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Copeptin Levels in Coronary Artery Disease: A Comparative Analysis

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ABSTRACT

Background: Coronary artery disease (CAD) is the most common heart disease, ranging from asymptomatic atherosclerosis and stable angina to acute coronary syndromes. Copeptin, a 39-amino acid glycoprotein, being stable, is easily measurable in peripheral blood and has potential as a biomarker in cardiac diseases like heart failure and acute coronary syndromes The objective of this study was to evaluate the differences in copeptin levels between CAD patients and healthy controls and to assess the potential of copeptin as a biomarker for CAD.

Methods: This observational case-control study, approved by the Institutional Ethics Committee, was carried out at S.C.B Medical College and Hospital, Cuttack, from 2020 to 2022. The study involved 80 CAD patients along with an equal number of age- and sex-matched controls. Exclusion criteria included acute or chronic kidney disease, traumatic heart disease, head injury, severe morbidity, or refusal to participate. Copeptin levels were measured by Enzyme-linked immunoassay (ELISA).

Results: Severe CAD was observed in 56.25% of the cases, with 30% having moderate CAD. CAD patients exhibited significantly higher copeptin levels compared to controls ($p<0.0001$). ROC curve analysis identified a cut-off value of 0.98, with a sensitivity of 83.8% and a specificity of 76.2%.

Conclusion: CAD patients exhibited higher copeptin levels compared to healthy controls, suggesting that copeptin can serve as a biomarker for CAD.

Key-words: Coronary Artery Disease, Copeptin, Arginine Vasopressin (AVP)

INTRODUCTION

Coronary artery disease (CAD) is the leading form of heart disease globally, representing a continuum of conditions from asymptomatic atherosclerosis and stable angina to acute coronary syndromes, including unstable angina, Non-ST-Elevation Myocardial Infarction (NSTEMI), and ST-Elevation Myocardial Infarction (STEMI). CAD is a multifactorial condition influenced by non-modifiable factors such as gender, age, family history, and genetics, as well as modifiable factors like smoking, obesity, lipid levels, and psychosocial variables [1,2]. In India, CVDs accounted for 28.1% of total deaths and 14.1% of disability-adjusted life years (DALYs) in 2016, with significant regional variations in CAD prevalence [3]. At present, India has the highest burden of acute coronary syndrome and ST-elevation myocardial infarction (MI) [4].

Clinical manifestations of CAD range from asymptomatic and stable chest pain to acute coronary syndromes and sudden cardiac death. Stable angina typically presents as mid-sternal chest pain, often described as squeezing or

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constricting, and may radiate to the arms, neck, jaw, back, or upper abdomen [5].

Advancements in biomarker research over the past two decades have enhanced the management of cardiovascular diseases, particularly in diagnosing and prognosticating acute coronary syndromes (ACS) and heart failure (HF). Traditional biomarkers such as myoglobin, creatine phosphokinase (CPK), and CPK-MB have limitations due to delayed release and lack of specificity. Troponin assessment remains the gold standard for early myocardial infarction (MI) detection, although its elevation occurs relatively late after ACS onset [5].

Copeptin, the C-terminal segment of pro-vasopressin, has emerged as a promising biomarker in cardiovascular diseases. Copeptin, a 39-amino acid glycosylated peptide with a leucine-rich core, is derived from pre-pro vasopressin along with AVP and neurophysin II. First described by Holwerda in 1972, copeptin is co-synthesized with vasopressin in response to increasing osmolality and is secreted into the circulation in equimolar concentrations, although its physiological function remains unknown [6].

Combining copeptin with troponin measurements can enhance the detection of acute coronary syndromes at admission and enable accurate exclusion of myocardial infarction, as copeptin levels rise earlier than CK-MB and troponin T, suggesting its utility in rapid diagnosis, patient triage, and predicting major adverse cardiovascular events [7,8]. Studies have demonstrated its prognostic value in ACS, showing that higher copeptin levels at hospital admission predict worse outcomes, including higher mortality rates [7,8]. Despite these findings, there is limited data on copeptin's diagnostic utility in the Indian population, prompting this study to evaluate copeptin levels in CAD patients. The objective of this study was to evaluate the differences in copeptin levels between CAD patients and healthy controls and to assess the potential of copeptin as a biomarker for CAD.

MATERIALS AND METHODS

Place of study- This observational case-control study received approval from the Institutional Ethics Committee. It was conducted at S.C.B. Medical College and Hospital, Cuttack, in the postgraduate department of biochemistry, in collaboration with the cardiology department.

Inclusion criteria- The study included 80 patients diagnosed with CAD between 2020 and 2022, either as outpatients or inpatients. CAD diagnosis was based on clinical evaluation, electrocardiographic changes, and angiographic findings. Age- and sex-matched healthy controls(n=80) were also enrolled for comparison. The study's sample size and matched controls provided good statistical power (80%) to detect significant differences in copeptin levels between CAD patients and healthy controls.

Exclusion criteria- Exclusion criteria for the study were the presence of acute or chronic kidney disease, traumatic heart disease, head injury, severe morbidity, or refusal to participate.

Research Design- Participants' demographic and clinical characteristics were recorded using a predesigned proforma. CAD severity was assessed using the Gensini score [9]. The Gensini score is a method used to quantify the severity of coronary artery disease by assigning a weighted score to the degree of luminal narrowing and the location of the lesions within the coronary arteries [9]. Routine biochemical parameters, including fasting plasma glucose, liver function tests, serum lipid profile, serum urea, and creatinine, were measured using auto-analyzer (TBA -120FR). Copeptin levels were determined by Enzyme-linked Immunoassay (ELISA) using the Abbkine Copeptin ELISA Kit following manufacturer's instruction, with a reference range of 0.75 pmol/L-12 pmol/L. [10]

Statistical Analysis- Data was recorded in Microsoft Excel Workbook 2019 and analysed using SPSS v21.0 (IBM, USA). Quantitative normative variables were presented as mean and standard deviation and compared using the independent t-test. Categorical variables were compared using the chi-square test. Quantitative non-normative variables were presented as median and interquartile ranges and compared using the Mann-Whitney U test. ROC curve analysis calculated sensitivity and specificity, with $p<0.05$ considered statistically significant.

Ethical Approval- Ethical approval for the study was obtained from the Institutional Ethics Committee (IEC) of the Department, of Biochemistry, SCB Medical College and Hospital, Cuttack, Odisha under reference number ECR/84/Inst/OR/2013/RR-20.

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RESULTS

Table 1 shows the baseline characteristics of the participants, revealing that the mean age and proportion of male participants were similar between controls and CAD cases, but the mean BMI was significantly higher in CAD cases (p<0.001).

Table 1: Baseline characteristics of study participants

	Controls (n=80)	**Cases (n=80)**	**p-value**
Age (years)	40.36±11.09	43.19±18.09	0.518
Male sex, n (%)	44 (55%)	48 (60%)	0.913
BMI (Kg/m^2)	24.12±1.38	26.99±3.76	<0.001*

**p-value ≤ 0.05: significant*

Table 2 highlights the laboratory characteristics, indicating that CAD cases had significantly higher fasting blood sugar (p<0.001), total cholesterol (p=0.004), serum HDL (p<0.001), serum LDL (p<0.001), total bilirubin (p<0.001), liver enzyme levels (SGOT and SGPT) (p<0.001) and alkaline phosphatase (p<0.001) compared to controls. Serum triglycerides (p=0.265), VLDL (p=0.110), urea (p=0.775), and creatinine (p=0.087) levels showed no significant differences between the groups, although CAD cases had slightly higher creatinine levels.

Table 2: Comparison of Biochemical parameters among study participants:

	Controls (n=80)	**Cases (n=80)**	**p-value**
FBS (mg/dl)	104.8±21.09	156.95±70.25	<0.001*
Total Cholesterol (mg/dl)	177.31±41.7	202.71±64.8	0.004*
Triglyceride(mg/dl)	123.59±47.77	131.6±42.7	0.265
HDL (mg/dl)	46.55±6.74	41.53±9.86	<0.001*
LDL (mg/dl)	110.81±39.4	129.95±19.3	<0.001*
VLDL (mg/dl)	23.64±10.37	26.06±8.62	0.110
Urea (mg/dl)	23.63±7.58	23.96±7.3	0.775
Creatinine(mg/dl)	0.8±0.17	0.86±0.27	0.087
Bil (T), mg/dl	0.57±0.23	0.85±0.53	<0.001*
Bil (D), mg/dl	0.3±0.15	0.22±0.11	<0.001*
SGOT (mg/dl)	47.7±30.14	350.76±11.21	<0.001*
SGPT (mg/dl)	35.66±5.81	237.6±28.9	<0.001*
Alkaline Phosphatase (mg/dl)	220.7±52.51	282.8±94.42	<0.001*
Copeptin(pmol/l)	0.74±0.38	1.98±0.65	<0.001*

** p-value ≤ 0.05: significant*

These findings underscore notable biochemical differences between CAD patients and healthy controls. Serum Copeptin levels were significantly higher in cases compared to controls (p<0.001).

Most patients exhibited severe CAD (56.25%), with 30% having moderate disease (Fig. 1). ROC curve analysis demonstrated an area under the curve of 0.901, with a sensitivity of 83.8% and specificity of 76.2% at a cut-off value of 0.98 (Fig. 3).

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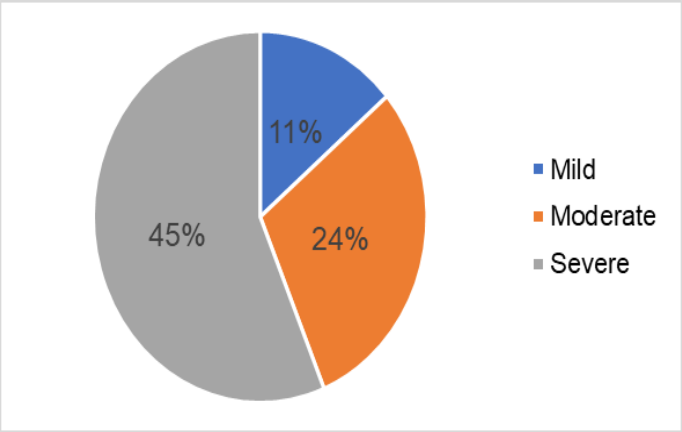

Fig. 1: Distribution of Coronary Artery Disease Severity Among Study Participants

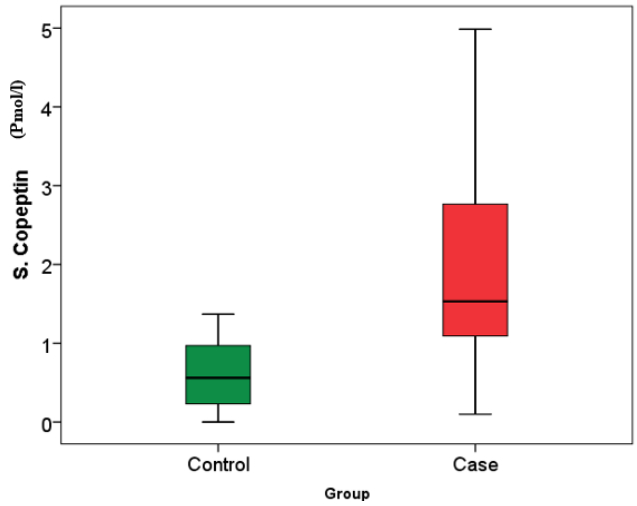

Fig. 2: Box plot comparing copeptin levels between controls and CAD cases.

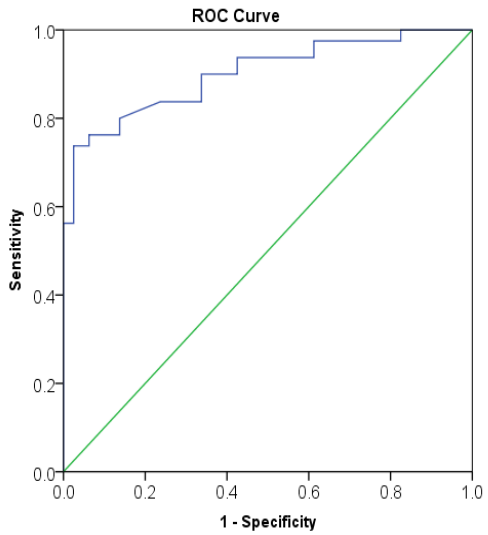

Fig. 3: ROC Curve Analysis for Copeptin Levels in Coronary Artery Disease Diagnosis

DISCUSSION

Copeptin is a stable glycosylated peptide released with arginine vasopressin (AVP) during precursor processing, making it robust and easy to measure in serum or plasma at room temperature [6]. Studies have shown that copeptin concentrations rise soon after acute MI onset and decline over the next few days, with higher levels observed in patients who died or were readmitted with heart failure. This finding led to the analysis of copeptin's potential role in the diagnosis of acute MI. For instance, the CHOPIN (Copeptin Helps in the Early Detection of Patients with Acute Myocardial Infarction) trial demonstrated that copeptin concentrations are already elevated within 0 to 4 hours after the onset of symptoms, at a time when troponin T levels are still undetectable in many patients. As copeptin levels decreased and troponin levels rose, the differing kinetics provided an additional diagnostic benefit for identifying acute MI. [11].

Copeptin itself does not directly act on V1, V2, or V3 Vasopressin receptors. Rather, it serves as an indirect indicator of arginine vasopressin (AVP) release. Copeptin is the C-terminal part of the AVP precursor (pre-pro vasopressin), and its levels in the blood correlate with AVP levels. AVP, also known as antidiuretic hormone (ADH), plays a crucial role in regulating water balance, blood pressure, and cardiovascular function. AVP exerts its effects by binding to tissue-specific G-protein-coupled receptors (GPCRs), including V1, V2, and V3 receptors. The V1 receptor mediates arteriolar vasoconstriction, contributing to blood pressure regulation, while the V2 receptor is responsible for the antidiuretic effect in the kidneys. V1 receptors are also present in cardiac myocytes, influencing cardiac function, although this effect is still debated. The V3 receptor is involved in the secretion of ACTH from the pituitary gland [6].

AVP interactions with other receptors, such as the oxytocin receptor and certain purinergic receptors, also influence cardiovascular function. For example, binding of AVP to the oxytocin receptor can induce nitric oxide-dependent vasodilation, while activation of cardiac purinergic receptors can cause coronary vasoconstriction and negative inotropy. These interactions highlight the complex role of AVP in cardiovascular health and its potential impact on conditions like CAD and acute MI [6].

Our study evaluated the baseline characteristics and biochemical parameters of controls and cases, revealing

significant differences in BMI, fasting blood sugar (FBS), lipid profile, bilirubin, liver enzymes, and copeptin levels. The cases had a higher BMI, consistent with findings from the STABILITY (STABILITY Trial (STabilisation of Atherosclerotic plaque By Initiation of darapLadIb TherapY) sub-study, which links very high BMI with poor cardiovascular prognosis. The STABILITY sub-study found that in patients with stable coronary heart disease, both underweight (BMI <20 kg/m²) and very high BMI (≥35 kg/m²) were strong risk markers for poor prognosis, while the lowest all-cause and cardiovascular mortality was observed in those with a BMI between 25 and 35 kg/m² [12]. Elevated FBS levels in cases suggest impaired glucose metabolism, a known cardiovascular disease (CVD) risk factor.

Significant differences were observed in total cholesterol ($p=0.004$), HDL ($p<0.001$), and LDL ($p<0.001$) levels, with cases showing higher total cholesterol and LDL levels, but lower HDL levels. This is supported by the findings of Zhao et al.,2021 a meta-analysis of prospective cohort studies which revealed that lipid profile variables, particularly high triglycerides and low high-density lipoprotein cholesterol (HDL-C), are significant predictors of major adverse cardiovascular outcomes and all-cause mortality in patients with coronary heart disease [13]. Elevated bilirubin and aminotransferase levels, including alanine aminotransferase (ALT) and alkaline phosphatase (ALP), have been implicated in CVD risk.

Bilirubin, a potent antioxidant, has been shown to have a protective role against CVD, with higher levels inversely associated with the risk of CHD and stroke. Conversely, the association between aminotransferases and CVD events appears weaker. While some studies suggest elevated ALT is linked to increased CVD risk, others indicate no significant association or even a potential inverse relationship with CHD but a positive association with stroke. Similarly, higher ALP levels have been consistently associated with increased CVD risk and mortality. These associations highlight the complex and varied roles that liver function markers play in CVD risk, suggesting potential mechanistic links through oxidative stress, inflammation, and metabolic processes [14].

Our study demonstrated that patients with CAD exhibit significantly higher levels of copeptin compared to healthy controls, suggesting its potential as a diagnostic biomarker for CAD. This aligns with previous research indicating elevated copeptin levels are linked to high mortality in patients with suspected acute coronary syndrome (ACS) at the time of hospital admission [15]. Balmelli *et al*. found that high copeptin levels measured at hospital arrival were associated with worse prognosis, including higher hospital mortality and 1-year mortality. Their prospective study involved patients presenting to the Emergency Department (ED) with symptoms suggestive of acute myocardial infarction (MI) within 12 hours. Despite only 15.9% of these patients being diagnosed with acute MI, the prognostic significance of copeptin was evident across various diagnoses, including unstable angina and non-coronary cardiac causes [16].

Similarly, Maisel *et al*. reported that elevated copeptin levels were a powerful predictor of death at 180 days and hospitalization in patients presenting with chest pain within 6 hours of onset. In their study, although the proportion of patients with acute MI was only 7.9%, the predictive value of copeptin for adverse outcomes remained significant [17].

Lattuca *et al.* further supported these findings by measuring copeptin and cardiac troponin I levels at the beginning of percutaneous coronary intervention in unselected patients with acute ST-segment elevation myocardial infarction. They observed higher copeptin levels in patients who died during hospitalization, within the first 30 days post-myocardial infarction, and at 1-year follow-up. Their multivariate analysis associated higher copeptin levels (>128.2 pmol/L) with increased 1-year mortality, particularly in the presence of cardiogenic shock and older age [18].

ROC curve analysis revealed an area under the curve (AUC) of 0.901, with a sensitivity of 83.8% and specificity of 76.2% at a cut-off value of 0.98, underscoring the diagnostic accuracy of copeptin for CAD. This high diagnostic performance is consistent with previous meta-analyses, which evaluated the prognostic value of copeptin in ACS patients. These studies concluded that elevated copeptin levels were associated with higher mortality, with pooled sensitivity and specificity values of 77% and 60%, respectively [19].

Current guidelines for ED physicians recommend a minimum ED stay of 3 to 6 hours or hospital admission for patients with a nondiagnostic ECG to rule out acute MI. As reported by Reichlin *et al.* combining copeptin with troponin T provided an additive diagnostic value for acute MI [16]. In their study, the AUC of troponin alone in the first blood sample taken in the ED was 0.86, which

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increased to 0.97 when combined with copeptin. This dual-marker strategy excluded acute MI with a negative predictive value (NPV) exceeding 99% [19].

CONCLUSIONS

Despite these promising results, our study had several limitations. First, we could not evaluate the temporal dynamics of copeptin levels, which might influence its diagnostic accuracy. Second, we could not determine whether copeptin levels were directly associated with adverse outcomes in CAD patients. Lastly, we have not followed up assessments to observe long-term patient outcomes. In conclusion, copeptin assessment is a valuable diagnostic tool for patients with acute MI, thanks to its high NPV. Combining copeptin with troponin markers can improve diagnostic accuracy and potentially reduce the time to diagnosis, enhancing patient outcomes and reducing healthcare costs. Further research is needed to establish its role and effectiveness fully in clinical practice.

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