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Copeptin As A Marker To Signal Kidney Disease In Patients With Type 2 Diabetes

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Abstract
Introduction*: Diabetic Kidney Disease is the term for the kidney damage caused by the main microvascular complications of diabetes. It is one of the most frequent effects of diabetes mellitus (DM) and the primary cause of end-stage kidney disease (ESKD). It is necessary to identify helpful biomarkers that can indicate the early onset of nephropathy to replace the gold standard biomarker, eGFR, and uACR.*
Materials and Procedures*: A total of 121 patients of Diabetes Mellitus with microalbuminuria (GROUP I) together with 121 diabetes mellitus II patients without microalbuminuria (GROUP II) were enrolled in the study. FPG, PPG, HbA1c, Creatinine, copeptin, eGFR, and uACR were all examined in the lab.*
Results*: Higher mean levels of Fasting and postprandial glucose, and HbA1c were found in Group I. However, the increase was not significant with 'p' values 0.161, 0.066, and 0.347 respectively. The increase in mean Urea, Uric Acid, Creatinine, uACR, and copeptin and the decrease in mean eGFR were significant when compared the both groups ('p'<0.001). In both groups, there was a positive correlation between serum copeptin levels and all other variables.*
Conclusion*: The results suggest that copeptin can be considered a valuable biomarker to signal kidney disease in patients with type 2 diabetes.*
Keywords*: Copeptin; Diabetic Kidney Disease; eGFR, uACR*

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I. Introduction

Diabetes mellitus (DM) is a metabolic illness that is highly prevalent and intricate. Because of the high incidence of diabetes-related complications and mortality, the disease is one of the biggest medical and socioeconomic problems in the world.[1] The International Diabetes Federation (IDF) has released data showing that 537 million adults worldwide between the ages of 20 and 79 had diabetes in 2021, accounting for 10.5% of the world's population.[2] Globally, the number of persons with diabetes will rise from 643 million in 2030 to 783 million in 2045.[3] India is the diabetes epicenter of the world. Currently, 40.9 million individuals in India have diabetes mellitus (DM).[4] An estimated 80–87 million Indians will have diabetes by 2030. Microvascular problems like retinopathy, neuropathy, and nephropathy have been linked to chronic diabetes.[5] Research indicates that diabetic nephropathy (DN) may develop in approximately 25% of patients with type 2 diabetes mellitus (T2DM).[6]

The identification of albuminuria and a progressive decline in the estimated glomerular filtration rate (eGFR), as determined by serum creatinine levels, are prerequisites for the diagnosis of diabetic kidney disease (DKD).[7] The degree of structural damage and renal function are clearly correlated, even at moderately low eGFR decrease levels during DKD.[8]

The GFR remains the primary clinical biomarker for evaluating prognosis in DKD and is frequently used in clinical practice and trials.[9] However, this association is less apparent in the initial stages of the disease when albuminuria is low or eGFR reduction is minimal.[10] due to compensatory changes in the remaining nephrons [11] In clinical practice and clinical trials, the GFR is still the predominant clinical biomarker used to assess prognosis in DKD.[9] However, when albuminuria is modest or eGFR decline is minor in the early stages of the disease, this connection is less evident.[10] because of adjustments made to compensate for the missing nephrons.[11]

Finding novel biomarkers is essential for the quick and precise detection of early DN given the shortcomings of the patient diagnostic techniques now in use. Recently, several biomarkers have been found as potential indicators of diabetic nephropathy; most of these indicators still need to be validated. In some infections, cardiovascular, pulmonary, cerebrovascular, and stressful circumstances, copeptin is employed as a marker for

AVP secretion.[12] Diabetes mellitus (DM) is associated with elevated AVP levels, which may be related to albuminuria and alterations in glomerular filtration rate (GFR) in individuals with chronic kidney disease (CKD) or diabetic renal disease.[13] The effectiveness of serum Copeptin in the early diagnosis of kidney impairment has only been studied in a small number of studies, and the findings are not very encouraging. Thus, the purpose of this investigation was to ascertain whether serum Copeptin is a reliable indicator of renal damage in individuals with type 2 diabetes.

II. Material & Methods

An investigation was carried out in the biochemistry department using a cross-sectional design following ethical clearance from the institutional Human Ethics Committee. In the study, 121 patients of Diabetes Mellitus II with microalbuminuria (Group I) and 121 patients of Diabetes Mellitus II without microalbuminuria (Group II) attended the Outpatient Department (OPD) of Index Medical College, Hospital & Research Centre, M.P were enrolled. The ADA recommendations were followed in the diagnosis of all diabetes patients. Based on an uACR >30 mg/g, patients with diabetic nephropathy (GROUP I) were identified. Following the physical examination and taking a history, the following investigations were conducted: 1. Morning midstream Urine samples were collected using single-use, preservative-free cups for quantitative analysis of urinary albumin and creatinine to determine the urinary albumin to creatinine ratio(uACR). 2. Blood samples were collected for estimation of fasting and postprandial glucose, HbA1c, Renal function test, and Copeptin (Sandwich ELISA). 3. Calculation of estimated glomerular filtration rate (MDRD).[14]

Inclusion and exclusion criteria

Male and female participants in the study between the ages of 40 and 70 who meet the requirements for Diabetes Mellitus II with or without microalbuminuria were invited to apply.

Exclusion criteria for this patient group included immunological disorders, hepatitis, pregnancy, urinary tract infections, acute diabetic ketoacidosis, and nonketotic hyperosmolar coma), other chronic kidney diseases, thyroid dysfunction and uncontrolled hypertension, coronary heart disease, myocardial infarction, peripheral vascular diseases, debilitating conditions, and social conditions that, in the investigator's opinion, would interfere with or be a contraindication to following the study protocol.

Statistical analysis: Statistical program SPSS VERSION 27.0 was used to evaluate all the parameters, and the findings were expressed as Mean ± SD. The independent student's "t" test was used to compare the levels of these variables among the patients. The relationship between serum copeptin and other lab variable levels has also been determined using Pearson's correlation coefficient.

III. Results

Each participant's biochemical characteristics are compiled by the study and shown in Table 1 as Mean ± SD. Group I had higher mean values of Fasting and postprandial glucose, and HbA1c than Group II. The increase, however, did not reach statistical significance ('p' values of 0.161, 0.066, and 0.347, respectively). Upon comparing the two groups, there was a substantial drop in mean eGFR and an increase in mean urea, uric acid, creatinine, uACR, and copeptin ('p'<0.001).

TABLE 1- Comparison of Laboratory Variables among Patients.

Parameters	Group I (Mean ± SD)	GROUP II (Mean ± SD)	'*p*' value
Fasting Plasma Glucose (mg/dl)	142.95 ± 11.44	140.87 ± 11.43	*0.161*
Post Prandial Glucose (mg/dl)	220.32 ± 21.21	215.29 ± 21.23	*0.066*
HbA1c (%)	7.60 ± 0.47	7.53 ± 0.62	*0.347*
Urea (mg/dl)	58.53 ± 7.51	32.51 ± 7.60	***<0.001***
Uric Acid (mg/dl)	7.35 ± 1.18	5.65 ±1.13	***<0.001***
Creatinine (mg/dl)	1.33 ± 0.31	0.86 ± 0.17	***<0.001***
eGFR (ml/min/1.73 m^2)	56.12 ± 15.31	90.96 ± 20.37	***<0.001***
uACR (mg/g)	106.20 ± 63.25	13.72 ± 5.81	***<0.001***

Serum Copeptin (pg/ml)	87.50 ± 30.65	28.39 ± 10.35	***<0.001***

A 'p' value < 0.05 was considered significant.
A 'p' value < 0.01 was considered highly significant.

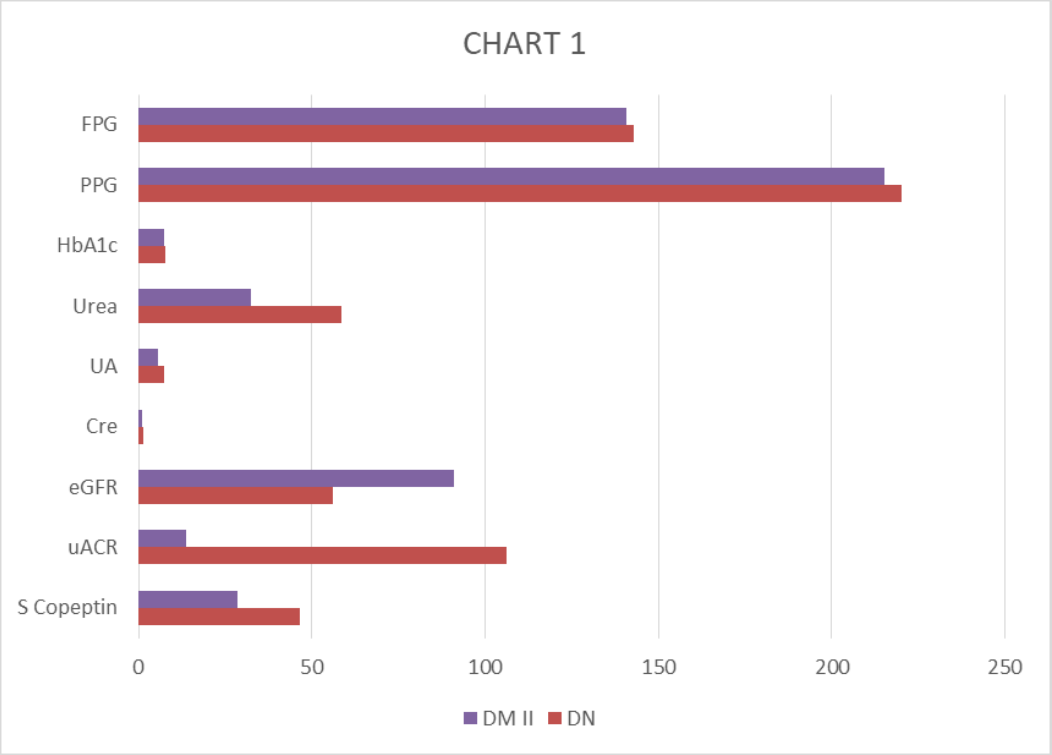

TABLE 2- Pearson Correlations

		Group I				Group II			
Lab variables		CRE	eGFR	uACR	Copeptin	CRE	eGFR	uACR	Copeptin
CRE	Pearson Correlation	1	-.843	.934	.925	1	-.746	.934	.833
	Sig. (2-tailed)		.000	.000	.000		.000	.000	.000
	N	121	121	121	121	121	121	121	121
eGFR	Pearson Correlation	-.843	1	-.871	-.746	-.746	1	-.836	-.931
	Sig. (2-tailed)	.000		.000	.000	.000		.000	.000
	N	121	121	121	121	121	121	121	121
uACR	Pearson Correlation	.934	-.871	1	.934	.934	-.836	1	.888
	Sig. (2-tailed)	.000	.000		.000	.000	.000		.000
	N	121	121	121	121	121	121	121	121
Copeptin	Pearson Correlation	.925	-.900	.907	.833	.833	-.931	.888	1
	Sig. (2-tailed)	.000	.000	.000	.000	.000	.000	.000	
	N	121	121	121	121	121	121	121	121

A 'p' value < 0.05 was considered significant.
A 'p' value < 0.01 was considered highly significant.

The results of Pearson's correlation analysis, which looked at the relationships between the lab variables in GROUP I and GROUP II, are shown in Table 2. Serum copeptin levels and all other variables showed a favorable connection in both patient groups (GROUP I & II). Copeptin levels in patients with GROUP I (r =.925,.934, and -.746) and GROUP II (r =.833,.888, and -.931) showed a positive connection with creatinine and uACR and a negative correlation with eGFR. Every variable showed a substantial association in both groups.

IV. Discussion

The purpose of the study was to determine the relationship between kidney damage in diabetes patients and serum copeptin levels. It was carried out in the Department of Biochemistry at Index Medical College, Hospital & Research Centre, Indore, M. P., India.

This cross-sectional study's findings demonstrated that, in comparison to type II diabetes (GROUP II), the group with diabetic nephropathy (GROUP I) had higher levels of fasting and postprandial glucose, HbA1c, urea, uric acid, creatinine, uACR, and serum copeptin. The averages of HbA1c, postprandial glucose, and fasting were not significantly higher; their corresponding "p" values were 0.347, 0.066, and 0.161 respectively. Nonetheless, there was a significant drop in mean eGFR and a rise in mean urea, uric acid, creatinine, and uACR. The rise in serum copeptin levels in Group I was found to be highly significant (p-value <0.001).

This supports the findings of Zhu et al.[15], who discovered a correlation between elevated blood copeptin and type-2 diabetes mellitus as well as diabetic comorbidities. This suggests that AVP/copeptin may have a role in the pathophysiology of type-2 diabetes mellitus. Comparing the control group and diabetic patients without nephropathy to the development of DN in T2DM, Nesen AO et al.[16] demonstrated a substantial rise in copeptin levels in blood serum. Patients with reduced glomerular filtration rate and albuminuria had the highest amounts of copeptin. According to El-Soudany et al.[17], patients with macroalbuminuria also had greater tt levels than those in the control, normoalbuminuric, and microalbuminuric groups.

We examined its associations with other laboratory studies to see whether this increase in serum copeptin is linked to renal function or diabetes itself. Serum copeptin and serum creatinine, or uACR, showed a positive association in the diabetic group, however, there was a substantial negative correlation with eGFR. Given that serum copeptin is linked to both eGFR and uACR, it could help to explain why diabetic patients with albuminuria have greater levels of the protein than those without. Our data matched the numbers published by El-Soudany et al.[17] and Boertien et al.[18] According to El-Soudany et al., there was a negative correlation between plasma copeptin level and eGFR, but a positive correlation with glycosylated hemoglobin, urine albumin/creatinine ratio, and serum creatinine. Conversely, Boertien et al.'s findings throughout the follow-up of individuals with type 2 diabetes mellitus demonstrated a robust correlation between serum copeptin and the progressive deterioration of renal functioning.

Serum copeptin's correlation with albuminuria and lower eGFR may be attributed to the protein's decreased excretion by the kidneys or to its increased co-secretion with the AVP to regulate urine concentration and water hemostasis.[19] Through several pathways, including hyperfiltration, albuminuria, glomerulosclerosis, prothrombotic impact, stimulation of the rennin-angiotensin-aldosterone system, hypertension, and vasoconstriction, AVP can cause diabetic patients to develop chronic kidney disease (CKD).[20]

V. Conclusion

Given that GROUP I patients have high levels of copeptin and that there is a link between copeptin levels and eGFR and uACR, it is reasonable to assume that serum copeptin levels could be important indicators for the early identification of nephropathy in DM II.

CONFLICT OF INTEREST: None

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