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Study About Role of Copeptin as a Diagnostic Marker and Cardiovascular Dysfunction in Patients with Chronic Kidney Disease in Tertiary Care Center

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ABSTRACT

Background: Chronic kidney disease (CKD) has a high prevalence around the world, which contributes to significant morbidity and mortality rate, and a huge expenditure is spent on CKD management, and it poses an enormous threat to public health.

Objective: The present study investigated the association of serum copeptin concentration with healthy volunteers as a control, CKD stage 3 with heart failure, CKD stage 3 and CKD stage 4 and 5 groups.

Methods: This study was designed to be a Cohort study, in which data were collected prospectively. Seventy-two chronic kidney disease individuals at different stages early stage (CKD 3a and 3b), advanced stage (CKD4 and5) and CKD with heart failure (CKD 3b) and 15 unrelated healthy individuals were included in this study. The important clinical characteristics of study participants such as haemoglobin (Hb), serum albumin, total cholesterol, triglycerides, calcium, phosphorus, uric acid and copeptin level were measured using standard protocols.

Results: We found that the serum copeptin concentration was significantly associated with the CKD stage 3 with heart failure, CKD stage 3 and CKD stage 4 and 5 groups. Further, the significant correlation was also observed between the serum copeptin and e GFR, creatinine, BNP and Copeptin/ creatinine, copeptin*BNP/ creatinine, and copeptin/ eGFR ratio, LVDd and LVMI.

Conclusion: In conclusion, the serum copeptin increased in patients with CKD with decreasing e GFR and also in patients with CKD and heart failure (EF <40%). There was a significant association of serum copeptin between groups 2, 3 and 4.

Key Words: Creatinine, CKD, Copeptin, EGFR

INTRODUCTION

Chronic kidney disease (CKD) has a high prevalence around the world, which contributes to significant morbidity and mortality rate. Cardiovascular problems are known to be the leading cause of death in CKD patients,[1] and the occurrence of cardiovascular events are remarkably higher in CKD patients than the non-CKD population. Patients with early to middle phase chronic kidney disease (CKD) commonly have CVD. The incidence of CVD has been shown to increase with decreasing glomerular filtration rate (GFR), which means that CVD has become a major cause of death, before patients progressing to ESRD.[2-4]. This highlights the urgency for early detection and effective intervention to control mortality.[5]

Vasopressin plays a central role in water homeostasis but it has been recognized to be associated with adverse effects in several chronic diseases. Recently, copeptin has been increasingly used as a surrogate marker instead of vasopressin, as they are co -secreted, and copeptin is easier to measure. AVP is a small non - peptide that must be isolated from plasma by chromatography and further concentrated before the assay, which notoriously complicates the analytical proce-

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dure. Even with RIAs, AVP remains difficult to measure: Its plasma $t_{1/2}$ is short, it is not stable in vitro, and it interferes with plasma components or factors such as heparin. Also, storage at - 20°C and freeze-thaw cycles result in a decline of plasma vasopressin levels over time. These issues have limited the use of AVP measurement in clinical practice. The C -terminal portion of pro- vasopressin (copeptin) is the precursor of vasopressin (AVP) and is more stable under physiological conditions than Vasopre in itself. In healthy populations and patients with various cardiovascular diseases, there is a significant positive correlation between copeptin and AVP levels. The association between copeptin and CVD in patients with CKD remains unknown. The present study was, therefore, undertaken to investigate the correlation between BNP and copeptin in non-dialysis patients with CKD.

The close correlation between different biomarkers likely reflects the complexity of the pathophysiological processes leading to CVD in CKD. Although promising, available data on serum biomarkers for risk prediction are currently insufficient to recommend their routine use for prognostication and as a guide to therapy in CKD patients. In the present study we aimed to study the role of copeptin as a diagnostic marker in various stages of CKD and its association with cardiovascular dysfunction and to assess the serum level of copeptin in Chronic kidney disease, and whether there is a significant correlation between eGFR, sodium, Potassium, Bicarbonate, serum and urine albumin, LVH, drug intake and comorbidities.

MATERIALS AND METHOD

Study Design

This study was designed to be a Cohort study, in which data were collected prospectively. Seventy-two chronic kidney disease individuals at different stages early stage (CKD 3a and 3b), advanced stage (CKD4 and 5) and CKD with heart failure (CKD 3b) and 15 unrelated healthy individuals were included in this study. The important clinical characteristics of study participants such as haemoglobin (Hb), serum albumin, total cholesterol, triglycerides, calcium, phosphorus, uric acid and copeptin level were measured using standard protocols. Furthermore, the age, gender, family history and lifestyle disorders such as diabetes mellitus and hypertension were collected using the standard questionnaire. This is an observational study with no interventions carried out on any subject.

Ethics statement

Procedures for the protection of human subjects, protocol of this study were approved by Institutional Ethical Review Committee of Sri Ramachandra Institute of Higher Education and Research, Chennai. Written informed consent will be collected from the study participants before collecting the blood samples. Following their clinical assessments by nephrologists, the peripheral blood samples were collected from 72 CKD and 15 controls individual s.

Subjects

The chronic kidney disease patients, visiting Department of Nephrology at Sri Ramachandra medical centre of Sri Ramachandra Institute of Higher Education and Research, Chennai, for their treatment were the main source of the samples for t his present study.

Sample size: n = 87 individuals

Inclusion criteria

Those patients within age 18 –80 years who satisfied the following criteria of CKD stage 3 and 4 and CKD (Non-HD) were offered enrollment in the study:

Exclusion criteria

Patients with Acute exacerbations of chronic renal insufficiency, Connective tissue disease, tumours, familial hyperlipidemia, nephrotic syndrome, Any medical, psychiatric, debilitating disease/ disorder or social condition that in the judgment of the investigator would interfere with or serve as a contraindication to adherence to the study protocol or ability to give informed consent or affect the overall prognosis of the patient. The patients selected none had been using hormones or immunosuppressive agents in the previous 3 months.

Biochemical variables

Haemoglobin: The haemoglobin levels of study subjects are calculated by flow cytometric SLS- haemoglobin method using Sysmex XT- 2000i/XT- 1800 automatic haematology analyser. The reference range of Hb: Female - 11.2 - 15.7 g/ Dl. Male- 13.7- 17. 5 g/ Dl.

Blood Urea Nitrogen (BUN)

The Blood Urea Nitrogen (BUN) is measured by Dimension® clinical chemistry system reuse/ glutamate dehydrogenase coupled enzymatic technique method.

Sodium, Potassium, Chloride: The sodium, potassium, Chloride levels of the present study were measured by Dimension® clinical chemistry system with QUIKLYTE module using Multiply Integrated Multisensor Technology (MIMT). The reference range of Sodium: 134 -145 mmol/ L Potassium: 3. 2 - 5.0 mmol/ L and Chloride: 96 - 106 mmol/ L

Bicarbonate: The ECO2 Flex- reagent method used by the Dimension® clinical chemistry system is an in vitro diagnostic test intended for the quantitative determination of bicarbonate in serum, plasma by the enzymatic carbonated method.

Calcium: The calcium levels of the present study were measured using Dimension® clinical chemistry system of modification of the calcium o- cresolphthalein complexone (OCPC) method. The reference range of calcium is 8.5 - 10.1 mg/d L.

Creatinine: The CREA method used on the Dimension® clinical chemistry system is an in vitro diagnostic test intended for the quantitative determination of creatinine in serum, plasma and urine.

Phosphorus: In 1925, Fiske and Subbarow described a method for the determination of phosphorus in protein-free blood filtrates using ammonium molybdate.

Uric acid: Uric acid can be determined by direct measurement, by measurement of oxygen consumed or by measurement of hydrogen peroxide produced by the uricase reaction. This Uric Acid estimated by Fossati method. Hydrogen peroxide reacts with 4 - amino antipyrine (4 -AAP) in the presence of N, N- bis(4 -sulfobutyl)- 3,5-dimethylaniline, disodium salt (MADB) to produce a chromophore which is read bi-chromatically at 660/800 nm. The amount of dye formed is proportional to the uric acid concentration in the sample.

Albumin: In 1965, Rodkey introduced a convenient, direct method for determining albumin concentrations in serum utilizing a neutral buffered solution of bromocresol green (BCG) as the dye-binding indicator.

Total cholesterol: Cholesterol dehydrogenase" was begun by Flegg and Richmond Previously, Hernandez and Chaikoff and Hyun et al. had isolated a cholesterol ester hydrolase which was effective in producing free cholesterol from cholesterol esters.

Calculation of eGFR: Glomerular filtration rate (GFR) is the best overall index of kidney function. Normal GFR varies according to age, sex, and body size, and declines with age. Creatinine values were used to calculate an estimated glomerular filtration rate (eGFR), using the CKD -EPI formula. The stages of CKD (Chronic Kidney Disease) are mainly based on measured or estimated GFR (Glomerular Filtration Rate). There are five stages but kidney function is normal in Stage 1, and minimally reduced in Stage 2. Normal GFR is approximately 100 ml/min/1.73m3 GFR>60 ml/min/ 1.73m3 Stages 1 and2 CKD GFR 30- 59 ml/min/ 1.73m3 Stage 3 CKD GFR<30 ml/min/ 1.73m 3 Stages 4and5 CKD

Echocardiography

Two dimensional trans-thoracic echocardiographic was performed. The presence of valvular calcification (aortic and mitral valve, separately) was assessed, without any quantification tool.

LV Size linear Measurements

LVID Diastole (LVIDD): Perform at end-diastole (defined as the first frame after mitral valve closure or the frame with the largest LV dimensions/volume)

LVID Systole (LVIDS): Inner edge to inner edge, perpendicular to the long axis of the LV, at or immediately below the level of the mitral valve leaflet tips. Perform at end-systole (defined as either as the frame after aortic valve closure or the smallest LV dimension/volume.).

LV Mass Calculations linear Method:

LVID, IVS, PW Diastole: Electronic callipers should be positioned on the interface between myocardial wall and cavity, and the interface between wall and pericardium. Perform at end-diastole (previously defined) perpendicular to the long axis of the LV, at or immediately below the level of the mitral valve leaflet tips. LV mass = 0.8x (1.04x [(IVS+ LVID+PWT)3 - LVID3] + 0. 6 grams.

Serum Copeptin (Human CPP)

This ELISA (Enzyme-linked immunosorbent assay) kit uses the Competitive-ELISA principle. The micro ELISA plate provided in this kit has been pre-coated with Human CPP.

The concentration of Human CPP in the samples is then determined by comparing the OD of the samples to the standard curve. Reference range 6.8-35 ng/ ml.

Statistical analysis

We examined participant's characteristics by quartile of serum copeptin concentrations. serum copeptin was skewed, and was therefore natural log-transformed or modelled in quartiles. The demographics and biochemical characteristics were evaluated using the one -way analysis of variance or the Kruskal-Wallis test, and the Pearson chi-square test for continuous variables and categorical variables, respectively. Continuous variables were expressed as mean ± standard deviation or medians with interquartile (25^{th} and 75^{th} percentiles) ranges, and categorical variables were presented as the number and percentage of patients. Comparisons of continuous variables among groups were performed using ANOVA or Kruskal - Wallis tests. Comparison of nominal variables among these groups was performed using the $\chi 2$ test. Spearman's rank correlation (ρ) was used to determine the correlations of variables. All statistical tests were two-tailed and $P<0.05$ was considered significant. The analyses were performed using the SPSS software (version 16. 0).

RESULTS

The present study includes 87 individuals, out of which 51 are males (59%) and 36 are females (41%), All of them were divided into 4 groups:

Group 1: The healthy volunteers (control) group consisted of 15 individuals with 80% males and 20% females; the mean ±SD age was 48.8±19.4 years.

Group 2: The CKD stage 3 with heart failure (EF<40%) group consists of 77% male and 23 % of female individuals with the mean ± SD age 57.3 ± 12. 6 years.

Group 3: CKD stage 3a and 3b patients with 55% of males and 45% of females; their mean age was 57.3 and SD is 8.1.

Group 4: CKD stage 4 and 5ND. This group consist of 51.8% of males and 48.1 % of female patients with the mean ±SD age was 56. 9±16.1.

The other clinical and biochemical variables are studied for different groups such as HB, BUN, creatinine, sodium, potassium, bicarbonate, uric acid, Cholesterol, Triglycerides, calcium, Albumin and BNP. Serum copeptin was measured for all the studied individuals and documented as ng/ ml. Following the CKD-EPI formula, the GFR was calculated for all the study subjects. The studied important clinical and biochemical variables are documented in table 1. Similarly, for all the group's important characteristics of mean age, mean creatinine, mean BNP, mean uric acid, mean LVMI, mean LVD, mean triglycerides, mean cholesterol and mean serum albumin is documented in figure 1.

Table 1: Characteristics of age, gender and Laboratory Findings (represented as mean ±SD).

Characteristics	Control (n=15)	CKD with Heart dysfunction (n=17)	CKD stage 3 (n=28)	CKD stage 4 and 5 (n=27)
Age (yrs)	48.8 ± 19.4	57.3 ± 12. 6	57.3 ± 8.1	56.9 ± 16. 1
Gender (M/F)	12M/3F	13M/4F	15 M/ 13 F	14 M/ 13 F
Systolic (bp) (mm Hg)	12.8 ± 8.4	133 ± 15	135. 5 ± 17.6	143. 3 ± 22.7
Diastolic (bp) (mm Hg)	78 ± 8. 4	80 ± 12.2	81 ± 9.7	81.9 ± 11. 1
BUN mg/dl	12.6 ± 6.1	34.6 ± 13	18.6 ± 3. 6	41.1 ± 21. 3
Creatinine mg/dl	0.8 ± 6.1	1.9 ± 0.2	1.6 ± 0.3	4.0 ± 2.05
Hb g/dl	13.6 ± 1.5	10.5 ± 1.5	11.5 ± 2. 1	10 ± 1. 63
Sodium	137. 8 ± 2. 2	135. 3 ± 5. 8	138 ± 2.3	133. 4 ± 6. 18
Potassium	4.2 ± 0.3	4.5 ± 0.8	4.4 ± 0.3	4.5 ± 0.87
Bicarbonate	25.4 ± 2.6	24.8 ± 5.2	26 ± 1.8	21.5 ± 4.53
Uric acid	5.56 ± 2.6	7.7 ± 2.7	6.1 ± 1.7	8.4 ± 2.21
Total chlosteral	168. 4 ± 12.2	185 ± 35	179 ± 52	199. 4 ± 36.2
Triglycerides	114. 2 ± 16.4	125. 8 ± 32.7	181. 3 ± 105	157. 5 ± 80.7
e GFR	99.7 ± 8.1	36.4 ± 4.2	43.9 ± 9. 6	17.6 ± 7.91
Copeptin	39.1 ± 10. 9	88.6 ± 15. 6	47.6 ± 9. 5	97.4 ± 25. 6
Characteristics	Control (n=15)	CKD with Heart dysfunction (n=17)	CKD stage 3 (n=28)	CKD stage 4 and 5 (n=27)
BNP	298 ± 532	1070.2 ± 158. 2	907. 3 ± 190.9	1088.3 ± 263. 5
LVDd	49.4 ± 11. 2	67 ± 1. 7	52.6 ± 6. 7	53.9 ± 9.61
LVDs	34.2 ± 6.8	44.7 ± 1.0	35.1 ± 5. 4	37.3 ± 5.91
LVMI	90.2 ± 12. 4	141. 3 ± 7. 1	97.3 ± 23.2	105. 7 ± 24.6
Copeptin/ creatinine	47.9 ± 18. 1	46.7 ± 7.0	30.4 ± 4. 2	26.7 ± 6.3
Copeptin* BNP /Creatinine	21840 ± 43443	50768.3 ± 14020	27614.3 ± 6880.2	28648.1 ± 8750.3
Copeptin/ BNP	0.475 ± 0. 3	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.02
Copeptin/ e GFR	0.397 ± 0. 1	2.5 ± 0.7	1.2 ± 0.5	8.8 ± 9.08
Calcium	9.4 ± 0.4	9.2 ± 0.5	9.2 ± 0.6	8.7 ± 0.83
Phosphorus	3.6 ± 0.2	3.6 ± 0.5	3.4 ± 0.7	4.4 ± 1.24
HbA1C	7.26 ± 1.4	6.3 ± 1.7	6.7 ± 1.9	6.0 ± 0.68
albumin	3.72 ± 0.3	3.7 ± 0.5	3.7 ± 0.5	3.6 ± 0.58

Figure 1: Comparative statistics of the mean distribution of four groups.

Comparative statistics between the control group and CKD stage 3 with heart dysfunction group (group 2):

The comparative analysis between control and CKD stage 3 with heart dysfunction was presented in table 2. This association analysis revealed that the BUN (p=0. 001), creatinine (p=0.001), Hb(p=0.012), GFR (p=0.001), copeptin (p=0.001), BNP (p=0.03), LVDd (p=0.024), DVDs (p=0.029), LVMI (p=0.09), Copeptin/ BNP (p=0. 034) and Copeptin/ e GFR (p=0.001) were found to be significantly associated between the groups. However, the other studied characteristics were not found to have a significant association (Table 2).

Table 2: Comparative statistics between the control group and CKD stage 3 with heart dysfunction group

Characteristics	Control (n=15)	CKD with Heart Dysfunction (n=17)	p-Value
Age	48.8 ± 19. 4	57.3 ± 12. 6	0.411
Gender (M/ F)	12M/3F	13M/4F	-
Systolic (mm Hg)	12.8 ± 8.4	133 ± 15	0.41
Diastolic (mm Hg)	78 ± 8. 4	80 ± 12.2	0.725
BUN	12.6 ± 6.1	34.6 ± 13	0.001
Creatinine	0.8 ± 6.1	1.9 ± 0.2	0.001
Hb	13.6 ± 1.5	10.5 ± 1.5	0.012
Sodium	137. 8 ± 2. 2	135. 3 ± 5. 8	0.28
Potassium	4.2 ± 0.3	4.5 ± 0.8	0.357
Bicarbonate	25.4 ± 2.6	24.8 ± 5.2	0.771
Uric acid	5.56 ± 2.6	7.7 ± 2.7	0.058
Total cholesterol	168. 4 ± 12.2	185 ± 35	0.224
Triglycerides	114. 2 ± 16.4	125. 8 ± 32.7	0.394
e GFR	99.7 ± 8.1	36.4 ± 4.2	0.001
Copeptin	39.1 ± 10. 9	88.6 ± 15. 6	0.001
BNP	298 ± 531. 9	1070.2 ± 158. 2	0.03
LVDd	49.4 ± 11. 2	67 ± 1. 7	0.024
LVDs	34.2 ± 6.8	44.7 ± 1.0	0.029
LVMI	90.2 ± 12. 4	141. 3 ± 7. 1	0.009
Copeptin/ creatinine	47.9 ± 18. 1	46.7 ± 7.0	0.892
Copeptin* BNP/ Creatinine	21840 ± 43443	50768.3 ± 14020	0.124
Copeptin/ BNP	0.475 ± 0. 3	0.1 ± 0.0	0.034
Copeptin/ e GFR	0.397 ± 0. 1	2.5 ± 0.7	0.001
Calcium	9.4 ± 0.4	9.2 ± 0.5	0.43
Phosphorus	3.6 ± 0.2	3.6 ± 0.5	0.914
HbA1C	7.26 ± 1.4	6.3 ± 1.7	0.31
albumin	3.72 ± 0.3	3.7 ± 0.5	0.82

Comparative statistics between the control group and CKD stage 3 group (group 3)

The comparative analysis between control and CKD stage 3 was presented in table 3. This association analysis revealed that the creatinine (p=0.001), triglycerides (p=0.013), eGFR (p=0.001), Copeptin/ BNP (p=0. 034) and Copeptin/e GFR (p=0.001) was found to have significant association between the control group and CKD stage 3 group. However, the other studied characteristics were not shown to have any significant association (Table 2).

Table 3: Comparative statistics between control group and CKD stage 3 group (group 3)

Characteristics	Control (n=15)	CKD stage 3 (n=28)	p-Value
Age	48.8 ± 19. 4	57.3 ± 8.1	0.391
Gender (M/ F)	12M/3F	15 M/ 13 F	
Systolic (mm Hg)	12.8 ± 8.4	135. 5 ± 17.6	0.189
Diastolic (mm Hg)	78 ± 8. 4	81 ± 9.7	0.51
BUN	12.6 ± 6.1	18.6 ± 3. 6	0.096
Creatinine	0.8 ± 6.1	1.6 ± 0.3	0.001
HB	13.6 ± 1.5	11.5 ± 2. 1	0.071
Sodium	137. 8 ± 2. 2	138 ± 2.3	0.861
Potassium	4.2 ± 0.3	4.4 ± 0.3	0.21
Bicarbonate	25.4 ± 2.6	26 ± 1.8	0.648
Uric acid	5.56 ± 2.6	6.1 ± 1.7	0.344
Total cholesterol	168. 4 ± 12.2	179 ± 52	0.409
Triglycerides	114. 2 ± 16.4	181. 3 ± 105	0.012
E GFR	99.7 ± 8.1	43.9 ± 9. 6	0.002
Copeptin	39.1 ± 10. 9	47.6 ± 9. 5	0.169
BNP	298 ± 531. 9	907. 3 ± 190. 9	0.062
LVDd	49.4 ± 11. 2	52.6 ± 6. 7	0.569
LVDs	34.2 ± 6.8	35.1 ± 5. 4	0.869
LVMI	90.2 ± 12. 4	97.3 ± 23.2	0.584
Copeptin/ creatinine	47.9 ± 18. 1	30.4 ± 4. 2	0.096
Copeptin* BNP/Creatinine	21840 ± 43443	27614.3 ± 6880. 2	0.782
Copeptin/ BNP	0.475 ± 0. 3	0.1 ± 0.0	0.024
Copeptin/ e GFR	0.397 ± 0. 1	1.2 ± 0.5	0.001
Calcium	9.4 ± 0.4	9.2 ± 0.6	0.413
Phosphorus	3.6 ± 0.2	3.4 ± 0.7	0.171
HbA1C	7.26 ± 1.4	6.7 ± 1.9	0.468
albumin	3.72 ± 0.3	3.7 ± 0.5	0.752

Comparative statistics between the control group and CKD stage 4 and 5 groups (group 4)

The comparative analysis between the control subjects and CKD stage 4 and 5 group has revealed that the systolic blood pressure (p=0. 016), BUN (p= 0. 001), BUN (0.001), creatinine (p= 0.001), Hb (P= 0.006), sodium (p=0.010), bicarbonate (p=0.025), uric acid (p=0. 001), cholesterol (p=0.002), Triglycerides (p=0. 017), eGFR (p=0. 001), copeptin (p= 0.001), BNP (p= 0.028), Copeptin/ BNP (p=0. 032), Copeptin/e GFR (p= 0.001), Calcium (p= 0.02) and Phosphorus (p= 0.004) was found to have a significant association between the groups. However, the other studied characteristics are not found to significant association between the groups (Table 4).

Table 4: Comparative statistics between the control group and CKD stage 4 and 5group (group 4)

Characteristics	Control (n=15)	CKD stage 4 and 5 (n=27)	p-Value
Age	48.8 ± 19. 4	56.9 ± 16. 1	0.422
Gender (M/ F)	12M/3F	14 M/ 13 F	-
Systolic (mm Hg)	12.8 ± 8.4	143. 3 ± 22.7	0.016
Diastolic (mm Hg)	78 ± 8. 4	81.9 ± 11. 1	0.401
BUN	12.6 ± 6.1	41.1 ± 21. 3	0.001
Creatinine	0.8 ± 6.1	4.0 ± 2.05	0.001
Hb	13.6 ± 1.5	10 ± 1. 63	0.006
Sodium	137. 8 ± 2. 2	133. 4 ± 6. 18	0.01
Potassium	4.2 ± 0.3	4.5 ± 0.87	0.232
Bicarbonate	25.4 ± 2.6	21.5 ± 4.53	0.025
Uric acid	5.56 ± 2.6	8.4 ± 2.21	0.001
Total cholesterol	168. 4 ± 12.2	199. 4 ± 36.2	0.002
Triglycerides	114. 2 ± 16.4	157. 5 ± 80.7	0.017
e GFR	99.7 ± 8.1	17.6 ± 7.91	0.001
Copeptin	39.1 ± 10. 9	97.4 ± 25. 6	0.001
BNP	298 ± 531. 9	1088.3 ± 263. 5	0.028
LVDd	49.4 ± 11. 2	53.9 ± 9.61	0.442
LVDs	34.2 ± 6.8	37.3 ± 5.91	0.449
LVMI	90.2 ± 12. 4	105. 7 ± 24.6	0.252
Copeptin/ creatinine	47.9 ± 18. 1	26.7 ± 6.3	0.057
Copeptin* BNP/ Creatinine	21840 ± 43443	28648.1 ± 8750.3	0.744
Copeptin/ BNP	0.475 ± 0. 3	0.1 ± 0.02	0.032
Copeptin/ e GFR	0.397 ± 0. 1	8.8 ± 9.08	0.001
Calcium	9.4 ± 0.4	8.7 ± 0.83	0.02
Phosphorus	3.6 ± 0.2	4.4 ± 1.24	0.004
HbA1C	7.26 ± 1.4	6.0 ± 0.68	0.129
Albumin	3.72 ± 0.3	3.6 ± 0.58	0.392

Copeptin to Other Biochemical Indices between CKD stage 3 with heart failure and CKD stage 3, CKD stage 4 and 5 groups

The Copeptin to Other Biochemical Indices between the CKD stage 3 with heart failure and CKD stage 3, CKD stage 4 and 5 are documented in table 5 and 6. The association analysis between the groups revealed that the copeptin/creatinine ratio is significantly associated with the groups (p-value < 0. 001). The mean ratio was significantly greater in CKD 3 with heart failure when compared to other groups (Table 5 and 6). The copeptin/ eGFR ratio significantly associated between the groups (p-value < 0.001). It was greater in CKD stage 3 patients with heart failure when compared with CKD patients (group 3 and 4). Similarly, Copeptin* BNP/Creatinine was also highly significant when compared to other CKD groups (p-value < 0.001) (Table 5 and 6). Likewise, most of the studied clinical and biochemical variables were found to have a significant association between the groups. These results suggest that the copeptin has a significant association between the groups and may be used as an early diagnostic marker for CKD patients with and without heart failure.

Table 5: Comparative statistics between CKD stage 3 with heart failure (group 2) and CKD stage 3 group (group 3)

Characteristics	CKD with Heart failure (n=17)	CKD stage 3 (n=28)	p-Value
Age	57.3 ± 12. 6	57.3 ± 8.1	0.986
Gender (M/ F)	13M/4F	15 M/ 13 F	
Systolic (mm Hg)	133 ± 15	135. 5 ± 17.6	0.737
Diastolic (mm Hg)	80 ± 12.2	81 ± 9.7	0.832
BUN	34.6 ± 13	18.6 ± 3. 6	0.006
Creatinine	1.9 ± 0.2	1.6 ± 0.3	0.007
Hb	10.5 ± 1.5	11.5 ± 2. 1	0.172
Sodium	135. 3 ± 5. 8	138 ± 2.3	0.217
Potassium	4.5 ± 0.8	4.4 ± 0.3	0.746
Bicarbonate	24.8 ± 5.2	26 ± 1.8	0.509
Uric acid	7.7 ± 2.7	6.1 ± 1.7	0.139
Total cholesterol	185 ± 35	179 ± 52	0.728
Triglycerides	125. 8 ± 32.7	181. 3 ± 105	0.042
e GFR	36.4 ± 4.2	43.9 ± 9. 6	0.007

Table 5: *(Continued)*

Characteristics	CKD with Heart failure (n=17)	CKD stage 3 (n=28)	p-Value
Copeptin	88.6 ± 15. 6	47.6 ± 9. 5	0.001
BNP	1070.2 ± 158. 2	907. 3 ± 190. 9	0.027
LVDd	67 ± 1. 7	52.6 ± 6. 7	0.001
LVDs	44.7 ± 1.0	35.1 ± 5. 4	0.001
LVMI	141. 3 ± 7. 1	97.3 ± 23.2	0.001
Copeptin/ creatinine	46.7 ± 7.0	30.4 ± 4. 2	0.001
Copeptin* BNP/ Creatinine	50768.3 ± 14020	27614.3 ± 6880.2	0.001
Copeptin/ BNP	0.1 ± 0.0	0.1 ± 0.0	0.001
Copeptin/ e GFR	2.5 ± 0.7	1.2 ± 0.5	0.001
Calcium	9.2 ± 0.5	9.2 ± 0.6	0.947
Phosphorus	3.6 ± 0.5	3.4 ± 0.7	0.255
HbA1C	6.3 ± 1.7	6.7 ± 1.9	0.647
albumin	3.7 ± 0.5	3.7 ± 0.5	0.975

Table 6: Comparative statistics between CKD stage 3 with heart failure (group 2) and CKD stage 4 and5 group (group 4)

Characteristics	CKD with heart failure (n=17)	CKD stage 4 and 5 (n=27)	p-Value
Age	57.3 ± 12. 6	56.9 ± 16. 1	0.927
Gender (M/ F)	13M/4F	14 M/ 13 F	
Systolic (mm Hg)	133 ± 15	143. 3 ± 22.7	0.147
Diastolic (mm Hg)	80 ± 12.2	81.9 ± 11. 1	0.694
BUN	34.6 ± 13	41.1 ± 21. 3	0.286
Creatinine	1.9 ± 0.2	4.0 ± 2.05	0.001
Hb	10.5 ± 1.5	10 ± 1. 63	0.441
Sodium	135. 3 ± 5. 8	133. 4 ± 6. 18	0.403
Potassium	4.5 ± 0.8	4.5 ± 0.87	0.911

Table 5: *(Continued)*

Characteristics	CKD with heart failure (n=17)	CKD stage 4 and 5 (n=27)	p-Value
Bicarbonate	24.8 ± 5.2	21.5 ± 4.53	0.118
Uric acid	7.7 ± 2.7	8.4 ± 2.21	0.48
Total cholesterol	185 ± 35	199. 4 ± 36.2	0.306
Triglycerides	125. 8 ± 32.7	157. 5 ± 80.7	0.104
e GFR	36.4 ± 4.2	17.6 ± 7.91	0.001
Copeptin	88.6 ± 15. 6	97.4 ± 25. 6	0.231
BNP	1070.2 ± 158. 2	1088.3 ± 263. 5	0.808
LVDd	67 ± 1. 7	53.9 ± 9.61	0.001
LVDs	44.7 ± 1.0	37.3 ± 5.91	0.001
LVMI	141. 3 ± 7. 1	105. 7 ± 24.6	0.001
Copeptin/ creatinine	46.7 ± 7.0	26.7 ± 6.3	0.001
Copeptin* BNP/ Creatinine	50768.3 ± 14020	28648.1 ± 8750.3	0.001
Copeptin/ BNP	0.1 ± 0.0	0.1 ± 0.02	0.058
Copeptin/ e GFR	2.5 ± 0.7	8.8 ± 9.08	0.001
Calcium	9.2 ± 0.5	8.7 ± 0.83	0.058
Phosphorus	3.6 ± 0.5	4.4 ± 1.24	0.013
HbA1C	6.3 ± 1.7	6.0 ± 0.68	0.591
Albumin	3.7 ± 0.5	3.6 ± 0.58	0.602

Correlation between serum copeptin and other parameters between the groups 2, 3 and 4:

The correlation coefficient was done to evaluate the correlation between serum copeptin and other biochemical parameters in group 2, 3 and 4. The obtained correlated statistical data are shown in table (7). The e-GFR (p=0. 001), BNP (p=0.001), LVMI (p=0.001), LVDd (p=0. 001) were found to have a significant correlation with serum copeptin levels.

Table 7: Correlation between serum copeptin and other parameters between the groups

CKD stage 3 with heart failure			CKD stage 3			CKD stage 4 and 5		
Characteristics	r- value	p-Value	Characteristics	r- value	p- Value	Characteristics	r- value	p-Value
creatinine	0.558	0.118	creatinine	0.781	0.001	creatinine	0.811	0.001
e GFR	0.972	0.001	e GFR	0.928	0.001	e GFR	0.917	0.001
BNP	0.971	0.001	BNP	0.698	0.001	BNP	0.508	0.006
Uric acid	0.281	0.463	Uric acid	0.207	0.379	Uric acid	0.41	0.033
LVMI	0.976	0.001	LVMI	0.367	0.111	LVMI	0.67	0.001
LVDd	0.941	0.001	LVDd	0.575	0.007	LVDd	0.603	0.001
Triglycerides	0.142	0.713	Triglycerides	0.113	0.634	Triglycerides	0.184	0.356
Cholestrol	0.193	0.616	Cholestrol	0.36	0.118	Cholestrol	0.09	0.652
Sr. albumin	0.278	0.467	Sr. albumin	0.138	0.56	Sr. albumin	0.391	0.043

DISCUSSION

In the present study, the key finding is that elevated baseline serum copeptin is independently associated with increased risk of heart failure in CKD patients and CKD development in our studied population. To our knowledge, this is the first study to evaluate copeptin as a marker of CKD risk in our Indian subcontinent population.

Previous reports from cohort studies dealt only with a subset of participants and/or l limited outcomes.[6,7] Other population-based studies supporting the link between high levels of vasopressin and kidney function decline used surrogate markers of vasopressin secretion, such as fluid or plain water intake assessed by questionnaires, urine volume, or estimated urine osmolality.[8] Copeptin was associated with kidney length and prevalence of simple cysts in a cross-sectional study of the general population.[9] Copeptin was also studied in association with other specific kidney disease diagnosis, including acute tubulointerstitial nephritis and hydronephrosis, in a population-based study, and with markers of disease severity, including glomerular filtration rate (GFR) and albuminuria, in patients with ADPKD.[10] Plasma copeptin was also associated with the risk of severe kidney outcomes, including the doubling of plasma creatinine concentration and/or the incidence of ESRD, in people with type 1 or type 2 diabetes.[11] However, our study was not population-based but kind of cohort which included controls with different CKD stages and heart dysfunction group which was by previous population-based studies conducted in different geographical locations.

In our study serum, copeptin levels increased with decreasing e GFR and had a significant positive correlation with BNP and LVMI.[9] Plasma copeptin and microalbuminuria were positively associated with the Dutch population-based PREVEND study.[12] In this large cross-sectional study involving 7593 participants, microalbuminuria (urinary albumin excretion ≥30 mg per 24 h) was observed two times more frequently in the upper versus lower quintile of copeptin distribution. The association remained significant. In previous studies, plasma copeptin concentrations were inversely associated with eGFR and kidney length and positively associated with 24 - h urinary albumin excretion, urine osmolality and with the presence of renal cysts.[9,13] In our study, there was no significant association with serum albumin or microalbuminuria.

A very recent study conducted by Sofia Enhorning et al in 2019 observed that the increased level of copeptin independently predicts the development of both CKD and other specified kidney diseases, suggesting that copeptin can be used to identify individuals at risk for kidney disease development [14]. Similarly, the other study conducted in general populations was also found that the high copeptin levels are associated with the development and the progression of CKD in the general population.[15]

A study in 2018 by Stanisław Niemczyk et al., found the significantly increasing trend in plasma copeptin in patients with CKD progression. Further, the copeptin was significantly greater in patients with CKD accompanied by heart failure compared with healthy volunteers. There were no significant changes in copeptin content between patients with CKD and heart failure compared with those without heart failure. It appears, therefore, that plasma copeptin content is a potential marker of chronic kidney disease. Furthermore, a decrease in copeptin/NT-pro BNP and an increase in copeptin x NT- pro BNP/ creatinine ratio are useful markers for the assessment of heart failure in chronic kidney disease [16]. In our study, we used BNP levels and found that the results were similar by showing a significant association between Copeptin/creatinine, copeptin/ eGFR and copeptin/ BNP with the different studied groups.

There are limitations to our study. We have not measured the true GFR with one of the gold-standard methods, as they are not easily applicable to large cohort studies. Instead, we used estimations based on plasma creatinine levels. Large sample size and longer follow -up are the major strengths of the prospective cohort study but, our study has a very small

number of study participants. However, the present study revealed that the increased levels of serum copeptin and Copeptin/ creatinine, copeptin/eGFR, copeptin/ BNP may be an early diagnostic marker for CKD and heart failure in CKD patients.

CONCLUSION

The study finally concluded that the serum copeptin increased in patients with CKD with decreasing e GFR. There was a significant association of serum copeptin between groups 2, 3 and 4. Hence serum copeptin may be a useful biomarker for early diagnosis and progression of CKD in patients with and without heart failure. However, further studies are warranted with a larger number of sample size and multicentric study in different population to confirm our results.

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Conflict of Interest

None

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