The Egyptian Journal of Hospital Medicine (July 2021) Vol. 84, Page 2242-2248

Value of Serum Copeptin Estimation for the Diagnosis of Diabetic Nephropathy in Type 2 Diabetes Mellitus Patients

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ABSTRACT:
Background: Serum copeptin, the terminal part of the arginine vasopressin (AVP), is stable in plasma. The AVP is increased in diabetic patients and may play a role in the development of diabetic kidney disease.
Objective: To evaluate the role of serum copeptin in the diagnosis of diabetic nephropathy in type-2 diabetes mellitus.
Patients and Methods: 40 type-2 diabetes mellitus (T2DM) patients; divided into two groups, (20 with poor glycemic control, and 20 with good glycemic control), in addition to 20 non-diabetic healthy control subjects. The following investigations had been made; HbA1C, FBS, blood urea, serum creatinine and sodium, creatinine clearance (Ccr), glomerular filtration rate (eGFR), urinary protein, and urinary sodium. Serum copeptin levels were measured using an enzyme-linked immunoassay (ELISA).
Results: Serum copeptin levels were significantly higher in (T2DM) patients with poor glycemic control than in (T2DM) patients with good glycemic control compared to the healthy control group. There was a significant positive correlation between serum copeptin and FBS, HbA1C, blood urea, serum creatinine, urinary Na, and 24-hour urinary protein, and a significant negative correlation with serum Na, eGFR, and creatinine clearance. The receiver operating characteristic (ROC) curve for the validity of serum copeptin, as a marker for diabetic nephropathy, at cutoff point 3452 pg/ml, showed 90% sensitivity, and 95% specificity.
Conclusion: Serum copeptin is independently related to markers of kidney injury in T2DM and may be used as a marker for diabetic nephropathy.
Keywords: Serum copeptin, Arginine vasopressin (AVP), Diabetic kidney disease.

INTRODUCTION

The arginine vasopressin (AVP), also known as the antidiuretic hormone (ADH), is important in maintaining fluid balance and vascular tone [(1)]. Copeptin is a glycopeptide co-secreted with the AVP, and its function is unknown. It is used as a marker for the AVP secretion, as it is stable in the serum, unlike the AVP [(2)]. Copeptin is used as a marker for the AVP secretion in some infections, cardiovascular, respiratory, cerebrovascular, and stressful conditions [(3)]. AVP level is increased in diabetes mellitus (DM) and may play a role in the albuminuria and the changes in glomerular filtration rate (GFR) in chronic kidney disease (CKD) or diabetic kidney disease [(4)]. The ADH secretion is stimulated by hyperosmolarity, hypotension, hypoxia, insulin-induced hypoglycemia, and stress [(5, 6)]. It binds to 3 types of receptors; V1a, V1b, and V2 receptors [(7)]; V1a mediates vasoconstriction (5), V1b mediates the secretion of adrenocorticotrophic hormone (ACTH), and insulin [(8)], and V2 mediates its antidiuretic effect, through the aquaporin-2 channels in the distal nephrons [(1)]. Elevated serum copeptin levels are related to increased mortality in hemodialysis (HD) patients with type-2 diabetes mellitus (DM) [(9)] and are correlated to the progression of chronic kidney disease (CKD) [(10)]. Serum copeptin is correlated to albuminuria, and renal decline in kidney transplant recipients [(11)] and can be used as a marker for kidney injury in preeclampsia, with high sensitivity and specificity [(12)]. Also, recurrent dehydration and hyperosmolarity may lead to chronic kidney injury, through its effect on AVP, and serum copeptin secretion [(13)].

This study was conducted to evaluate the role of serum copeptin in the diagnosis of diabetic kidney disease, in type-2 diabetes mellitus.

PATIENTS AND METHODS

This case-control study was carried out, during the period from January 2019 to March 2020, at the inpatient wards, and the outpatient clinics, of the Internal Medicine Department, Nephrology Unit, and the Biochemistry Department, Faculty of Medicine, Zagazig University Hospitals, Egypt.

A total of 40 age-matched patients with type-2 diabetes mellitus (DM) were divided into; 20 diabetics with poor glycemic control (glycosylated hemoglobin (HbA1C) more than 7%) and 20 diabetics with good glycemic control (HbA1C) less than 7%. Diabetic patients had criteria for diagnosis as type 2 DM on regular oral hypoglycemic treatment, for 5 years or more [(14)], in addition to 20 age-matched healthy non-diabetic subjects served as the control group.

In our work, we excluded patients with other conditions affecting serum copeptin including sepsis, malignancy, chronic obstructive pulmonary disease, S-T elevation-myocardial infarction, or cerebrovascular stroke.

Ethical approval:

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Received:19 /4 /2021
Accepted:15 /6 /2021

Informed consent had been taken from all participants, according to Helsinki's Declaration. Also, approvals were taken from the Ethical Committee, the Institutional Research Board (IRB) of the Faculty of Medicine, Zagazig University, Egypt. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

All patients were subjected to:

Following history taking and physical examination, these investigations had been made; glycosylated hemoglobin (HbA1C), fasting blood sugar (FBS), serum creatinine, blood urea, serum uric acid, calculated creatinine clearance, by Cockcroft-Gault equation (creatinine clearance ={ (l40–age) x weight) / (72xSerum creatinine) }x 0.85 (if female) [15], calculated glomerular filtration rate (eGFR), by the Modification of Diet in Renal Disease (MDRD) calculator (186 x serum creatinine-1.154 x age-0.203) x (0.742 if female) [16], urine analysis, urinary protein, serum and urinary sodium (Na).

Measurement of serum copeptin: Serum copeptin level was measured using Human Vasopressin-neurophysin 2-Copeptin, by an enzyme-linked immunosorbent assay (ELISA) Kit; No: E0462h, manufactured by EIAab, China.

Statistical analysis:

Data were analyzed, using SPSS 20.0 for windows. Quantitative data were presented as mean ± SD and were compared by one-way ANOVA test. Spearman's Equation for correlation coefficient was used when appropriate. Multivariate regression analysis was used when appropriate. The Receiver operating characteristic (ROC) curve was calculated for specificity and sensitivity of serum copeptin levels, with the cutoff point, the area under the curve (AUC), confidence index (CI), positive predictive value (PPV), negative predictive value (NPV), and accuracy. All tests were two-sided, and the results were considered statistically significant when the p-value was < 0.05.

RESULTS

The analysis of demographic data and vital signs of the studied groups showed no significant difference as regards the age, but a significant difference was found as regards the body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP) (Table 1).

There was a significant difference among the studied groups as regards the following laboratory findings; FBS, HbA1C%, blood urea, serum creatinine, serum uric acid, serum albumin, GFR, creatinine clearance, 24-hour urinary proteins, and sodium, but no significant difference as regards serum sodium or serum total proteins (Table 1).

There was a significant difference as regards serum copeptin levels, being significantly higher in diabetic patients with poor glycemic control group than diabetic patients with good glycemic control group, compared to healthy non-diabetic group (Table 1 and Figure 1).

Table 1: Demographic data, laboratory findings, and serum copeptin levels among the studied groups

Variables	DM with poor glycemic control (n=20)	DM with good glycemic control (n=20)	Healthy control (n=20)	P-value
Age (years)	52.8±11.6	52.4±7.6	52.62 ± 9.7	0.992
BMI (kg/m^2)	31.5±3.4	30.8±4.4	28.4±1.12	0.011*
SBP (mmHg)	142.1±15.3	140.2±10.22	112.5±13.2	<0.001*
DBP (mmHg)	86.7±8.4	84.5±9.65	69.1±11.8	<0.001*
FBS (mg/dl)	143.7±3.8	95.4±7.2	92.65±3.2	<0.001*
HbA1C (%)	8.3±0.53	6.1±0.42	5.7±0.23	<0.001*
S. Na (mmol/l)	133.1±3.7	136.0±3.17	135.4±6.2	0.114
Bl. urea (mg/dl)	55.6±12.2	37.9±1.3	19.7±8.9	<0.001*
S. creat. (mg/dl)	2.6±0.7	1.4±0.35	0.86±0.19	<0.001*
S. alb. (gm/dl)	3.4±0.24	3.71±0.3	3.75±0.38	0.001*
S. prot. (mg/dl)	6.8±1.2	7.27±0.4	7.32±0.35	0.065
S. uric A. (mg/dl)	6.07±1.19	5.78±1.84	4.2±0.19	<0.001*
GFR (ml/min)	29.0±5.0	59.59±5.9	124.7±11.9	<0.001*
Ccr. (ml/min)	43.7±2.9	81.18±3.3	129.2±12.6	<0.001*
U. Na (mmol/l/day)	39.9±8.6	32.1±8.4	31.4±7.2	0.002*
U. prot. (gm/l/day)	1.5±0.08	0.6±0.07	0.03±0.05	<0.001*
S. copeptin (pg/ml)	4448.7±358.8	3044.6±288.8	386.9±37.6	<0.001*

Data are presented as mean±SD, *Statistically significant difference. DM (diabetes mellitus), BMI (Body mass index), SBP (Systolic blood pressure), DBP (Diastolic blood pressure), FBS (Fasting blood sugar), HbA1C (Hemoglobin A1C), S. (serum), Na (Sodium), bl. (Blood), creat. (Creatinine), alb. (Albumin), prot. (Protein), GFR (Glomerular filtration rate), min (Minute), Ccr (Creatinine clearance), U (Urinary).

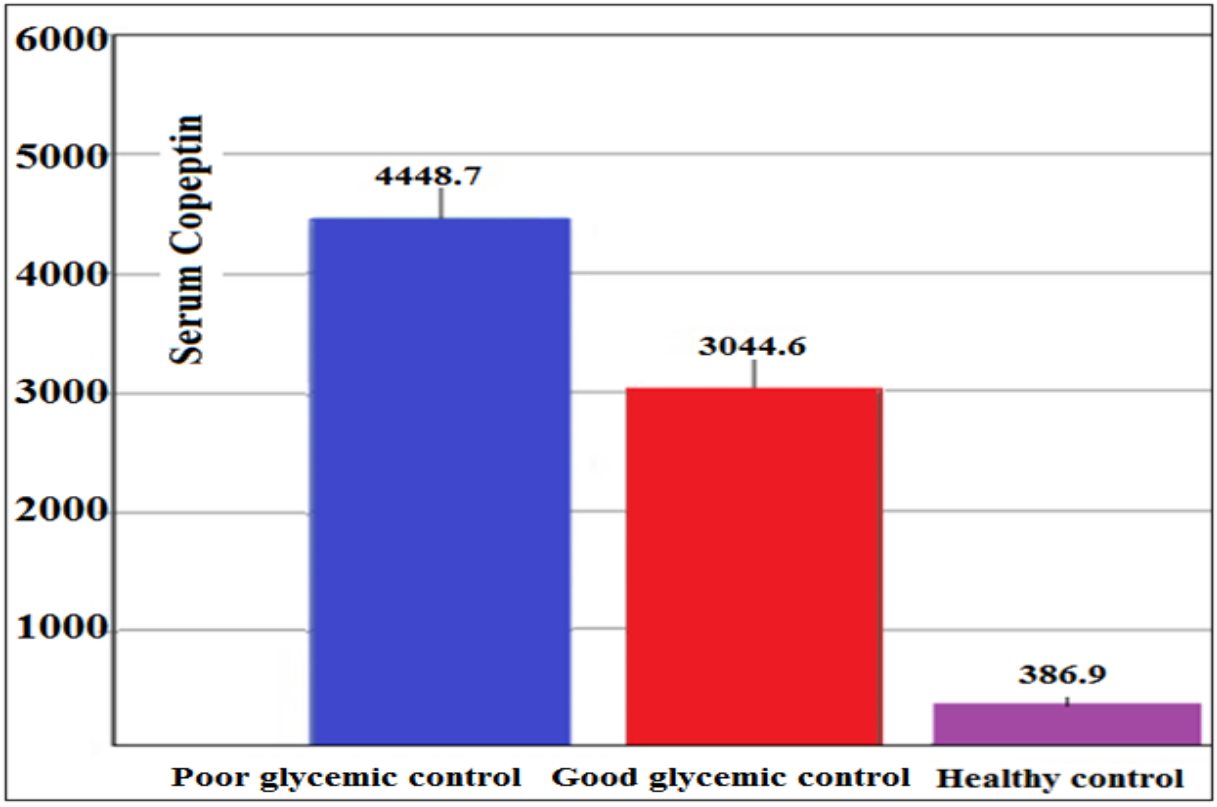


Figure (1): Serum copeptin levels in the studied groups

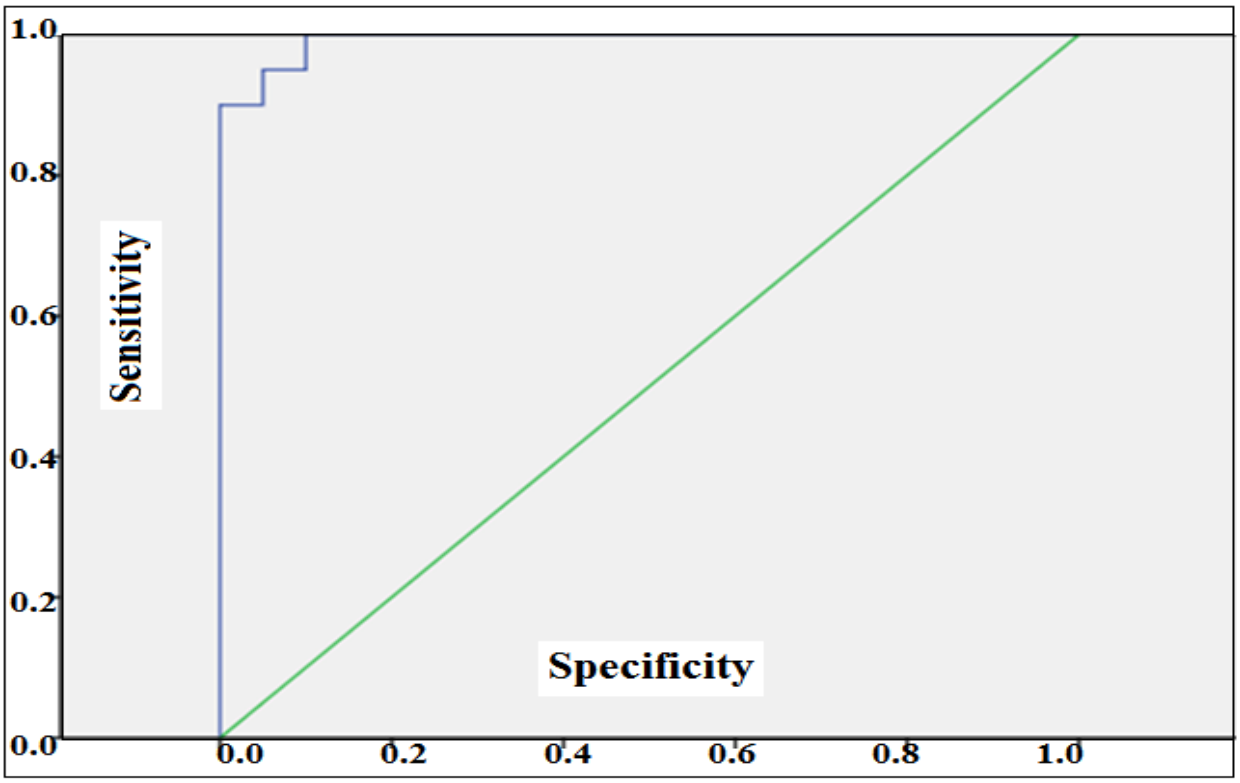
There was a positive correlation between serum copeptin and FBS, HbA1C, blood urea, serum creatinine, urinary Na and urinary protein, while there was a significant negative correlation with serum Na, eGFR, and creatinine clearance (Table 2).

Table (2): Correlation of serum copeptin level with other laboratory results in the diabetic patients

Laboratory investigations	Copeptin in pg/ml	
	R	P-value
Systolic blood pressure (SBP) in mmHg	-0.083	0.612
Diastolic blood pressure (DBP) in mmHg	-0.132	0.415
Fasting blood sugar (FBS) in mg/dl	0.695	0.001*
Hemoglobin A1C (HbA1C) (%)	0.820	0.001*
Serum sodium (Na) in mmol/l	-0.380	0.016*
Blood urea in mg/dl	0.446	0.002*
Serum creatinine in mg/dl	0.715	0.001*
Glomerular filtration rate (GFR) in ml/minute	-0.707	0.001*
Creatinine clearance in ml/minute	-0.639	0.001*
24 Hours urinary sodium (Na) in mmol/l	0.372	0.04*
24 Hours urinary protein in gm/l	0.485	0.01*

R: Correlation coefficient, *Statistically significant difference.

The receiver operating characteristic (ROC) curve for the validity of serum copeptin level, as a marker for kidney injury in diabetic patients was studied (Figure 2).



Copeptin	AUC	98%CI	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
	0.925	0.9-1.0	>3452	90.0%	95.0%	94.7%	90.5%	92.5%

Figure (2): Receiver operating characteristic (ROC) curve for serum copeptin as a marker of diabetic nephropathy

Using the multivariate regression analysis for serum copeptin levels versus laboratory investigations (quantitative) showed that serum copeptin is independently correlated to HbA1C, but not with FBS, blood urea, serum creatinine, total serum protein, serum albumin, urinary protein, urinary sodium, creatinine clearance or eGFR (Table 3).

Table (3): Multivariate regression analysis for serum copeptin level versus laboratory results (Quantitative)

Model		Unstandardized coefficients		Standardized coefficients	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta		Lower Bound	Upper Bound
1	**Constant**	-288.7	2010.4		0.88	-4400.6	3823.1
	S. creat. (mg/dl)	234.9	255.3	0.25	0.36	-287.4	757.2
	Bl. Urea (mg/dl)	-2.57	7.61	-0.05	0.73	-18.1	13.1
	U. Prot. (gm/l/day)	57.04	106.8	0.08	0.59	-161.5	275.6
	U. Na (mmol/l/day)	5.04	8.4	0.07	0.55	-12.1	22.2
	T. prot.	5.43	81.6	0.01	0.94	-161.6	172.5
	S. alb. (gm/dl)	207.1	285.1	0.09	0.47	-376.1	790.1
	HbA1c (%)	383.8	182.7	0.59	0.04*	10.1	757.5
	Ccr (ml/min)	-0.100	7.1	-0.01	0.98	-14.6	14.4
	eGFR (mL/min)	-2.568	14.1	-0.06	0.85	-31.2	26.1
	FBS (mg/dl)	-0.393	5.7	-0.02	0.94	-12.1	11.3

Dependent variable: serum copeptin. *Statistically significant difference, S. (Serum), creat. (Creatinine), Bl. (Blood), U. (Urinary), Na (Sodium), T. (Total), prot. (Protein), alb. (Albumin), HbA1C (Hemoglobin A1C), Ccr (Creatinine clearance), GFR (Glomerular filtration rate), FBS (Fasting blood sugar).

Using the multivariate analysis for serum copeptin levels as an independent variable (Qualitative, divided at the cutoff) showed that serum copeptin is independently correlated to serum creatinine, blood urea, urinary protein, eGFR, creatinine clearance, HbA1C, and FBS, but not with total serum protein, serum albumin, or urinary sodium (Table 4).

Table (4): Multivariate analysis for serum copeptin as an independent variable (Qualitative; divided at the cutoff)

Items	Type III Sum of Squares	df	Mean Square	Sig.	Partial Eta Squared	Noncent Parameter	Observed Power[k]
S. creat. (mg/dl)	11.71[a]	1	11.71	0.001*	0.42	28.3	0.99
Bl. Urea (mg/dl)	2753.4[b]	1	2753.36	0.001*	0.27	14.1	0.95
U. prot. (gm/l/day)	7.85[c]	1	7.85	0.011*	0.15	7.1	0.73
U. Na (mmol/l/day)	281.6[d]	1	281.6	0.122	0.06	2.4	0.33
T. prot.	4.69[e]	1	4.69	0.080	0.07	3.2	0.41
S. alb. (gm/dl)	0.026[f]	1	0.026	0.655	0.01	0.2	0.07
HbA1c (%)	34.95[g]	1	34.95	0.001*	0.62	62.4	1.00
Ccr (ml/min)	10306.4[h]	1	10306.4	0.001*	0.35	21.31	0.99
eGFR (mL/min)	6445.2[i]	1	6445.2	0.001*	0.41	27.27	0.99
FBS (mg/dl)	16561.5[j]	1	16561.5	0.001*	0.42	28.02	0.99

Dependent variable: serum copeptin. *Statistically significant difference, S. (Serum), create. (Creatinine), Bl. (Blood), U. (Urinary), Na (Sodium), T. (Total), prot. (Protein), alb. (Albumin), HbA1C (Hemoglobin A1C), Ccr (Creatinine clearance), eGFR (Estimated glomerular filtration rate), FBS (Fasting blood sugar).

DISCUSSION

Copeptin is co-secreted with the arginine vasopressin (AVP), upon hemodynamic or osmotic stimuli. Unlike the AVP, copeptin is stable in serum and plasma at room temperature and can be measured as a marker for AVP secretion [(17)].

This case-control study was conducted to find out the relation between serum copeptin level and kidney injury in diabetic patients.

In this study, there was a significant difference among the studied groups as regards FBS, HbA1C%, blood urea, serum creatinine, serum uric acid, serum albumin, eGFR, creatinine clearance, 24-hour urinary proteins, and urinary sodium.

In our study, serum copeptin levels were significantly higher in diabetic patients with poor glycemic control than diabetic patients with good glycemic control than healthy non-diabetic group, this agrees with **Zhu *et al.*** [(18)], who found that serum copeptin elevation is associated with type-2 diabetes mellitus and diabetic complications, suggesting a role for AVP/copeptin in the pathogenesis of type-2 diabetes mellitus. Similarly, **Asferg *et al.*** [(19)] found that serum copeptin is associated with insulin resistance, obesity, and metabolic syndrome.

To differentiate whether this elevation in the serum copeptin is related to diabetes itself, or kidney function, we tested its correlations with other laboratory investigations. Within the diabetic group, there was a positive correlation between serum copeptin and FBS, HbA1C, blood urea, serum creatinine, urinary Na and urinary protein, while there was a significant negative correlation with serum Na, eGFR, and creatinine clearance. This may explain the higher levels of serum copeptin in diabetic patients with poor glycemic control than those with good glycemic control, as it is correlated to FBS and HbA1C. This is consistent with **Boertien *et al.*** [(20)], who showed that there was a strong association between serum copeptin and the gradual decline of the kidney functions during follow-up of patients with type-2 diabetes mellitus. Similarly, in kidney transplant recipients, the increased serum copeptin levels were associated with a rapid decrease in the eGFR during follow-up [(21)]. The association of serum copeptin with albuminuria and reduction of eGFR could be explained by its decreased excretion by the kidneys, or due to its increased co-secretion with the AVP, as an attempt to correct water hemostasis and urine concentration [(22)].

AVP can lead to the development of chronic kidney disease (CKD) in diabetic patients, through various mechanisms, leading to hyperfiltration, albuminuria, glomerulosclerosis, prothrombotic effect, activation of the rennin-angiotensin-aldosterone system, hypertension, and vasoconstriction [(23)].

In the current study, serum copeptin showed a positive correlation with urinary sodium and a negative correlation with serum sodium. Patients with diabetic nephropathy and CKD may develop hyponatremia due to decreased water excretion, and diabetic patients with hyporeninemic hypoaldosteronism may have excessive natriuresis, volume depletion, increase in ADH secretion, decreased water excretion, and mild hyponatremia [(24)].

The ROC curve for the validity of serum copeptin level in pg/ml, as a marker for kidney injury in diabetic patients, at a cutoff point 3452 pg/ml, showed 90.0% sensitivity, 95.0% specificity, 94.7% positive predictive value (PPV), and 90.5% negative predictive value (NPV).

The measurement of serum AVP is difficult and inaccurate, due to its short half-life, small size, and its binding to platelets [(25, 26)]. Unlike the AVP, copeptin is stable, and can be measured easily, within minutes, and with accuracy [(27,28)].

Using the multivariate regression analysis for serum copeptin levels versus laboratory investigations (quantitative) serum copeptin was

independently correlated to HbA1C, but not with blood urea, urinary protein, urinary sodium, FBS, serum creatinine, total serum protein, serum albumin, creatinine clearance or eGFR.

Whereas, by using the multivariate analysis for serum copeptin levels as an independent variable (Qualitative, divided at the cutoff) serum copeptin was independently correlated to serum creatinine, blood urea, urinary protein, eGFR, creatinine clearance, and HbA1C, but not with total serum protein, serum albumin, urinary sodium, or FBS.

This shows that patients with type-2 diabetics have higher levels of serum copeptin than healthy control, which may reflect the increase in AVP secretion. Even in controlled diabetic patients, serum copeptin levels were markedly elevated, even before the rise in serum creatinine, or the marked reduction of eGFR, or creatinine clearance. Thus, the estimation of serum copeptin may help in the early diagnosis of diabetic kidney disease. This agrees with **Tasevska *et al.*** [29], who found that increased serum copeptin was independently associated with a significantly greater annual decline of eGFR. Also, in agreement with **Velho *et al.*** [30], who studied patients with type-2 diabetes and albuminuria and found that each standard deviation (SD) increase of serum copeptin independently predicted CKD, thus it may independently predict the decline in eGFR and higher risk of new-onset CKD.

Other researchers reported a significant increase in serum levels of copeptin among type-2 diabetes mellitus patients without and with nephropathy than control [31]. Also, serum copeptin can be an independent risk factor of early decline in renal function of type-2 diabetes mellitus, especially when combined with 24-hours urinary protein estimation [32].

Elevated serum copeptin levels play a role in the development of kidney injury or diabetes mellitus [33, 34], and increasing the daily intake of water can help reduce serum copeptin and its harmful effects [35]. Increased serum copeptin and AVP may increase eGFR and proteinuria, and their blockage may help to prevent the development of CKD [23].

CONCLUSION

Serum copeptin is a useful marker for kidney injury in type-2 diabetes mellitus, with high sensitivity and specificity. Further research is recommended to study the possible benefit of targeting the AVP/copeptin pathway, to prevent/delay the progression of diabetic kidney disease.

Conflicts of Interest/Financial Disclosures: Nothing to declare.

REFERENCES:

1. **Morgenthaler N, Struck J, Jochberger S (2008):** Copeptin: clinical use of a new biomarker. Trends Endocrinol Metab., 19: 43-9.
2. **Golembiewska E, Machowska A, Stenvinkel P *et al.* (2017):** Prognostic value of copeptin in chronic kidney disease: from general population to end-stage renal disease. Curr Protein Pept Sci., 18 (12): 1232-43.
3. **Meijer E, Bakker S, Halbesma N *et al.* (2011):** Copeptin, a surrogate marker of vasopressin, is associated with microalbuminuria in a large population cohort: copeptin and albuminuria. Clin J Am Soc Nephrol., 6 (2): 361–8.
4. **Enhorning S, Wang T, Nilsson P (2010):** Plasma copeptin and the risk of diabetes mellitus. Circulation, 121: 2102–8.
5. **Balanescu S, Kopp P, Gaskill M (2011):** Correlation of plasma copeptin and vasopressin concentrations in hypo-, iso-, and hyperosmolar states. J Clin Endocrinol Metab., 96: 1046–52.
6. **Dedovic K, Duchesne A, Andrews J (2009):** The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. Neuroimage, 47: 864–71.
7. **Egashira N, Mishima K, Iwasaki K (2009):** New topics in vasopressin receptors and approach to novel drugs: Role of the vasopressin receptor in psychological and cognitive functions. J Pharmacol Sci., 109: 44–9.
8. **Holt N, Haspel K (2010):** Vasopressin: a review of therapeutic applications. J Cardiothorac Vasc Anesth., 24: 330–47.
9. **Fenske W, Wanner C, Allolio B (2011):** Copeptin Levels Associated with Cardiovascular Events in Patients with ESRD and Type 2 Diabetes Mellitus. J Am Soc Nephrol., 22: 782–90.
10. **Roussel R, Matallah N, Bouby N (2015):** Plasma copeptin and decline in renal function in a cohort from the community: The prospective D.E.S.I.R. study. Am J Nephrol., 42: 107–14.
11. **Bankir L, Bouby N, Ritz E (2013):** Vasopressin: a novel target for the prevention and retardation of kidney disease? Nat Rev Nephrol., 9: 223-39.
12. **Ghorab A, Al-Barshomy S, Mahmoud O *et al.* (2021):** Value of serum copeptin estimation in the diagnosis of kidney injury in preeclampsia. https://zumj.journals.ekb.eg/article_173188.html
13. **Garcia-Arroyo F, Cristóbal M, Arellano-Buendía A (2016):** Rehydration with soft drink-like beverages exacerbates dehydration and worsens dehydration-associated renal injury. Am J Physiol Regul Integr Comp Physiol., 311(1): 57–65.
14. **American Diabetes Association (2014):** Diagnosis and classification of diabetes mellitus. Diabetes Care, 37 (1): 81–90.
15. **Coresh J, Stevens L (2006):** Kidney function estimating equations: where do we stand? Curr Opin Nephrol Hypertens, 15 (3): 276- 84.
16. **Levey A, Stevens L (2010):** Estimating GFR using the CKD epidemiology collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. Am J Kidney Dis., 55 (4): 622-27.
17. **Katan M, Morgenthaler N, Widmer I *et al.* (2008):** Copeptin, a stable peptide derived from the vasopressin precursor, correlates with the individual stress level. Neuro Endocrinol Lett., 29: 341–6.
18. **Zhu F, Wu H, Tu K *et al.* (2016):** Serum levels of copeptin are associated with type 2 diabetes and diabetic

complications in Chinese population. J Dia Comp., 30 (8): 1566-70.

19. **Asferg C, Andersen U, Linneberg A *et al.* (2014):** Copeptin, a surrogate marker for arginine vasopressin secretion, is associated with higher glucose and insulin concentrations but not higher blood pressure in obese men. Diabet Med., 31: 728–732.
20. **Boertien W, Meijer E, Zittema D (2012):** Copeptin, a surrogate marker for vasopressin, is associated with kidney function decline in subjects with autosomal dominant polycystic kidney disease. Nephrol Dial Transplan., 27: 4131–37.
21. **Meijer E, Bakker S, de Jong P (2009):** Copeptin, a surrogate marker of vasopressin, is associated with accelerated renal function decline in renal transplant recipients. Transplantation, 88: 561– 67.
22. **Zittema D, Boertien W, van Beek A *et al.* (2012):** Vasopressin, copeptin, and renal concentrating capacity in patients with autosomal dominant polycystic kidney disease without renal impairment. Clin J Am Soc Nephrol., 7: 906–13.
23. **Afsar B (2017):** Pathophysiology of copeptin in kidney disease and hypertension. Clin Hypertens., 23: 13.
24. **Liamis G, Tsimihodimos V, Elisaf M (2015):** Hyponatremia in diabetes mellitus: clues to diagnosis and treatment. J Diabetes Metab., 6: 6.
25. **Gunebakmaz O, Celik A, Inanc M (2011):** Copeptin level and copeptin response to percutaneous balloon mitral valvuloplasty in mitral stenosis. Cardiology, 120: 221-6.
26. **Lippi G, Plebani M, Di Somma S (2012):** Considerations for early acute myocardial infarction rule-out for emergency department chest pain patients: the case of copeptin. Clin Chem Lab Med., 50: 243–53.
27. **Stoiser B, Mortl D, Hulsmann M (2006):** Copeptin, a fragment of the vasopressin precursor, as a novel predictor of outcome in heart failure. Eur J Clin Invest., 36: 771–8.
28. **Struck J, Morgenthaler N, Bergmann A (2005):** Copeptin, a stable peptide derived from the vasopressin precursor, is elevated in serum of sepsis patients. Peptides, 26: 2500–4.
29. **Tasevska I, Enhörning S, Christensson A (2016):** Increased levels of copeptin, a surrogate marker of arginine vasopressin, are associated with an increased risk of chronic kidney disease in a general population. Am J Nephrol., 44: 22–28.
30. **Velho G, Bouby N, Hadjadj S (2013):** Plasma copeptin and renal outcomes in patients with type 2 diabetes and albuminuria. Diabetes Care, 36: 3639–45.
31. **Ali D, Al-Ashmawy G, Aboelnasr S *et al.* (2021):** Copeptin: a promising biomarker for nephropathy in type II diabetes. J Adv Med Pharm Res., 2 (1): 1-7.
32. **Hu W, Ni Y, Ma L (2015):** Serum copeptin as a new biomarker in the early diagnosis of decline in renal function of type 2 diabetes mellitus patients. Int J Clin Exp Med., 8 (6): 9730–36.
33. **Wannamethee S, Welsh P, Papacosta O *et al.* (2015):** Copeptin, insulin resistance, and risk of incident diabetes in older men. J Clin Endocrinol Metab., 100 (9): 3332–39.
34. **Noor T, Hanif F, Kiran Z *et al.* (2020):** Relation of copeptin with diabetic and renal function markers among patients with diabetes mellitus progressing towards diabetic nephropathy. Arch Med Res., 51 (6): 548-55.
35. **Lemetais G, Melander O, Vecchio M *et al.* (2018):** Effect of increased water intake on plasma copeptin in healthy adults. Eur J Nutr., 7 (5): 1883–90.