El-Soudany *et al.*
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RESEARCH

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Plasma copeptin level in type 2 diabetic patients and its role in diabetic nephropathy

Nevein Nabil El-Soudany[1*], Sahar Saad El-Din Bessa[1], Heba Ahmed Morad[2] and Amal Abdel Moniem Selim[1]

Abstract

Background Copeptin, the stable COOH-terminal portion of pre-provasopressin and a surrogate marker of vasopressin, was shown to be positively associated with the decline in kidney function in the general population. However, the impact of copeptin on renal function in diabetic patients remains unclear. This study aims to assess the clinical significance of plasma copeptin level in type 2 diabetic patients with and without nephropathy and to evaluate its relation to various clinical and laboratory parameters.

Methods This study was carried out on 45 type 2 diabetic patients, divided according to urinary albumin/creatinine ratio into 15 with normoalbminuria, 15 with microalbminuria and 15 with macroalbminuria. Also, 15 healthy subjects were included as a control group. Plasma copeptin level, glycosylated hemoglobin percentage, urinary albumin/creatinine ratio and serum creatinine were measured. Estimated glomerular filtration rate (eGFR) was calculated.

Results The mean plasma copeptin level was statistically significantly higher in patients with microalbuminuria as compared to the control and normoalbuminuric groups. It was also, higher in patients with macroalbuminuria as compared to the control, normoalbuminuric and microalbuminuric groups. Plasma copeptin level was positively correlated with glycosylated hemoglobin, urinary albumin /creatinine ratio and serum creatinine but negativey correlated with eGFR.

Conclusion An increased plasma copeptin level is considered as a good predictor for deterioration of renal function in diabetic patients, suggesting that copeptin can be used to identify diabetics at risk for diabetic kidney disease development. Clearly, further well-designed prospective studies are required to prove this hypothesis.

Keywords Copeptin, Type 2 diabetes, Diabetic nephropathy

Introduction

Diabetes mellitus (DM) is a heterogeneous metabolic disorder characterized by the presence of hyperglycemia due to impairment of insulin secretion [1], defective insulin action or both. The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for cardiovascular disease [1].

Diabetic nephropathy (DN) has become the most common cause of chronic kidney disease and the first cause of dialysis initiation in the Western world, with the same trend observed in developing countries [2]. It is characterized pathophysiologically by an early phase with glomerular hypertrophy, hyperfiltration and microalbuminuria that over the course of years leads to an advanced phase with progressive glomerulosclerosis, proteinuria, and decline in renal function [3].

Although major advances have been made in uncovering the mechanism of DN, the exact pathophysiology remains incompletely understood. Many biologically

*Correspondence:
Nevein Nabil El-Soudany
dr.neveinelsoudany@Gmail.com
[1] Internal Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt
[2] Clinical Pathology Department, Faculty of Medicine, Tanta University, Tanta, Egypt

active peptides that play an important role in the kidney have been involved such as angiotensin II, endothelin-1, neuropeptide Y, urotensin II, atrial natriuretic peptide, adrenomedullin, urocortin and vasopressin [3].

It is well documented that circulating levels of vasopressin (anti-diuretic hormone) are elevated in type 1 or type 2 diabetic patients and in animal models with spontaneous or streptozotocin- induced DM [4]. The cause of increased vasopressin in DM is not fully elucidated, but it could result from a relative contraction of extracellular volume induced by glycosuria, and/or from an increased sensitivity of hypothalamic osmoreceptors to the plasma osmolarity [5].

From an adaptive perspective, high levels of vasopressin may be beneficial in the short term by limiting the water loss in urine induced by glycosuria. However, in the long term, persistently high levels of vasopressin might be deleterious to renal function [6].

Copeptin, the stable COOH-terminal portion of preprovasopressin and a surrogate marker of vasopressin, was shown to be positively associated with the decline in kidney function in the general population [7]. However, a few studies investigated the impact of high copeptin levels on renal function in diabetic patients [8–11].

Several studies have shown that serum copeptin is increased in patients with CVD and this is associated with an increased risk of adverse outcomes, including mortality, in these patients. Copeptin either alone, but especially in combination with other cardiac biomarkers, can improve the determination of the diagnosis and prognosis of different CVDs including Acute coronary syndrome, stable coronary artery disease, heart failure, and ischemic stroke [12].

Myocytes of the cardiac vascular smooth muscle express V_{1A} receptors (V1aR). While AVP can protect the heart from myocardial injuries [13], AVP activates a family of distinct G-protein–coupled receptors: V_{1A}-R in the heart, vasculature, and liver; and V_2 receptors (V_2-R) in the kidney. Activation of V_2-Rs causes reabsorption of free water, with excessive activation leading to hyponatremia. The V_2 antagonists increase serum levels of sodium but do not have a salutary effect on clinical outcome in patients with HF, and they increase serum levels of AVP [14], high levels of circulating AVP and V1aR overexpression have been associated with heart failure, indicating the importance of V1aR signaling strength [15].

Elevated vasopressin is an independent risk factor for the development of DM and cardiorenal disease, and extensive epidemiological and experimental data suggest a causal link. In the future, the vasopressin marker copeptin may help detect individuals who are at higher risk for disease development and who might benefit from vasopressin-lowering therapy and lifestyle interventions such as increased hydration [16].

The role played by vasopressin, via its V2 receptor, in the early stage of DN was highlighted by the use of a selective, non-peptide, orally active V2R antagonist (*SR 121,463*) in Wistar rats with streptozotocin-induced DM. Blockade of vasopressin V2R prevented the typical rise of urinary albumin excretion [17]. Thus, vasopressin could be a potential therapeutic target for the prevention and treatment of DN [18].

In an attempt to clarify the potential role of copeptin in type 2 diabetic patients with and without nephropathy and to evaluate its relation to various clinical and laboratory parameters, this work was designed.

Methods

This study is a cross-sectional study that was carried out on sixty subjects. Forty five type 2 diabetic patients were selected from those admitted to the Internal Medicine Department, Tanta University Hospital. Fifteen healthy subjects were included as a control group. They were classified into 4 groups: Group I (included 15 healthy subjects as a control group), group II (included 15 type 2 diabetic patients with normoalbuminuria), group III (included 15 type 2 diabetic patients with microalbuminuria) and group IV (included 15 type 2 diabetic patients with macroalbuminuria).

All cases were subjected to the following: Full history taking, complete clinical examination, abdominal ultrasonography, fundus examination of the eyes and laboratory investigations including: Complete urine analysis, fasting blood glucose, postprandial glucose level, glycosylated hemoglobin (HbA1c %), lipid profile, urinary albumin/creatinine ratio, blood urea, serum creatinine, estimated glomerular filtration rate [19] and plasma copeptin level.

Estimation of plasma copeptin level using ELISA

Principal of the assay

In this assay, a biotinylated copeptin peptide is spiked into the samples and standards. The samples and standards are then added to the plate, where the.biotinylated copeptin peptide competes with endogenous (unlabeled) copeptin for binding to the anti-copeptin antibody. After a wash step, any bound biotinylated copeptin then interacts with horseradish peroxidase (HRP)-streptavidin, which catalyzes a color development reaction. The intensity of the colorimetric signal is directly proportional to the amount of captured biotinylated copeptin peptide and inversely proportional to the amount of endogenous copeptin in the standard or samples. A standard curve of known concentration of copeptin peptide can be

established and the concentration of copeptin peptide in the samples can be calculated accordingly [20].

Statistical analysis

The collected data were organized, tabulated, and statistically analyzed using the IBM® SPSS statistical soft-ware, version 21 (Statistical Package for Social Studies) created by IBM, Illinois, Chicago, USA. In this study, the qualitative data were described using number and percentage. Quantitative data were presented as mean and standard deviation (SD). In all applied tests, the *P*-values associated with test statistics indicated the significance level at which the null-hypothesis (the hypothesis of no difference) was rejected, and it was set at 0.05 so that a *P*-values > 0.05 are statistically non-significant, *P*-values ≤ 0.05 are significant, and *P*-values < 0.001 are highly significant. Quantitative data were tested for normality using Pearson Chi-square (χ2) test to compare between two or more groups regarding one qualitative variable, Fisher's Exact Test was used instead of Chi-Square (χ^2) test when the assumption that at least 80% of the expected frequencies are greater than five was violated, one-way ANOVA test was used for continuous data to test for significant difference between more than two normally distributed groups, Scheffe test was used to adjust for multiple comparisons after significant ANOVA test to indicate which significant difference between pairs of groups, Non parametric correlations were assessed by Spearman's correlation coefficient (rho). ROC curve was constructed to detect cutoff value of copeptin with optimum sensitivity and specificity in prediction of nephropathy among diabetic patients. Multivariate logistic regression analysis was run to assess if copeptin is a predictor of diabetic nephropathy. The accepted level of significance in this work was stated at 0.05 ($P < 0.05$ was considered significant).

Results

Clinical and laboratory parameters of the studied groups: Diferent demographic and laboratory parameters of subjects in the studied groups are shown in Table 1. Figure 1 show that the mean plasma copeptin level was statistically 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 statistically significantly higher in macroalbuminuric group as compared to the control, normoalbuminuric and microalbuminuric groups with p value ($P < 0.001$). In diabetic patients, there was a statistically significant positive correlation between copeptin level and UACR ($r = 0.47$, $p < 0.001$) is shown in Fig. 2. However, there was a statistically significant negative correlation between copeptin level with eGFR ($r = -0.502$, $P < 0.001$) is shown in Fig. 3.

ROC curve analysis was performed to compare the cut off value of different parameters implicated in diabetic nephropathy (Fig. 4) showed that the area under the ROC curve of ACR was (0.667), the best cut off value of ACR was (57.69) which denoted sensitivity (82.3%) and specificity (66.7%) with P value ($p = 0.05$). As regard to eGFR, the area under the ROC curve of eGFR was (0.333), the best cut off of eGFR was (45.5) which denoted sensitivity (73.2%) and specificity (53.2%) with P value ($p = 0.077$).

As regard to copeptin, the area under the ROC curve of copeptin was (0.756), the best cut off of copeptin was (3.88) which denoted sensitivity (93.3%) and specificity (71.1%) with P value ($p = 0.002$).The area under the ROC curve (AUC) of copeptin for detecting diabetic nephropathy was significantly larger than that of albumin/ creatinine ratio and estimated glomerular filteration rate proving that copeptin is an excellent predictive biomarker and very sensitive parameter for diabetic nephropathy.

The multivariate logistic regression analysis was performed to test for independent predictors of diabetic nephropathy. The model included the important parameters implicated in the pathogenesis of renal impairment in type 2 diabetic patients. Copeptin, UACR, eGFR and DM duration. The logistic regression coefficient of copeptin ($\beta = 0.693$, $p < 0.001$) UACR ($\beta = 0.261$, $p = 0.041$), eGFR ($\beta = -0.123$, $p = 0.065$), DM duration ($\beta = 0.916$, $p = 0.273$). This analysis demonstrated that copeptin is an independent predictor for diabetic nephropathy in type 2 diabetic patients was shown in Table 2.

Discussion

It is well documented that circulating levels of vasopressin (anti-diuretic hormone) are elevated in type 1 or type 2 diabetic patients and in animal models with spontaneous or streptozotocin- induced DM [4]. The cause of increased vasopressin in DM is not fully elucidated, but it could result from a relative contraction of extracellular volume induced by glycosuria, and/or from an increased sensitivity of hypothalamic osmoreceptors to the plasma osmolarity [5]. From an adaptive perspective, high levels of vasopressin may be beneficial in the short term by limiting the water loss in urine induced by glycosuria. However, in the long term, persistently high levels of vasopressin might be deleterious to renal function [6].

The current study was conducted to assess the clinical significance of plasma copeptin level in type 2 diabetic patients with and without nephropathy and to evaluate its relation to various clinical and laboratory parameters.

Table 1 Clinical and laboratory parameters of the studied groups

	Group I (Control) [*N*= 15]	Group II DM with (Normo) [*N*= 15]	Group III DM with (Micro) [*N*= 15]	Group IV DM with (Macro) [*N*= 15]	Test of Significance
Sex (F/M)	5/10	5/10	7/8	6/9	*P* = 0.126
Age (years)	56.27 ± 6.22	54.87 ± 5.74	54.20 ± 6.86	58.13 ± 6.06	*P* = 0.330
BMI (Kg/m^2)	28.73 ± 4.20	30.67 ± 4.97	31.33 ± 3.31	32.53 ± 4.14	*P* = 0.104
SBP (mmHg)	124.67 ± 11.87	134.00 ± 19.19	135.33 ± 14.07	141.33 ± 21.99	*P* = 0.078
DBP (mmHg)	78.67 ±10.60	82.00 ± 14.28	85.33 ± 14.07	88.67 ± 13.55	*P* = 0.201
Duration of DM (years)	……..	7.73 ± 4.44	9.40 ± 4.37	13.40 ± 4.45	***P* < 0.001***
BUN (mg/dl)	14.53 ± 2.84	15.91 ± 2.96	41.85 ± 2.39	62.91 ± 4.91	***P* < 0.001***
Serum creatinine (mg/dl)	0.97 ± 0.21	1.38 ± 0.18	1.72 ± 0.16	2.85 ± 0.36	***P* < 0.001***
eGFR (ml/min/1.73 m^2)	92.18 ± 2.13	90.52 ± 8.22	78.23 ± 4.81	58.19 ± 6.69	***P* < 0.001***
UACR(mg/g cr)	23.49 ± 3.82	25.82 ± 3.45	184.66 ± 75.10	332.80± 12.77	***P* < 0.001***
Fasting blood glucose level(mg/dl)	99.73 ± 8.89	122.68 ± 26.25	138.74 ± 25.14	176.50 ± 27.75	***P* < 0.001***
2-hpostprandial glucose level (mg/dl)	130.07± 18.39	181.50 ± 38.17	220.08 ±45.19	264.50 ± 65.17	***P* < 0.001***
HbA1C (%)	5.48 ± 0.719	6.44 ± 0.93	8.45 ± 0.38	9.57 ± 0.27	***P* < 0.001***
Triglycerides(mg/dl)	138.80 ± 35.83	146.73 ± 45.61	171.47 ± 44.18	197.43 ± 42.88	***P* = 0.016***
Total cholesterol (mg/dl)	136.13 ± 12.14	171.13 ± 38.93	213.07 ± 56.09	222.73 ± 59.83	***P* = 0.024***
HDL-C (mg/dl)	58.80 ± 10.56	51.87 ± 12.57	43.73 ± 11.24	39 .27 ± 9.60	***P* < 0.001***
LDL-C (mg/dl)	103.07 ±19.41	112.87 ± 31.58	129.53 ± 38.38	136.07 ± 35.25	***P* = 0.005***
Copeptin (pmol/L)	2.09 ± 0.50	2.92 ± 0.71	4.11 ± 0.83	4.98 ± 0.72	***P* < 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, *HbA1C* Glycated haemoglobin, *eGFR* Estimated Glomerular filtration rate, *U* Urinary, *ACR* albumin-to-creatinine ratio, *HDL-C* High-density lipoprotein-cholesterol, *LDL-C* Low density lipoprotein-cholesterol

In the current study, the mean plasma copeptin level was statistically significantly higher in the normoalbuminuric group as compared to the control group. Also, it was significantly higher in patients with microalbuminuria as compared to the control and normoalbuminuric groups. Furthermore, the mean plasma copeptin level was significantly higher in the macroalbuminuric group as compared to the control, normoalbuminuric and microalbuminuric groups. Plasma copeptin level was positively correlated with

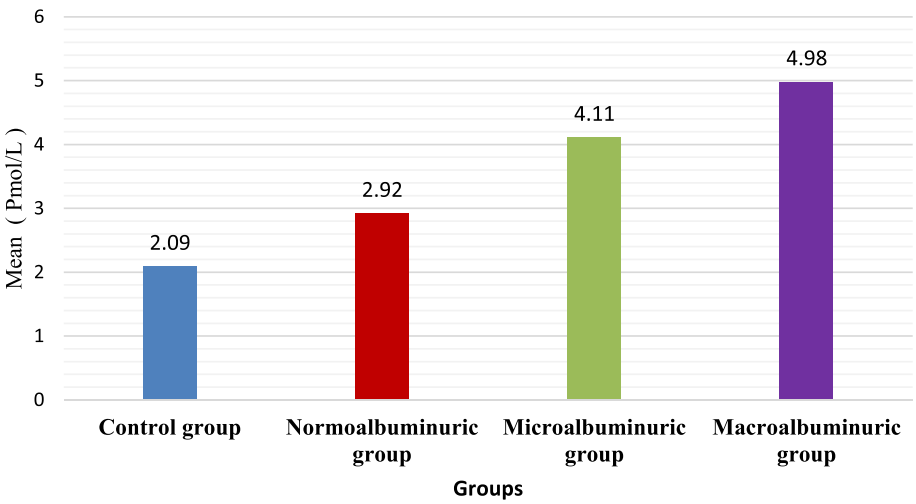

Fig. 1 Copeptin in the studied groups. The mean plasma copeptin level was statistically significantly higher in the normo group as compared to the control group, it was statistically significantly higher in micro group as compared to the control and normo groups. Also, it was statistically significantly higher in macro group as compared to the control, normo and micro groups. Abbreviations: pmol/L; Picomole per litre

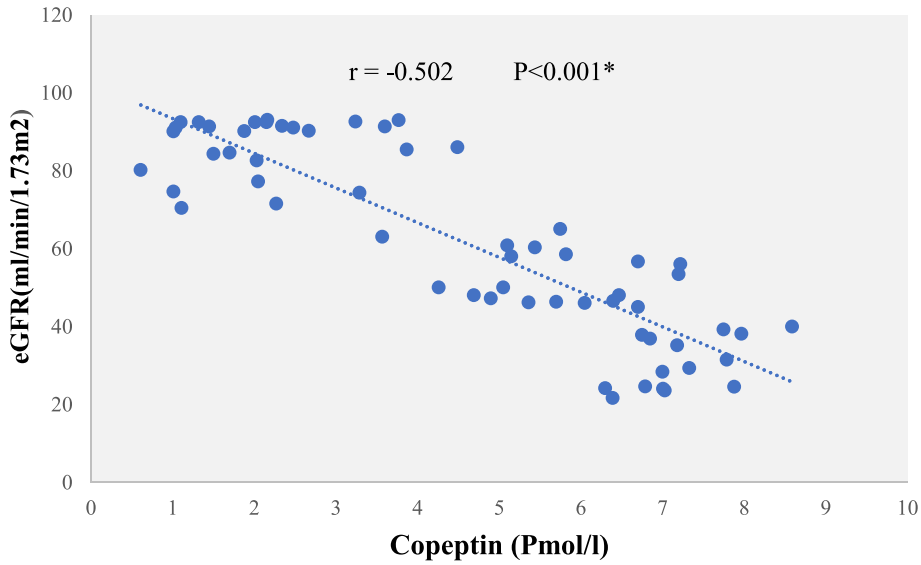

Fig. 2 Correlation between copeptin level and eGFR in type 2 diabetic patients ($n=45$). In diabetic patients, there was a statistically significant negative correlation between copeptin level with eGFR. Abbreviations: eGFR; Estimated Glomerular filtration rate, r: Pearson's correlation coefficient, *: Statistically significant ($p \leq 0.05$)

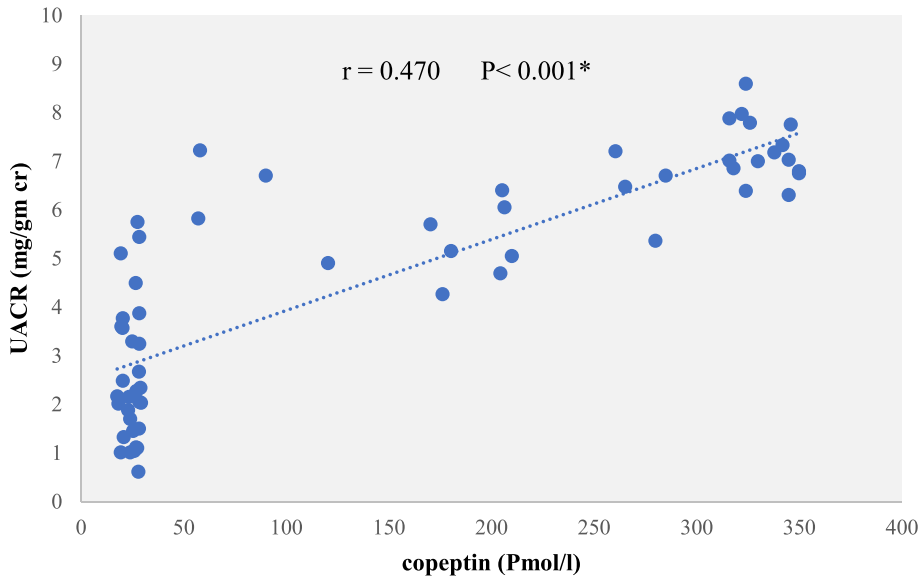

Fig. 3 Correlation between copeptin level and UACR in type 2 diabetic patients ($n=45$). Figure shows a statistically significant positive correlation between copeptin level with urinary albumin creatinine ratio. Abbreviations: U; Urinary, ACR; albumin-to-creatinine ratio, r: Pearson's correlation coefficient, *: Statistically significant ($p \leq 0.05$)

glycosylated hemoglobin, urinary albumin creatinine ratio and serum creatinine but negativey correlated with eGFR. In the current study, the diagnostic value of plasma copeptin in identifying DN was demonstrated by using the ROC curve analysis. The best cut off point of plasma copeptin was 3.88 pmol/L with 93.3% sensitivity and 71.1% specificity.

These findings are supported by Bjornstad P et al. (2017), [21] reported that copeptin was significantly higher in patients with stages 2 to 5 of CKD in comparison with stage 1 CKD patients. In addition, plasma copeptin is significantly higher in type 1 diabetic patients with albuminuria compared with normoalbuminuric group.

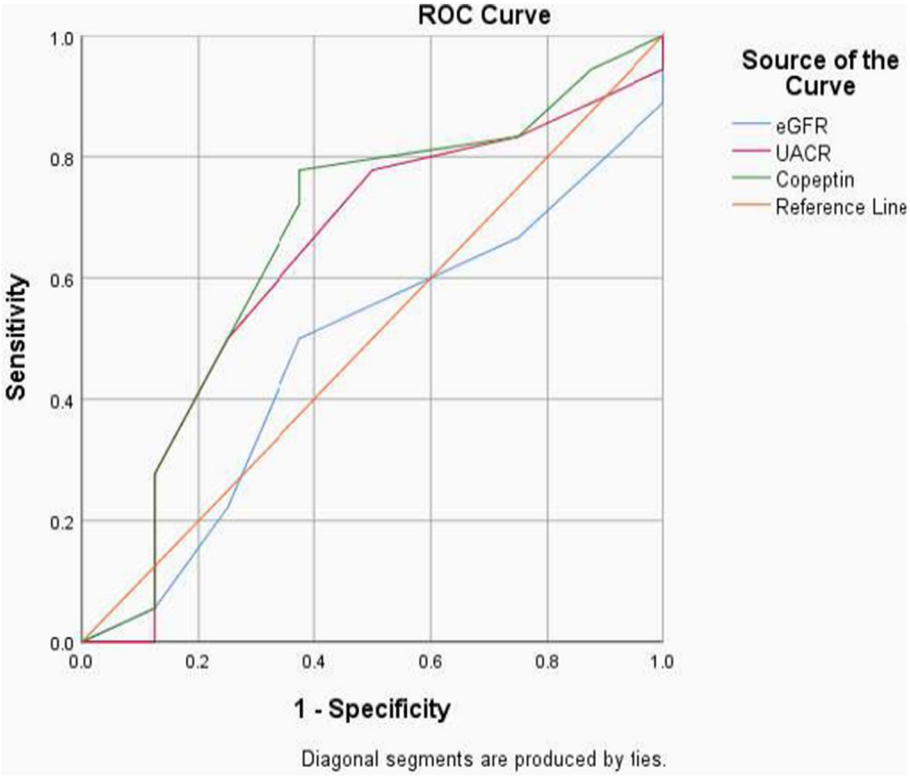

Fig. 4 ROC curve analysis of eGFR and UACR and copeptin implicated in the pathogenesis of diabetic nephropathy. Figure shows that copeptin is an excellent predictive biomarker and very sensitive parameter for diabetic nephropathy. Abbreviations: eGFR; Estimated Glomerular filtration rate, U; Urinary, ACR; albumin-to-creatinine ratio

Table 2 Multivariate regression analysis of predictors of nephropathy among type 2 diabetic patients

Parameters	β	S.E	Exp (B)	95% C.I. for EXP(B)		*P* value
				Lower limit	Upper limit	
Copeptin (Pmol/L)	0.693	0.225	0.320	1.258	2.640	< 0.001*
UACR (mg /g Cr)	0.261	0.041	1.337	0.825	0.994	0.041*
eGFR (ml/min/1.73m^2)	-0.123	0.046	0.847	0.724	0.908	0.065
DM duration (years)	0.916	0.037	1.199	0.499	0.671	0.273

eGFR Estimated Glomerular filtration rate, *U* Urinary, *ACR* albumin-to-creatinine ratio, *DM* diabetes mellitus, *β (Beta)* Standard coefficient

* Statistically significant ($p \leq 0.05$), SE; Standard Error

On the other hand, Meijer et al. (2009) [22] reported that copeptin levels are associated with an accelerated decline of kidney function. They found an association of copeptin at baseline with changes in eGFR through a multivariante regression analysis and during follow-up, this association remained significant after adjustment for age, gender, baseline eGFR, and known risk factors for renal function decline.

Conversely, copeptin level was found to be non-significantly raised in the diabetic nephropathy patients (230.72 ± 226.75 pg/mL) and then in patients with DM without nephropathy (161.71 ± 38.75 pg/mL) as compared with the healthy control group (139.72 ± 112.34 pg/mL) [23]. The difference could be explained due to small sample size among the cases included in this study. This also could be explained due to differences in the degree of disease severity.

Within the same context, Villela-Torres et al. (2018) [24], showed that plasma copeptin levels inversely correlated with eGFR, sodium, albumin, and Hb; and positively with plasma osmolality, serum glucose, years of T2DM diagnosis, uric acid and mean blood pressure.

Also, microalbuminuria correlated with uric acid levels.

Similar to our results, Pikkemaat et al. (2015) [10], and Velho et al. (2016) [25] presented a positive association of plasma copeptin with markers of kidney function and with kidney function decline in populations with CKD or at high risk of CKD, such as people with DM. However, only limited prospective data are available on the association of plasma copeptin with the risk of new onset CKD in the general population as decalared by Roussel et al. (2015) [26], and Tasevska et al. (2016) [7].

It is worthnoting that vasopressin is associated with cardio-renal complications in T2DM. A large body of data supports a direct role for vasopressin, through the activation of V2 receptors, in the development and progression of CKD, including DKD. Impaired kidney function may aggravate other cardiovascular risk factors such as hypertension, oxidative stress, insulin resistance, dyslipidemia, body fat distribution, inflammation, and arterial calcification. Thus, the association of copeptin with CVD could be accounted for, at least in part, by the deleterious effects of vasopressin on the kidney [11].

Plasma copeptin could possibly help to target patients with high risk of DKD and CVD development and progression. Increased plasma osmolality is the main stimulus for vasopressin and copeptin secretion, which are thus strongly dependent on the hydration status. It remains to be established if an effective reduction of vasopressin secretion or action, achieved by increased water intake or by treatment with vasopressin receptor antagonists (vaptans), could improve the cardiometabolic and kidney risks in people with T2DM [11].

Experimental evidence strongly supports a causal role of vasopressin in aggravation of diabetic CKD through V2-receptor activation. Besides well-known antidiuretic effects at the collecting duct level, a V2-receptor agonist was shown to induce glomerular hyperfiltration and to increase UAE in normal rats. The mechanisms of these deleterious effects of vasopressin are not clear. They may involve changes in the composition of the tubular fluid at the macula densa that influence tubuloglomerular feedback control of GFR, as well as an increase in intraglomerular pressure subsequent to afferent arteriole vasodilatation. The latter hemodynamic effect is supposed to be one of the main drivers in the decline of renal function in diabetic CKD [8]. However, our study cannot preclude or confirm any of these mechanisms because of its observational nature. Further experimental studies are needed in that regard.

Notably, a significant advantage of vasopressin blockers is their dual site of action (glomerular and tubular), which is mechanistically attractive in DKD because these patients are at risk for both glomerular and tubulointerstitial injury. V2 antagonism has been shown to reduce albuminuria and prevent hyperfiltration in an animal model of DKD. However, there are no published human data available on the effects of vasopressin receptor antagonism on mechanisms of disease or clinical DKD progression in the setting of DM [27].

Conclusion

From this work, it could be concluded that:

An increased plasma copeptin level is considered as a good predictor for deterioration of renal function in diabetic patients, suggesting that copeptin can be used to identify diabetics at risk for diabetic kidney disease development. Clearly, further well-designed prospective studies are required to prove this hypothesis.

Abbreviations

ACR	Albumin creatinine ratio
ADH	Antidiuretic hormone
AUC	Area Under Curve
β (Beta)	Standard coefficient
BMI	Body mass index
CVDs	Cardiovascular diseases
DBP	Diastolic blood pressure
DN	Diabetic nephropathy
eGFR	Estimated Glomerular filtration rate
HbAlc	Glycated haemoglobin
HF	Heart failure
ROC	Receiver operating characteristic
SBP	Systolic blood pressure

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Authors' contributions

All authors had the same contribution in this work. The author(s) read and approved the final manuscript.

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Availability of data and materials

The data of this study are available upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved in October 2019 by the research ethical committee of faculty of medicine, Tanta University. Institutional Review Board (IRB) for human studies (Approval code is 33401). Our study conforms to provisions of the Declaration of Helsinki. Informed written consent to participate in this study was provided by all participants before the starting of data collection.

Consent for publication

Participants provided consent for the study findings to be published.

Competing interests

The authors declare they have no competing interests.

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References

1. Punthakee Z, Goldenberg R, Katz P (2018) Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. Can J Diabetes 42:S10–S15
2. El Boustany R (2018) Vasopressin and diabetic kidney disease. Ann Nutr Metab 72(suppl 2):17–20
3. Schrijvers BF, De Vriese AS, Flyvbjerg A (2004) From hyperglycemia to diabetic kidney disease: the role of metabolic, hemodynamic, intracellular factors and growth factors/cytokines. Endocr Rev 25:971–1010
4. Bankir L, Bardoux P, Ahloulay M (2001) Vasopressin and diabetes mellitus. Nephron 87:8–18
5. Zerbe RL, Vinicor F, Robertson GL (1985) Regulation of plasma vasopressin in insulin-dependent diabetes mellitus. Am J Physiol 249:E317–E325
6. Roussel R, Velho G, Bankir L (2017) Vasopressin and diabetic nephropathy. Curr Opin Nephrol Hypertens 26:311–318
7. Tasevska I, Enhörning S, Christensson A et al (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
8. Velho G, Bouby N, Hadjadj S et al (2013) Plasma copeptin and renal outcomes in patients with type 2 diabetes and albuminuria. Diabetes Care 36:3639–3645
9. Boertien WE, Riphagen IJ, Drion I et al (2013) Copeptin, a surrogate marker for arginine vasopressin, is associated with declining glomerular filtration in patients with diabetes mellitus (ZODIAC-33). Diabetologia 56:1680–1688
10 Pikkemaat M, Melander O, Boström KB (2015) Association between copeptin and declining glomerular filtration rate in people with newly diagnosed diabetes. The Skaraborg Diabetes Register. J Diabetes Complications 29:1062–5
11. Velho G, Ragot S, El Boustany R et al (2018) Plasma copeptin, kidney disease, and risk for cardiovascular morbidity and mortality in two cohorts of type 2 diabetes. Cardiovasc Diabetol 17:1–10
12. Parizadeh SM, Ghandehari M, Parizadeh MR et al (2018) The diagnostic and prognostic value of copeptin in cardiovascular disease, current status, and prospective. J Cell Biochem 119:7913–7923
13. Zhu W, Tilley DG, Myers VD et al (2014) Increased vasopressin 1A receptor expression in failing human hearts. J Am Coll Cardiol 63:375–376
14. Lanfear DE, Sabbah HN, Goldsmith SR et al (2013) Association of arginine vasopressin levels with outcomes and the effect of V2 blockade in patients hospitalized for heart failure with reduced ejection fraction: Insights from the Everest trial. Circ HF 6:47–52
15. Wasilewski MA, Myers VD, Recchia FA et al (2016) Arginine vasopressin receptor signaling and functional outcomes in heart failure. Cell Signal 28:224
16. Enhörning S, Melander O (2018) The vasopressin system in the risk of diabetes and cardiorenal disease, and hydration as a potential lifestyle intervention. Ann Nutr Metab 72(Suppl 2):21–27
17. El Boustany R, Taveau C, Chollet C et al (2017) Antagonism of vasopressin V2 receptor improves albuminuria at the early stage of diabetic nephropathy in a mouse model of type 2 diabetes. J Diabetes Complications 31:929–932
18. Bankir L, Bouby N, Ritz E (2013) Vasopressin: a novel target for the prevention and retardation of kidney disease? Nat Rev Nephrol 9:223–239
19. Levey AS, Coresh J, Greene T et al (2006) Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 145:247–254
20. Morgenthaler NG, Struck J, Alonso C et al (2006) Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. Clin Chem 52:112–119
21. Bjornstad P, Johnson RJ, Snell-Bergeon JK et al (2017) Albuminuria is associated with greater copeptin concentrations in men with type 1 diabetes: a brief report from the T1D exchange Biobank. J Diabetes Complications 31:387–389
22. Meijer E, Bakker SJ, de Jong PE et al (2009) Copeptin, a surrogate marker of vasopressin, is associated with accelerated renal function decline in renal transplant recipients. Transplantation 88:561–567
23. 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 51:548–555
24. Villela-Torres ML, Higareda-Mendoza AE, Gómez-García A et al (2018) Copeptin plasma levels are associated with decline of renal function in patients with type 2 diabetes mellitus. Arch Med Res 49:36–43
25. Velho G, El Boustany R, Lefèvre G et al (2016) Plasma copeptin, kidney outcomes, ischemic heart disease, and all-cause mortality in people with long-standing type 1 diabetes. Diabetes Care 39:2288–2295
26. Roussel R, Matallah N, Bouby N et al (2015) Plasma copeptin and decline in renal function in a cohort from the community: the prospective DESIR study. Am J Nephrol 42:107–114
27. Lytvyn Y, Bjornstad P, Raalte D et al (2020) The new biology of diabetic kidney disease—mechanisms and therapeutic implications. Endocr Rev 41:202–231

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