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Role of Serum Copeptin as Potential Biomarkers for Chronic Kidney Disease Patients with andwithout Type 2 Diabetes Mellitus

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Abstract

The article investigates the potential of serum copeptin as biomarkers for Chronic KidneyDisease (CKD) patients, with and without coexisting Type 2 Diabetes Mellitus (T2DM). Copeptin independently defines the development of new-onset of chronic kidney disease and it leads to a faster decrease in Glomerular filtration rate over duration of time. The intricate relationship between CKD and T2DM necessitates the exploration of novel biomarkers to enhance early detection, risk stratification, and therapeutic interventions. The rising global burden of Chronic Kidney Disease, exacerbated by the prevalence of Type 2 Diabetes mellitus underscores the need for innovative approaches to patient care. Here by we suggest that copeptin may be helpful in the identification of individuals who are at high risk for Chronic Kidney Disease beyond well-known risk factor groups like diabetes mellitus. This section introduces the significance of biomarkers in CKD and T2DM, highlighting the potential contributions of serum copeptin. We should must perform an intense monitoring program with regular measurements of kidney function, and possibly should provide treatment of the same; it may be a motivation in a population that with elevated values of copeptin should be monitored in order to prevent CKD.

Keywords: Chronic Kidney Disease, Type 2 Diabetes Mellitus, Biomarkers, Serum Copeptin, Pathophysiology

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1. Introduction

A complicated metabolic illness known as diabetes causes high blood glucose levels because of either insulin resistance, inadequate insulin production, or both. Hyperglycemia is the primary clinical symptom of the diabetic condition [34]. But anomalies in lipid and protein metabolism, as well as problems with minerals and electrolytes, are also linked to insulin shortage and/or resistance. The vast majority of diabetic patients fall into one of two broad categories: type 2 diabetes mellitus, which is characterized by the presence of insulin resistance with an insufficient compensatory increase in insulin secretion, or type 1 diabetes mellitus, which is brought on by an absolute or nearly absolute deficiency of insulin. Additionally, gestational diabetes is a term used to describe women who develop diabetes while pregnant [35]. The prevalence of end-stage renal illness and chronic kidney disease in the Western world is significantly influenced by diabetes mellitus. Notably, in the United States during 2018, it accounted for a substantial 47% of cases requiring renal replacement therapy initiation [2]. While type 1 and type 2 diabetes mellitus share numerous clinical traits and enduring complications, they are distinct maladies with differing underlying mechanisms [3]. In type 2 diabetes, more commonly observed in White populations, is characterized predominantly by insulin resistance and an insufficient insulin response. Both type 1 and type 2 diabetes mellitus can lead to persistent micro vascular and macro vascular complications, contributing to

heightened levels of morbidity and mortality within this patient demographic [4]. In India, 77 million people were estimated to have diabetes in 2019, and by 2045, that number is projected to reach over 134 million. About 57% of these people are still undiagnosed [32], also the reported prevalence of CKD varies by area and ranges from 1% to 13%; most recently, statistics from the Kidney Disease statistics Center Study of the International Society of Nephrology revealed a prevalence of 17%.[33]. The manifestation of kidney disease in individuals with diabetes can result from microvascular complications linked to diabetes, concurrent kidney ailments of alternative origins, or a combination thereof. For those with type 1 diabetes, kidney disease most frequently stems from secondary microvascular complications arising from diabetes. Conversely, in type 2 diabetes patients, kidney disease can be triggered by a range of factors, contributing to a more varied spectrum of etiologies. In the year 2018, it was the primary diagnosis for commencing renal replacement therapy in the United States, encompassing a significant 47% of cases [2]. Although sharing numerous clinical traits and enduring complications, type 1 and type 2 diabetes mellitus are fundamentally distinct diseases with varying pathophysiologies [3]. The former arises from the autoimmune degradation of insulin- producing beta cells nestled within the pancreatic islets of Langerhans, while the latter, prevalent among individuals of Caucasian ethnicity, is predominantly characterized by insulin resistance coupled with insufficient insulin secretion [6]. The lasting microvascular and macrovascular complications inflicted by both type 1 and type 2 diabetes mellitus contribute substantially to heightened morbidity and mortality rates within these patient cohorts [7]. Kidney afflictions resulting from diabetes can stem from microvascular complications inherent to the condition itself, coexisting kidney ailments of alternative origins, or a fusion of the two [8]. In diabetes patients, microvascular disorders emerging from diabetes hold primacy as the chief etiological factor for chronic kidney disease, whereas the spectrum of etiologies giving rise to kidney dysfunction in type 2 diabetes patients is more diverse [9]. Also it is has been found a positive correlation of Proprotein convertase subtilisin/kexin type-9 (PCSK-9) which plays a significant role in the control of LDL-C, but its link to other metabolic issues cannot be overlooked. The co-occurrence of inflammatory cascades and redox imbalance has provided. Important insight into the aetiology of hyperglycemia. [36], and in control that the potential bioactive secondary metabolites of B. aristata , Phyllanthus virgatus forst extract and drug Ezetimibe in treating a range of acute and chronic illnesses, such as diabetes [37-39]. Copeptin, a stable COOH-terminal fragment derived from prepro vasopressin and regarded as a surrogate marker for vasopressin, has exhibited a positive correlation due to the overall population's deterioration in renal function [1,5]. However, limited research has explored the influence of elevated copeptin levels on renal function, specifically in diabetic patients [10-14], numerous investigations have established an elevation in serum copeptin levels among individuals with cardiovascular disease (CVD), and this elevation has been linked to an augmented risk of unfavorable outcomes, including mortality, in these patients.

Copeptin, either on its own or in conjunction with other cardiac biomarkers, has demonstrated its potential in enhancing the accuracy of diagnosing and prognosticating various cardiovascular conditions such as stable coronary artery disease, acute coronary syndrome, stroke, heart failure, and ischemic stroke [15]. Myocytes within cardiac vascular smooth muscles express V1A receptors (V1aR), creating a complex landscape where vasopressin (AVP) serves both cardio protective and stimulating roles. AVP engages a distinct family of G-protein-coupled receptors, including V1A-R in the heart, vasculature, and liver, as well as V2 receptors (V2-R) in the kidney. The activation of V2-Rs prompts the reabsorption of free water, a process that, when excessive, can lead to hyponatremia. Patients is less beneficial because they simultaneously increase AVP levels [16]. Elevated circulating AVP levels and over expression of V1aR have been associated with heart failure [17]. Elevated levels of vasopressin independently enhance the susceptibility to developing diabetes mellitus and cardio renal disease. This correlation is supported by a wealth of epidemiological and experimental evidence. In the future, the vasopressin marker copeptin could potentially function as a tool for identifying individuals with an escalated risk of disease progression. Such individuals could potentially gain advantages from Therapeutic approaches focused on reducing vasopressin levels and implementing lifestyle modifications such as increased fluid intake [18]. The significance of vasopressin, acting through its V2 receptor, becomes particularly evident during the early stages of diabetic nephropathy. This is highlighted by experiments in which a in elderly men competing levels are directly related to diabetes type II and have also been associated positively with renal dysfunction, insulin resistance metabolic risk factors (blood pressure, triglycerides, and liver function), C-reactive protein, tissue plasminogen activator, and von Willebrand factor (endothelial dysfunction) [19]. This underscores the potential of vasopressin as a target for therapy, both in preventing and treating diabetic nephropathy.

2. Materials and Methods

This study was carried out on 150 CKD patients, who were divided accordingly into diabetes and non-diabetes control groups. The patient differentiated on the basis of measured serum copeptin level, serum creatinine, urea, Blood urea nitrogen (BUN), sodium, potassium, and calcium levels, and estimated glomerular filtration rate (eGFR). This study was carried out on 150 CKD patients aged 40-65 years who were admitted to Integral Hospital Lucknow. The patients were later divided based on CKD with diabetes and CKD with no diabetes, which is further taken as control in this study. The blood samples were collected in fasting and postprandial states, integral institute of ethical committee approved analyzed. The study, and scientific research, Integral institute of medical science and research IIMS&R, Integral University (IEC/IIMS&R/2021/13).

2.1. Sample collection

Samples of the whole blood were collected and processed in the Department of Biochemistry, IIMS&R, Lucknow.5 ml of blood samples were collected from clinically diagnosed cases of diabetes mellitus and healthy controls under aseptic conditions. 1 ml of blood is separated in EDTA vial to measure HbA1c and rest 4ml of fasting sample and 1ml of postprandial sample will be immediately

centrifuged at 3000 rpm for5 minutes, and serum will be separated and stored for further analysis. For blood investigation, 5 ml ofvenous blood was taken by disposable syringe from the medial cubital vein under aseptic precautions.

2.2. Inclusion criteria

Patients aged between 40 and 65 years, who met the specified criteria for chronic kidney disease (CKD), were eligible for participation in the study. Enrollment was determined based on the defined inclusion and exclusion criteria [3].

2.3. Exclusion criteria

Patients experiencing acute exacerbations of chronic renal insufficiency, those with connective tissue disease, tumors, familial hyperlipidemia, or nephritic syndrome, were excluded from the study. Additionally, individuals with any medical, psychiatric, debilitating condition, disorder, or social circumstances that, as determined by the investigator, could impede adherence to the study protocol, hinder informed consent, or influence the patient's overall prognosis were not included. It's important to note that none of the selected patients had been utilizing hormones or immunosuppressive agents in the three months prior to enrollment [3].

2.4. Subject selection

In each group of case and control 75 each patient is taken according to the following criteria:- The following measures are taken for the patients involved in the study have: Taking their full history, Complete clinical examination.

2.4.1. Biochemical variables

Plasma glucose levels – Glucose estimation is done by the enzymatic kit method of GOD/POD.

Glycated hemoglobin (HbA1C) – It is estimated by the colorimetric method Ref.Fluckiger, R. and Winter halter, K.H. (1976).

Sodium & Potassium: Ion selective electrode (ISE) method (Ref.chem.libretexts.org).

Calcium: Arsenazo 3 combines with calcium ions at pH 6.5 to form colored chromospheres, theabsorbance of which is measured at 650 nm Teitz Text book of clinical chemistry, 1994).

Creatinine: Modified Jaffe's Method (Ref.Myers G.L., Greg Miller (2006).

Uric acid: Based on Tinder reaction Ref.Searcy R.L (1969), Henery R.J.(1964).

Albumin: Albumin binds with bromocresol green (BCG) at pH 4.2 causing a shift in absorbance ofthe yellow BCG dye (Ref.Doumas, B.T.,Aeends R.L.pinto(1972).

Blood urea: Urea is hydrolyzed in the presence of water and urease to produce ammonia and carbondioxide. (Teitz Text book of clinical chemistry, 1994).

Calculation of eGFR: An estimation is done by the abbreviated MDRD equation: 186 x (Creatinine/88.4)-1.154 x (Age)-0.203 x (0.742 if female) x (1.210 if black).

Serum copeptin levels estimation using sandwich ELISA:

The GENLISATM ELISA kits are usedfor assessing the specific biomarker in sample analytes, which may be serum, plasma, and cell culturesupernatant as validated with the kit. The kit employs a sandwich ELISA technique, which leads to a higher specificity and increased sensitivity, compared to conventional competitive ELISA kits which employ only one antibody. Double antibodies are used in this kit. Concentrations in serum samples were assayed quantitatively using commercial ELISA kits (Human Copeptin Genlisa TM ELISA, Krishgen BioSystems).

2.5. Statistical analysis

The collected data was meticulously organized, tabulated, and subjected to comprehensive statistical analysis utilizing SPSS statistical software. For the qualitative data in this study, numerical and percentage, representations were employed. Quantitative data were presented in terms of mean values along with their corresponding standard deviations (SD). To determine the significance of the findings,P-values associated with the relevant test statistics were evaluated, with a significance level set at 0.05.P-values exceeding 0.05 were regarded as statistically insignificant, while those equal to or less than 0.05 was considered significant. To assess the normality of the quantitative data, the unpaired t-test was employed to compare biochemical parameters between the case and control groups. Correlation and regression analysis were utilized to investigate the relationship between Copeptin levels and various biochemical parameters. Additionally, ROC analysis was conducted to determine the optimal Copeptin level cutoff for disease detection, along with sensitivity and specificity assessments.

3. Results and discussion

In summary, this analysis reveals significant differences in various parameters between the Controland Case groups, particularly in blood sugar levels, HbA1C, urea, calcium, eGFR, and copeptin. These differences may have clinical implications and should be further investigated. The parameters taken on the basis of Clinical and laboratory investigation of the enrolled groups are shown in Table 1 which depicts a significant correlation of the mean plasma copeptin level in the CKD group having diabetes.

Table 1. Intergroup Comparison of Study Parameters

Parameter	Control	Case	p-value
AGE (year)	48.91 ± 9.71	49.39 ± 8.4	0.747
Body mass index (Kg/ m2)	29.93 ± 4.14	29.93 ± 4.14	1.000
Systolic Blood Pressure (mmHg)	141.75 ± 11.72	141.75 ± 11.72	1.000
Diastolic Blood Pressure (mmHg)	81.24 ± 7.47	81.24 ± 7.47	1.000
FBS (mg/dl)	98.85 ± 11.05	147.2 ± 60.61	<0.001
PPBS(mg/dl)	145.49 ±23.21	248.58 ±102.31	<0.001
HbA1C %	5.88 ± 0.38	6.98 ± 0.87	<0.001
UREA (mg/dL)	95.91 ± 82.28	130.25 ± 62.48	0.005
CREATININE (mg/dl)	6.27 ± 3.11	5.96 ± 2.8	0.519
BLOOD UREA NITROGEN (BUN) (mg/dl)	79.18 ± 69.3	74.57 ± 46.32	0.633
URIC ACID (mg/dl)	7.31 ± 11.97	6.43 ± 1.91	0.531
SODIUM (mmol/L)	138.95 ± 6.82	138.05 ± 5.51	0.375
POTASSIUM(mmol/L)	4.59 ± 0.81	4.65 ± 0.8	0.652
CALCIUM (mg/dL)	10.29 ± 10.07	6.05 ± 1.12	<0.001
ALBUMIN (gm/dl)	4.01 ± 0.58	4.04 ± 0.6	0.779
eGFR (mL/min/1.73m²)	102.72 ± 6.45	51.29 ± 5.28	<0.001
COPEPTIN (pg/mL)	1.86 ± 0.72	6.32 ± 1.18	<0.001

*eGFR = Estimated Glomerular Filteration Rate
*HbA1c = Glycosylated Hemoglobin
*FBS = Fasting Blood Sugar
*PPBS = Post Prandial Blood Sugar

Table 2. Correlation & Regression Analysis Showing Relationship of Copeptin withBiochemical Parameters

Variable	COPEPTIN	
	R-value	**p-value**
CREATININE (mg/dl)	-.061	0.460
UREA (mg/dL)	0.221	0.007
HbA1C %	0.585	<.001
SODIUM (mmol/L)	-.084	0.304
POTASSIUM(mmol/L)	0.005	0.948
CALCIUM (mg/dL)	-.272	0.001
ALBUMIN (gm/dl)	0.007	0.931
eGFR (mL/min/1.73m²)	-.888	<.001
URIC ACID (mg/dl)	-.057	0.493

*HbA1C: Glycosylated Hemoglobin
*eGFR: Estimated Glomerular Filtration

Table 3. ROC Analysis to predict Cases by Copeptin level

Parameter	Value
AUROC	0.990
Optimum cut off for case	Copetin>3.025
Sensitivity	100
Specificity	98.7

*AUROC = Area under Receiver Operating Curve

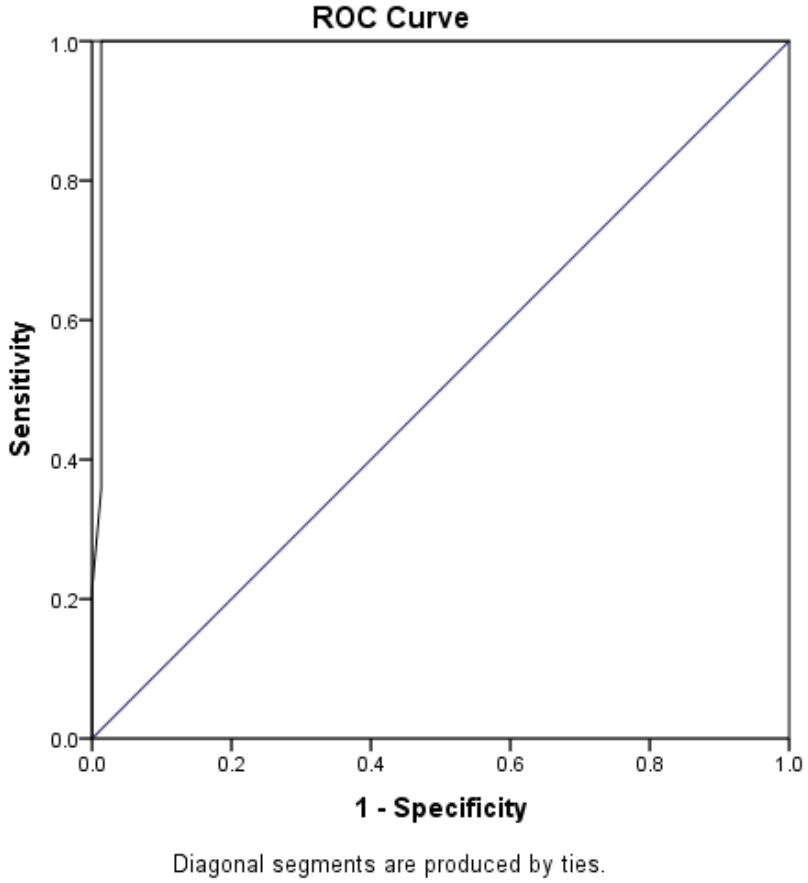

Figure 1. ROC Analysis to predict Cases by Copeptin level

An elevated level is observed was statistically significant in cases (CKD with diabetes) as compared to the control group, control (CKD with no diabetes) i.e. (1.86 ± 0.72 vs. 6.32 ± 1.18) (p-value < 0.001) as shown in Table 1 and to bring out more specificity the Table 2 and Table 3 and figure 1 showing correlation and regression analysis and ROC analysis. The ROC (Receiver Operating Characteristic) analysis was performed to evaluate the ability of Copeptin levels to predict cases. The ROC analysis demonstrates that Copeptin levels have a very high AUROC, indicating strong predictive power for identifying cases. The suggested optimum cut-off of 3.025, combined with a sensitivity of 100% and specificity of 98.7%, suggests that Copeptin is an excellent biomarker for effectively distinguishing between cases and non-cases in the given context, making it a valuable tool for diagnostic purposes. The increase in circulating vasopressin (also known as ant diuretic hormone) levels has been extensively observed in both type 1 and type 2 diabetic patients, as well as in vivo animal study of spontaneous or streptozotocin-induced diabetes [21]. The exact reason for this elevated vasopressin in diabetes is not fully understood, but it could potentially result from a relative decrease in extracellular volume due to glycosuria, and/or an enhanced sensitivity of hypothalamic osmoreceptors to changes in plasma osmolarity [22]. While the temporary rise in vasopressin levels might offer short-term benefits by reducing water loss caused by glycosuria, sustained elevation could potentially negatively impact kidney function over an extended period [23].This study aimed to investigate the clinical significance of serum copeptin levels in individuals with type 2 diabetes, both with and without nephropathy. The study also sought to examine the correlation between serum copeptin levels and various clinical and laboratory parameters. The findings revealed that the average serum copeptin level was notably higher in the diabetic group compared to the control group (1.86 ± 0.72 vs. 6.32 ± 1.18) (p-value < 0.001). Additionally, there are positive associations between serum copeptin levels and markers such as glycosylated hemoglobin, urinary albumin creatinine ratio, and serum creatinine. Conversely, there was a negative correlation between serum copeptin levels and estimated glomerular filtration rate (eGFR). The study identified a significant difference of , These findingsare congruent with a study that observed higher copeptin levels in CKD patients across stages 2–5 in comparison to stage 1 CKD patients. Similarly, serum copeptin was found to be elevated in type 1 diabetic patients with albuminuria relative to the normoalbuminuria group. [1]. Conversely, there is an association between copeptin levels and an accelerated decline in kidneyfunction. This association persisted even

after accounting for various factors, indicating a predictive value for copeptin in kidney function decline [25]. An inverse correlation between serum copeptin levels and parameters like eGFR, sodium, and albumin, along with positive correlations with plasma osmolality, serum glucose, duration of type 2 diabetes mellitus, uric acid, and mean blood pressure. [26]. Consistent with our results, the data also established a positive association between serum copeptin and kidney function markers, as well as kidney function decline, particularly inpopulations at risk of or with chronic kidney disease (CKD), such as those with diabetes mellitus. However, limited prospective data exist on the link between serum copeptin and new- onset CKD in the general population, as mentioned previously [3]. It is noteworthy that vasopressin's association with cardio-renal complications in type 2 diabetes mellitus is significant. A substantial body of evidence suggests that vasopressin, through V2 receptor activation, plays a direct role in the development and progression of chronic kidney disease, including diabetic kidney disease. Impaired kidney function can exacerbate other cardiovascular risk factors, thereby contributing to complications such as hypertension, oxidative stress, insulin resistance, dyslipidemia, body fat distribution, inflammation, and arterial calcification. Consequently, the link between copeptin and cardiovascular disease may be attributed, at least in part, to the detrimental effects of vasopressin on kidney function [30]. Serum copeptin could potentially aid in identifying individuals at high risk for developing diabetic kidney disease and cardiovascular disease, thus facilitating targeted interventions. Given that plasma osmolality is the primary stimulus for vasopressin and copeptin secretion, and these secretions are closely tied to hydration status, further investigation is required to establish whether reducing vasopressin secretion or action through increased water intake or treatment with vasopressin receptor antagonists (vaptans) could ameliorate cardiometabolic and kidney-related risks in type 2 diabetes mellitus patients [15]. Experimental findings strongly support the concept that vasopressin, activated through the V2 receptor, significantly contributes to the worsening of diabetic chronic kidney disease. Beyond its recognized antidiuretic effects at the collecting duct level, experiments have shown that a V2 receptor agonist can lead to glomerular hyperfiltration and increased urinary albumin release in normal rats. However, the precise mechanisms driving these harmful impacts of vasopressin are not fully understood, potentially involving changes in the composition of tubular fluid at the macula densa, affecting the control of glomerular filtration rate (GFR) through tubuloglomerular feedback. Additionally, vasodilation of the afferent arteriole would result in heightened intraglomerular pressure, considered a significant contributor to the decline of kidney function indiabetic CKD [11]. It is important to highlight that our study's observational nature prevents definitive confirmation or rejection of these mechanisms, necessitating further experimental exploration in this domain. A noteworthy and compelling benefit of dual action mechanisms of vasopressin blockers is necessary targeting both glomerular and tubular sites. This characteristic is particularly appealing in the context of diabetic kidney disease (DKD), as individuals with DKD are vulnerable to damage in both the glomerular and tubulointerstitial regions. In the realm of DKD, research has indicated that inhibiting V2 receptors can effectively reduce albuminuria and counteract hyperfiltration in animal models. However, it's crucial to acknowledge the shortage of data of human study available or published in addition investigating the different impact of copeptin on the fundamental mechanisms of the disease or the clinical progression of DKD in the context of diabetes mellitus [31].

4. Conclusions

Hence the available data shows that copeptin has a prominent role and can serve a valuable prognostic marker in prediction of different cardiovascular events. In addition, the study done shows the copeptin value can act as a future indicator or predictor of outcome in patients with chronic kidney disease. The advancement of CKD can be increased with an elevated level of serum Copeptin. Hence the presence of serum copeptin could serve as a means to detect individuals with diabetic chronic kidney disease who are particularly susceptible to a decline in renal function.

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***Conflict of interes*t**

The authors declare no conflict of interest.

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