.890	.493	—	.345	.223
Calcium	R	.175	.323*	−.146	—	−.156
	P value	.255	.033	.345	—	.312
Sodium	R	.066	.069	.188	−.156	—
	P value	.669	.655	.223	.312	—

BMI: body mass index

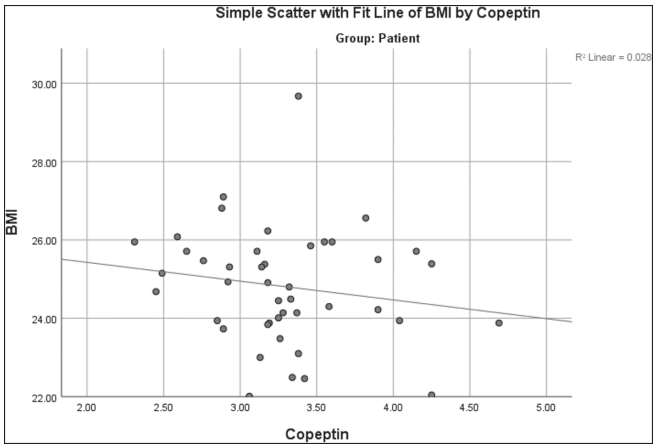

Figure 1: Correlation between copeptin and body mass index

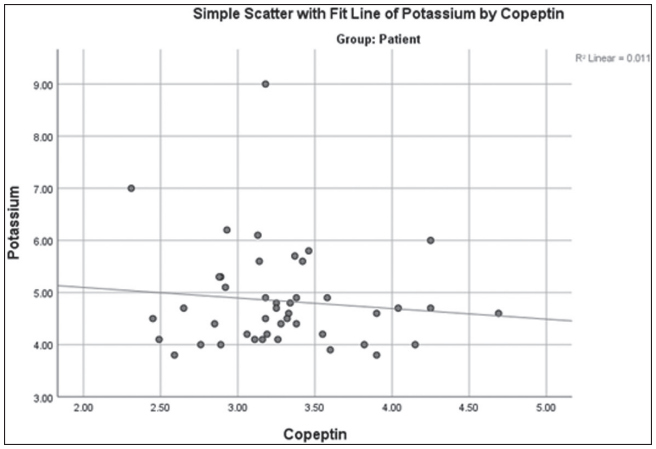

Figure 2: Correlation between copeptin and potassium

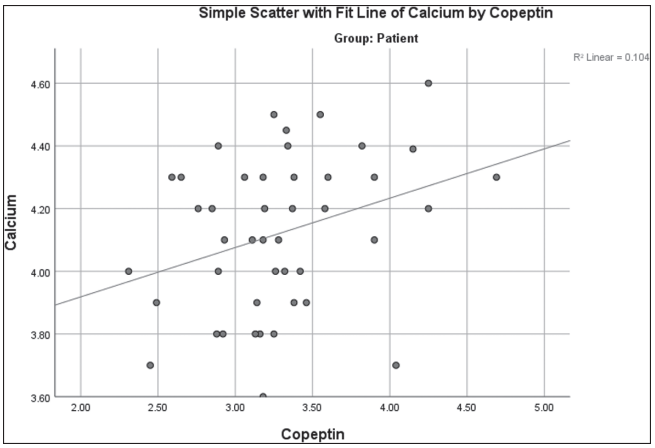

Figure 3: Correlation between copeptin and calcium

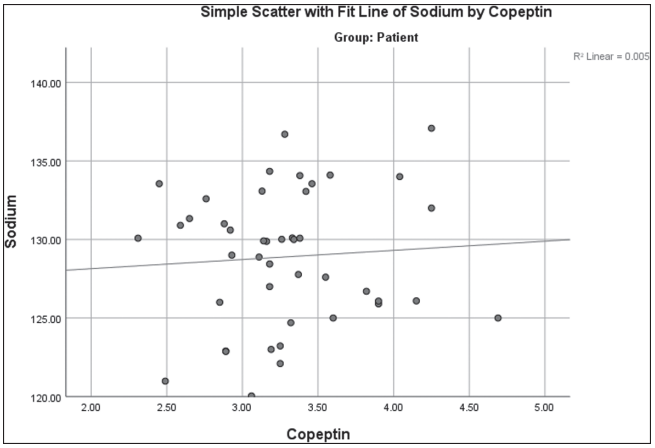

Figure 4: Correlation between copeptin and sodium

of reasons, including sickness, altered tastes, and dietary limitations.[26] This lower food intake has been linked to BMI decline and weight loss.[27] BMI might drop and weight loss due to malnutrition.[28] Correlation between measured parameters as illustrated in Figures 1–4.

The findings of the current study indicated that copeptin, potassium, sodium, and BMI were not related in the patient group (*P* value > 0.05). However, copeptin and calcium levels showed a significant positive connection (*P* value = 0.033, r = 0.323), as illustrated in Table 3. Results from ROC analysis showed a substantial discriminative value, suggesting that patients with chronic renal disease may benefit from using it as a diagnostic marker or predictor as shown in Table 4 and Figure 5.

ROC analysis presents results that indicate a strong discriminative value that could be used as a

Table 4: Area under the curve for copeptin between the patient and control group

Test Result Variable: copeptin						
AUC	Specificity	Sensitivity	SE	*P* value	95% Confidence Interval	
					Lower Bound	Upper Bound
.994	100%	97%	0.05	**0.000**	.984	1

SE: standard error, AUC: area under the curve

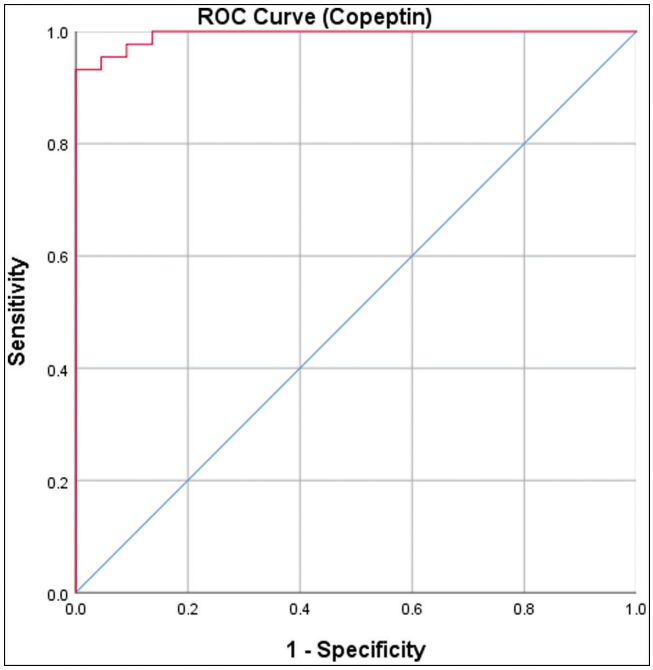

Figure 5: Receiver operating characteristic curve analysis for copeptin between the patients and control group

prediction or diagnostic marker for patients with CKD.

Conclusion

This study demonstrated that patients with CKD had higher levels of copeptin, potassium, and lower levels of calcium and sodium. In addition, there was no correlation between copeptin, K, and Na; however, there was a correlation between copeptin and calcium. Further, copeptin can be a prognostic marker in CKD.

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Conflicts of interest

There are no conflicts of interest.

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