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Original Article

Copeptin-As A Biomarker in the Stratification of Diabetic Nephropathy in Type-2 Diabetes Mellitus

Dr Saswati Prajna Jena[1], Dr Madhusmita Acharya[2], Dr Malati Murmu[3], Dr Sumitra Bhoi[4], Dr Neelam B. Tirkey[5]

[1]Post Graduate, Department of Biochemistry, VIMSAR, BURLA, SAMBALPUR, ODISHA
[2,3]Professor, Department of Biochemistry, VIMSAR, BURLA, SAMBALPUR, ODISHA
[4]Associate Professor, Department of Biochemistry, VIMSAR, BURLA, SAMBALPUR, ODISHA
[5]Assistant Professor, Department of Biochemistry, VIMSAR, BURLA, SAMBALPUR, ODISHA

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Corresponding Author:

Dr Saswati Prajna Jena
Post Grduate, Department of Biochemistry, VIMSAR, BURLA, SAMBALPUR, ODISHA

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ABSTRACT

Background: Diabetic Nephropathy (DN) has become one of the most common causes of CKD.A multicenter study from India reported a composite prevalence of Diabetic-CKD is around 62.3%. DN is characterized by glomerular hypertrophy and microalbuminuria in early stage that progresses to advance stage with glomerulosclerosis, proteinuria and declined renal function. Several studies have shown that serum Copeptin (carboxy-terminal portion of preprovasopressin) is a good predictor of decline in renal function seen in Diabetic Nephropathy in Type-2 Diabetes Mellitus (T2DM) patients.
Objective: To estimate the level of copeptin with the progression of DN in T2DM and to check correlation of copeptin with other parameters like eGFR and UACR of DN in T2DM.
Methodology: A cross-sectional study was carried out on 60 T2DM patients divided into 3 groups based on urinary albumin-creatinine ratio (normoalbuminuric, microalbuminuric and macroalbuminuric).20 healthy subjects were included as control group. Serum samples for all the groups were taken and analyzed for FBS, PPBS and HbA_1C by COBAS-311 fully automated bioanalyzer. Serum copeptin levels were assayed in ELISA (by sandwich technique). eGFR was calculated using MDRD formula.Urine samples were evaluated for urinary albumin-creatinine ratio (UACR).
Results: In this study, it was inferred that serum copeptin level was significantly higher in macroalbuminuric group as compared to other 3 groups with p-value <0. 001.There was statistically significant positive correlation between copeptin and UACR (r-value = 0.731, p-value <0.001) and negative correlation between copeptin and Estimated Glomerular Filtration Rate(eGFR)(r-value = -0.651,p-value <0.001).
Conclusion: Increased serum copeptin level can be considered as a biomarker of DN in T2DM.

Keywords*: Diabetic Nephropathy (DN), Copeptin (carboxy-terminal portion of preprovasopressin), Type-2 Diabetes Mellitus (T2DM), urinary albumin-creatinine ratio (UACR), eGFR (estimated glomerular filteration rate).*

INTRODUCTION

Diabetes Mellitus is a heterogeneous metabolic disorder characterized by hyperglycemia which in long term causes microvascular complications affecting several organs like kidneys[2]. Diabetic Nephropathy (DN) has become one of the most common causes of chronic kidney disease. A multicenter study from India reported the composite prevalence of Diabetic-CKD is around 62.3%[4]. DN is characterized by glomerular hypertrophy and microalbuminuria in early stage that progresses to advance stage with glomerulosclerosis, proteinuria and declined renal function[2]. AVP (Arginine vasopressin), a neurohormone released from neurohypophysis, is seen in several cardiometabolic disorders like Heart failure, PCOS, Pre-eclampsia, and Renal diseases[6]. In situations like this, the body releases AVP since, it functions in

osmoregulation, lipid metabolism, ACTH secretion, glucose homeostasis via hepatic gluconeogenesis and glycogenolysis, insulin, and glucagon release from pancreatic cells[7]. But AVP is a short-lived peptide, unstable in isolated plasma and its measurement in biological fluids is difficult to manage. So, COPEPTIN, whose invitro stability, stable serum levels (due to its long circulating disappearance half-life by virtue of its glycosylation), and its length allowing more epitopes for raising antibodies for immunoassay development, make it an ideal surrogate biomarker for vasopressin release. Copeptin, the stable carboxy-terminal portion of preprovasopressin (surrogate marker of vasopressin) was shown to be positively associated with the decline in kidney function[1]. In the kidneys, Copeptin mediates antidiuresis function through V2 Receptors. The tubular fluid composition is thus changed causing increased intraglomerular pressure subsequent to afferent arteriole vasodilation and decline in renal function in diabetic nephropathy[5].

MATERIALS AND METHODS

Place of study: VSS Institute of Medical science and Research Centre, Burla, Odisha

Setting of Study: Department of Biochemistry in collaboration with the Department of General Medicine.

Study type: Cross-sectional analytical study.

Study Population: 60 type-2 diabetes mellitus patients divided into 3 groups based on urinary albumin-creatinine ratio (normoalbuminuric, microalbuminuric and macroalbuminuric) .20 healthy subjects as control group.

Study technique: consecutive sampling was done till the sample size reached.

Methodology

The demographic data of patients were collected using case record form. After taking written informed consent, all the study participants underwent physical examination, and the biochemical parameters were investigated. Serum samples were analyzed for FBS, PPBS and HbA_1C by COBAS-311 fully automated bioanalyzer. Serum creatinine and eGFR were also evaluated. Serum copeptin levels were assayed in ELISA (by sandwich technique) in accordance with the described method of manufacturer. Spot urine samples were evaluated for Urinary Albumin-Creatinine ratio (UACR). According to the World Health Organization (WHO) and American Diabetes Association (ADA) criteria, the participants were categorized into normoalbuminuric (UACR value <30 mg/g),microalbuminuric(UACR value 30-300mg), macroalbuminuric(UACR value >300mg/g).Estimated Glomerular Filtration Rate(eGFR) was calculated using MDRD (Modification of Diet in Renal Disease) formula[17]

$eGFR = 175 \times (SCr^{-1.154} \times Age^{-0.203} \times 0.742$ (if female) $\times 1.212$ (if Black)

Inclusion criteria : Adults aged 41-75years (willing to participate)
Type-2 Diabetic patients

Exclusion criteria : Type-1Diabetes mellitus
Liver disease
Cardiovascular diseases
Critical illness or any malignancy
Patients on drugs affecting vasopressin system
Pregnant and lactating women

Statistical analysis

The collected data were organized, tabulated and statistically analyzed using SPSS statistical software. The data were presented and analyzed in terms of mean and standard deviation(SD).

RESULT

In this study, the clinical and laboratory parameters of subjects of the studied groups were evaluated and shown that the mean ± SD values of serum copeptin levels were significantly higher in the normoalbuminuric group as compared to the control group and in those with microalbuminuria as compared to the control and normoalbuminuric groups. Also, it was significantly higher in macroalbuminuric group as compared to the other three groups with p value ($P < 0.001$).[Table 1/Fig 1]. In diabetic patients, there was a statistically significant positive correlation between copeptin level and UACR ($r= 0.731$, $p < 0.001$) is shown in Fig.2.However, there was a statistically significant negative correlation between copeptin level with eGFR ($r= -0.651$,$p<0.001$)is shown in Fig. 3.This analysis demonstrated that copeptin can be used as an independent biomarker for predicting the decline in renal function in type 2 diabetes mellitus patients.

Table. 1 demographic and laboratory parameters of subjects in the studied groups

	Group-I (control)	Group-II (DM with	Group-III (DM with	Group-IV (DM with

	n = 20	normoalbuminuria) n= 24	microalbuminuria) n= 13	macroalbuminuria) n= 23
Age (years)	56.27 ± 11.74	54.83±7.29	56.27±6.38	60.13±8.04
BMI (kg/m^2)	26.73 ± 4.20	30.67±4.97	32.03±3.31	33.54±4.16
SBP (mmHg)	124.67 ± 11.87	134.0±19.29	136.73±14.07	143.13±21.89
DBP (mm Hg)	78.79 ± 10.61	82.06±12.48	83.35±14.70	86.78±15.35
Duration of DM (years)	----------	7.73±4.24	9.80±4.37	13.40±4.45
FBS (mg/dl)	99.37 ± 8.97	126.35±19.86	139.19±24.73	178.50±26.14
PPBS (mg/dl)	130.39 ± 17.07	182.17±38.05	237.19±45.43	276.94±64.28
HbA_1C (%)	5.43 ± 0.819	6.54±0.391	8.54±0.485	9.67±0.924
Serum creatinine (mg/dl)	0.96 ± 0.26	1.39±0.18	1.72±0.86	3.01±0.94
eGFR(ml/min/1.73m^2)	108.13 ± 10.75	91.32±14.64	56.53±16.70	33.91±11.47
UACR (mg/g Cr)	21.38 ± 3.39	26.82±3.89	189.66±41.22	337.47±23.90
Copeptin (pg/ml)	98.60 ± 21.73	219.72±26.31	296.20±21.34	358.28±31.12

Data are presented as mean + SD, *Statistically significant difference, *DM* diabetes mellitus, *BMI* Body mass index, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *HbA1C* Glycated haemoglobin, *eGFR* Estimated Glomerular filtration rate, *UACR* Urinary albumin-to-creatinine ratio, *HDL-C* High-density lipoprotein-cholesterol, *LDL-C* Low density lipoprotein-cholesterol

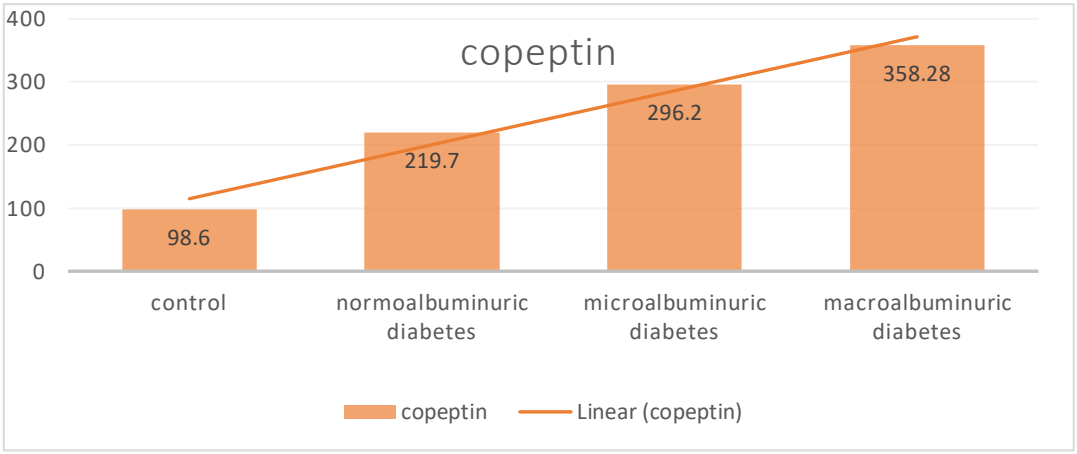

Fig. 1 Copeptin in the studied groups. The mean serum copeptin level was significantly higher in group-II as compared to control group and higher in group-III as compared to control and group-II, it was statistically higher in group-IV as compared to other groups($p < 0.001$)

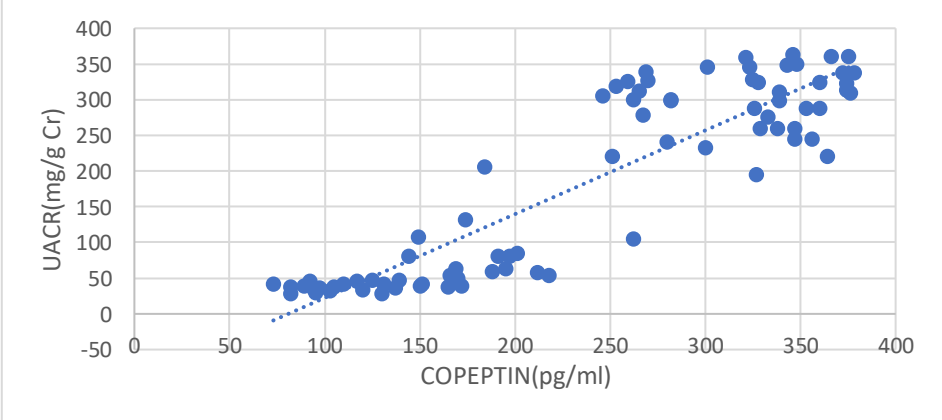

Fig. 2 correlation between copeptin and UACR (r value = 0.731, p value <0.001)

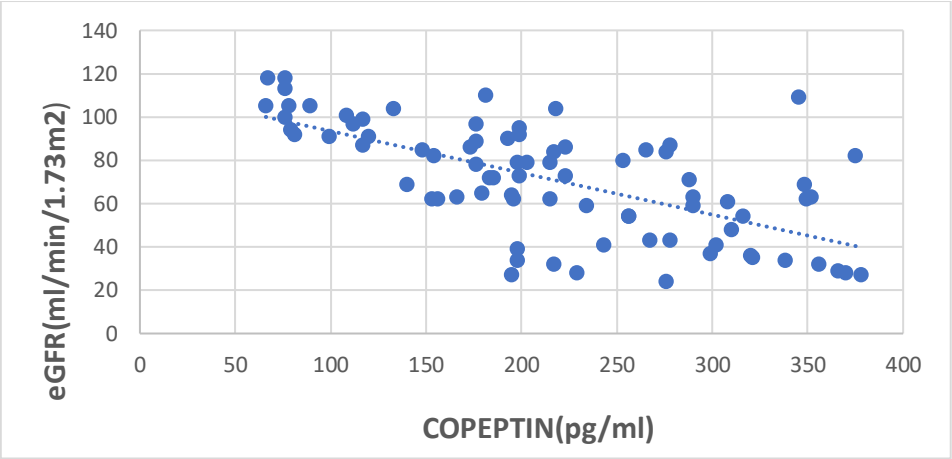

Fig. 3 correlation between copeptin and eGFR (r value = -0.651, p value <0.001).

DISCUSSION

This study showed the association of copeptin concentration in patients with type 2 diabetes mellitus, and is progression to develop nephropathy. Serum copeptin level was significantly raised in the patients with type 2 diabetes mellitus as compared to the healthy controls, with progressively higher levels observed as the severity of albuminuria increased. Serum copeptin level was highest in patients with macroalbuminuria as compared to the other groups, which indicates strong association between copeptin and the progression of diabetic nephropathy.

In addition, there was a positive correlation between copeptin and HbA_1C, urinary albumin-creatinine ratio, and serum creatinine. However, it showed a statistically significant negative correlation between copeptin and estimated glomerular filtration rate (eGFR). These observations suggested that increased copeptin level is associated with the decline in renal function in the diabetic patients.

Although the exact mechanism behind the increased copeptin which is the surrogate marker of vasopressin in diabetes still remains unclear , it has been observed that chronic hyperglycaemia may lead to relative contraction of extracellular fluid volume due to glycosuria, as well as increased sensitivity of hypothalamic osmoreceptors to the plasma osmolality[8]. Increased vasopressin secretion may primarily serve a compensatory role by decreasing the urinary water loss. However, the persistent increase in vasopressin level may exert gradual deleterious impact on kidneys[9].

The results of this study are consistent with the earlier publications. Bjornstad et al.[10] observed considerably higher copeptin levels in patients with advanced stages of chronic kidney disease compared to those with early-stage illness, and also found elevated copeptin level in diabetic patients with albuminuria. Similarly, Meijer et al.[11] observed an association between elevated copeptin levels and accelerated decline in renal function. Furthermore, studies by Pikkemaat et al.[12] and Velho et al.[5] have identified a positive correlation between copeptin and markers of renal dysfunction, as well as an increased risk of progression to chronic kidney disease.

Current evidence regarding the role of copeptin in determining the new-onset chronic kidney disease in the general population is still limited. However, the results from the DESIR cohort study reported by Roussel et al.[13] demonstrated the positive correlation between copeptin levels and progressive renal damage. Increasing evidence also suggests that vasopressin contributes to cardio-renal complications seen in type 2 diabetic patients. Activation of renal V2 receptors by vasopressin can have direct impact on the onset and progression of diabetic nephropathy, worsening hypertension, oxidative stress, insulin resistance, dyslipidaemia and vascular calcification[16].

Given that plasma copeptin levels reflect vasopressin secretion and are influenced by hydration status, therapeutic approaches aimed at lowering vasopressin activity—such as increased water intake or use of vasopressin receptor antagonists may lower the cardiometabolic and renal risk in patients with type 2 diabetes mellitus[16]. A multivariate logistic analysis demonstrated the strong predictive value of copeptin for diabetic nephropathy, signifying its potential role as a sensitive and reliable biomarker for early renal impairment in diabetic patients[5].

CONCLUSION

This study demonstrated that increased serum copeptin levels were negatively correlated with eGFR and positively correlated with UACR, indicating a strong association with progressive renal damage in patients with type 2 diabetes mellitus. Thus it suggests that copeptin can be a potential predictor for the development and progression of diabetic nephropathy . This study identifies these clinical associations, but its observational design limits the ability to confirm

exact underlying causal mechanisms. Therefore, further experimental studies are required to validate these pathways and to better establish the clinical utility of copeptin in diagnostic settings.

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