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Association of serum copeptin levels with cardiovascular disease among adults with type 2 diabetes mellitus: A comparative cross-sectional study

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Cardiovascular disease (CVD) remains one of the leading causes of illness and death among individuals with type 2 diabetes mellitus (T2DM), underscoring the need for dependable biomarkers that can improve early cardiovascular risk prediction. Copeptin, the stable C-terminal fragment of the arginine vasopressin prohormone, has recently attracted attention as an indicator of vascular stress and metabolic imbalance; however, its role in predicting cardiovascular complications in diabetic populations remains unclear. This cross-sectional study evaluated 200 adults with T2DM, equally divided based on the presence or absence of CVD, to examine the association between serum copeptin and cardiovascular risk. Serum copeptin concentrations were determined using an enzyme-linked immunosorbent assay, and associations with clinical variables were analyzed through multivariate logistic regression. Participants with CVD demonstrated significantly higher copeptin levels (14.8 ± 4.5 pmol/L) compared with those without CVD (9.2 ± 3.1 pmol/L; $P< 0.001$). Copeptin correlated positively with HbA1c, diabetes duration, and blood pressure but negatively with renal function. Multivariate analysis identified age, diabetes duration, and serum copeptin as independent predictors of CVD (AUC = 0.85). These findings suggest that elevated copeptin serves as a promising biomarker for cardiovascular risk stratification in T2DM, complementing established clinical and laboratory indicators.

Keywords: Biomarkers, Cardiovascular risk, Endothelial dysfunction, Logistic regression, Metabolic regulation, Vasopressin precursor

The global prevalence of type 2 diabetes mellitus (T2DM) has increased dramatically over recent decades, accounting for nearly 90–95% of all diabetes cases and affecting more than 422 million people worldwide[1,2]. Despite major advances in treatment, the rising incidence of T2DM continues to impose a substantial global health burden[1,3]. This growing prevalence underscores the urgent need for early detection and reliable biomarkers that can help identify individuals at high cardiovascular risk[3,4].

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM), even though considerable progress has been made in both prevention and management strategies[5-7]. Determining novel and reliable biomarkers that can predict cardiovascular risk in this high-risk group is critical to offer better patient outcomes. Recent research has put forward the potential role copeptin plays in this regard, the C-terminal portion of the arginine vasopressin prohormone, as a promising biomarker[8,9].

Copeptin is secreted in an equimolar ratio with vasopressin in different physiological and pathological situations, and increased serum copeptin levels have been associated with elevated risk of macrovascular and micro-vascular complications in T2DM patients[7-9]. Several reports demonstrate a strong link between high levels of serum copeptin and development of coronary artery disease (CAD), heart failure and cardiovascular (CV)-mortality, especially in subjects with diabetes whereas these associations seem to be weaker or are not evident in non-diabetics[8,9]. Furthermore, copeptin is associated with conventional risk factors including glycaemic control, renal function, and prevalence of diabetic nephropathy, indicating its participation in several aetiologic pathways[7-9].

However, the association between serum-copeptin and CVD risk in patients with T2DM has not been elucidated well yet, especially in ethnically diverse populations and other clinical settings. The objective of the present study was to address the relationship between serum copeptin levels and cardiovascular risk in patients with type 2 diabetes mellitus (T2DM), in an attempt to determine whether copeptin could be

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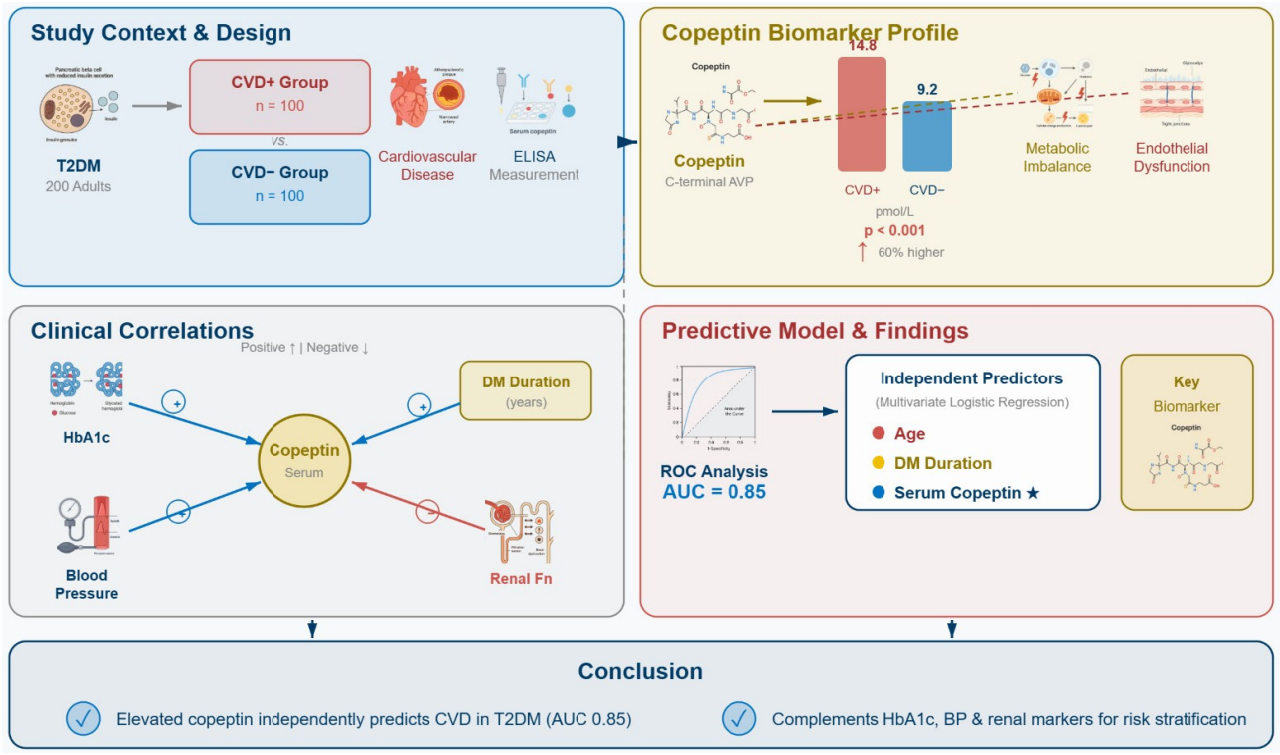

Graphical abstract

an independent predictor of such events in this population.

Materials and Methods

This was a cross-sectional study conducted on 200 adult T2DM patients who attended our institute between July 2024 and July 2025. Subjects were divided into two groups, consisting of 100 individuals with type 2 diabetes mellitus (T2DM) who had a history of cardiovascular disease (CVD) and 100 individuals with T2DM who had no evidence of CVD, as assessed using clinical symptoms/medical records/standard diagnostic criteria. Demographic and clinical information were recorded for each patient. Serum copeptin concentrations were measured by a commercial enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions[10]. Laboratory technicians examined all the samples and were blinded to the CVD status of the participants.

Continuous variables were described with the mean and standard deviation and categorical variables with frequency and percentage. Between-group comparisons were performed with the Student's t-test and the Chi-square test as appropriate. To test for correlations between serum copeptin and clinical parameters, Spearman's correlation coefficients were calculated. Independent predictors of CVD were examined by multivariable logistic regression analysis with copeptin and established risk factors as covariates. The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the prognostic ability of the constructed model. Statistical significance was assumed for $P< 0.05$.

Baseline characteristics of the 200 patients with T2DM, according to CVD status, are represented in (Table 1). Patients with CVD were older (61.3 years *vs*. 55.2 years, $P< 0.001$) and had more duration of diabetes (9.8 years *vs*. 7.1 years, $P< 0.001$) and a higher waist-hip ratio (0.95 *vs*. 0.90; p = 0.002). Significant differences were not observed between genders, BMI, glycemic control, blood pressure, lipid profile, and renal function. Serum copeptin measurement. In the CVD group, circulating copeptin levels were markedly higher compared with controls (14.8 *vs*. 9.2 pmol/L; $P< 0.001$)

As shown in Table 2, serum copeptin showed correlation with several clinical factors in T2DM patients, particularly among those with cardiovascular disease. Stronger correlations were observed between copeptin and HbA1c, as well as with the duration of

diabetes, highlighting the link between copeptin levels and diabetes severity. Blood pressure showed a moderately positive relationship with copeptin in the CVD group, suggesting its role in vascular stress. Notably, renal function, reflected by eGFR, negatively correlated with copeptin in the CVD group.

Table 1 — Baseline characteristics of study participants by cardiovascular disease status

Variable	T2DM without CVD (n=100)	T2DM with CVD (n=100)	p-value
Age (years)	55.2 ± 9.8	61.3 ± 8.4	<0.001*
Gender (male), n (%)	58 (58%)	62 (62%)	0.58
BMI (kg/m²)	27.4 ± 3.5	28.1 ± 4.1	0.15
Waist-Hip Ratio	0.90 ± 0.07	0.95 ± 0.08	0.002*
Duration of diabetes (yrs)	7.1 ± 4.2	9.8 ± 5.0	<0.001*
HbA1c (%)	7.8 ± 1.2	8.1 ± 1.4	0.08
SBP (mmHg)	131.2 ± 14.6	134.8 ± 16.1	0.12
DBP (mmHg)	80.8 ± 8.7	81.5 ± 9.1	0.64
Total cholesterol (mg/dL)	192 ± 46	198 ± 52	0.28
LDL cholesterol (mg/dL)	112.6 ± 29.8	115.3 ± 33.4	0.44
HDL cholesterol (mg/dL)	44.7 ± 9.8	43.5 ± 11.1	0.39
Triglycerides (mg/dL)	159 ± 73	165 ± 82	0.51
eGFR (mL/min/1.73m²)	89.4 ± 13.6	87.1 ± 14.9	0.17
Serum copeptin (pmol/L)	9.2 ± 3.1	14.8 ± 4.5	<0.001*

*Statistically significant

Table 2 — Correlation of serum copeptin with clinical variables in T2DM patients by CVD status

Variable	Spearman's rho (r) without CVD	p-value	Spearman's rho (r) with CVD	p-value
HbA1c	0.22	0.03*	0.30	0.002*
Duration of diabetes	0.18	0.07	0.28	0.004*
Systolic BP (SBP)	0.15	0.12	0.24	0.01*
Diastolic BP (DBP)	0.12	0.22	0.19	0.05
Total cholesterol	0.10	0.29	0.15	0.13
LDL cholesterol	0.08	0.40	0.12	0.22
HDL cholesterol	-0.14	0.15	-0.20	0.04*
Triglycerides (TG)	0.11	0.26	0.18	0.06
eGFR	-0.20	0.05	-0.32	0.001*

*Statistically significant

Multivariate logistic regression analysis of independent predictors of cardiovascular disease (CVD) in patients with T2DM is represented in (Table 3). After adjusting for covariates, older age and longer diabetes duration showed a significant association with the risk of CVD, which is in accordance with their well-known effects on cardiovascular risk. Serum copeptin, in particular, was identified as a powerful independent risk indicator associated with an odds ratio of approximately 30% for each unit increase. Other covariates, such as sex, HbA1c, and systolic blood pressure, were not associated in this study.

As a result, copeptin levels are significantly higher in patients with CVD as illustrated in (Fig. 1).

In Figure 2, A ROC curve for the logistic regression model predicting CVD in T2DM patients shows strong diagnostic ability. With an Area Under the Curve (AUC) = 0.85, the model can positively differentiate patients with and without cardiovascular disease.

Results and Discussion

In this study, adults with T2DM, the findings were that patients with cardiovascular disease (CVD) were

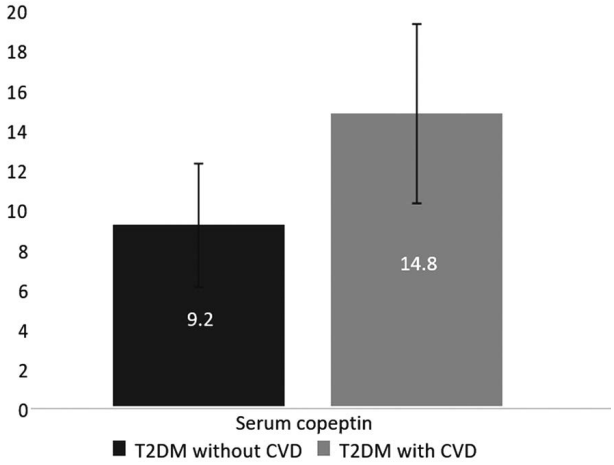

Fig. 1 — Serum Copeptin Levels in T2DM patients with and without cardiovascular disease

Table 3 — Multivariate logistic regression for cardiovascular disease in T2DM patients

Variable	Coefficient (β)	Standard Error	Adjusted Odds Ratio (95% CI)	p-value
Constant	-16.65	3.38	—	<0.001*
Age (per year)	0.08	0.03	1.08 (1.03 – 1.15)	0.005*
Sex (male = 1)	0.47	0.35	1.60 (0.80 – 3.20)	0.181
Duration (years)	0.14	0.05	1.14 (1.04 – 1.26)	0.006*
HbA1c (%)	0.09	0.17	1.10 (0.78 – 1.54)	0.598
Systolic BP (mmHg)	0.01	0.01	1.01 (0.99 – 1.04)	0.255
Serum Copeptin	0.26	0.07	1.30 (1.13 – 1.48)	<0.001*

*Statistically significant

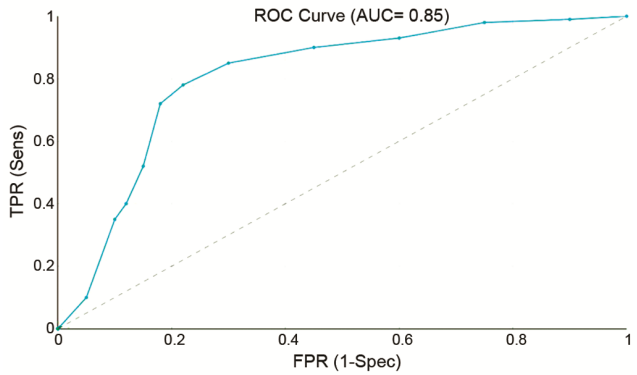

Fig. 2 — ROC Curve for Logistic Regression Model Predicting Cardiovascular Disease

significantly older, had a longer diabetes duration, and a higher waist-hip ratio than those without CVD, which is supported by several studies[11,12]. For instance, Jong M *et al.* have shown that diabetes duration is one of the most important risk factors for CVD[13].

Furthermore, findings of the present study that increased levels of serum copeptin were related to CVD in T2DM patients are supported by Velho *et al*, who reported that higher plasma copeptin levels were associated with a higher risk of cardiovascular events in diabetic populations[14]. This is consistent with the pattern of association between copeptin and HbA1c and duration of diabetes, blood pressure, and renal function among participants with CVD, which shows its association with metabolic and vascular Disturbance[14,15].

The value of copeptin as an independent predictor of CVD, which has been demonstrated by the multivariate analysis in this study, is significant. Although copeptin is related to both cardiovascular and all-cause mortality, there is only a minimal increment in risk prediction for new biomarkers after the inclusion of traditional clinical markers, as emphasized by studies[15,16]. Also, the research of Ulambayar *et al*., other clinical laboratory markers such as eGFR and triglyceride may have a meaningful role in the estimation of cardiovascular risk that may oppose to single focus on copeptin[17]. Furthermore, the study by Wang *et al*. also indicates that C-peptide is an independent risk factor of CAD in patients with T2DM, which may require several biomarkers to predict the overall risk factors[18]. Likewise, even copeptin is a higher-performance biomarker in predicting a high-risk T2DM patient; therefore, its use would have to be associated with other clinical laboratory markers to increase the predictive power and improve clinical decision-making.

Conclusion

This study shows that serum copeptin was closely associated with the presence of CVD in adult patients with T2DM beyond traditional risk factors. Raised copeptin values were associated with poorer glycemic control, longer diabetes duration, higher blood pressure, and impaired renal function, particularly in participants with CVD. Multivariable analysis validated copeptin as an independent predictor of CVD, and the prediction model performed well in discrimination. These data provide further evidence for the potential of copeptin as a useful biomarker associated with cardiovascular risk assessment among diabetic patients; however also point out that it should be incorporated alongside established clinical and laboratory markers in patient management.

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Conflicts of interest

All authors declare no conflict of interest.

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