

Copeptin: Promising Biomarker for Nephropathy in Type II Diabetes

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ABSTRACT

Kidney injury is a dangerous diabetic microvascular complication responsible for the mortality of diabetics, which would require biomarkers for early detection of diabetic nephropathy. Copeptin, the C-terminal portion of vasopressin prohormone, is rapidly released in severe endogenous stress. So, the current work was carried out to evaluate and estimate copeptin as a marker for diabetic nephropathy. This cross-sectional work was conducted on 60 female and male type II diabetic cases. Diabetic cases were divided as normoalbuminuric (urinary albumin was <30 mg/24 h) without nephropathy and macroalbuminuric (urinary albumin was >300 mg/24 h) with nephropathy. The Control group was designated from fifteen matched healthy subjects. Controls and patients were evaluated for fasting blood glucose, glycosylated hemoglobin (HbA1c), urinary albumin, serum creatinine, and serum copeptin. Copeptin concentrations were significantly increased in type II diabetics with macroalbuminuria comparing to healthy controls and diabetics with normoalbuminuria. Serum copeptin concentrations were correlated positively with gold standard urinary albumin, serum creatinine, and HbA1c. Higher serum copeptin concentration in type II diabetics particularly in diabetics with nephropathy and its correlation with urinary albumin and HbA1c reflect the potential role of copeptin as a predictor of diabetes mellitus and development of diabetic nephropathy among type II diabetics considering other risk factors.

Keywords: Diabetes, Macroalbuminuria, Copeptin, Creatinine, Nephropathy

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease with serious health complications. Patients with DM are presented with hyperglycemia due to insulin release lack and/or

resistance to insulin action. The metabolic complications include carbohydrate, fat, and protein metabolism. Diabetes mellitus disturbs all ages with a higher incidence in adults. Kidney injury is a serious diabetic microvascular disorder that may cause mortality of diabetics.¹ Blood glucose elevation develops chronic renal disease and renal injury via formation of active protein kinase C, augmented generation of diacylglycerol, and synthesis of advanced glycosylation end products. Also, hyperglycemia is accountable for hemodynamic changes like stress, glomerular hyperfiltration,

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and microalbuminuria.² The changes donate to irregular activation of resident renal cells which increase glucose transporter-1 and upregulate intracellular transport and uptake of glucose as results of transforming growth factor beta-1 (TGFβ-1) generation. TGFβ-1 results in extracellular matrix protein, such as collagen types I, IV, V, and VI, fibronectin, and laminin, deposition at the glomeruli, producing mesangial expansion and thickening of glomerular basement membrane.³

Copeptin, the COOH-terminal stable part of vasopressin precursor, is a simply quantifiable substitute biomarker of vasopressin.⁴ Researches on healthy subjects have reported that plasma vasopressin and copeptin levels strongly correlate over a different osmolalities range.⁵ Christ-Crain, 2019 found that vasopressin level is increased in diabetics and selective vasopressin V2-receptor antagonist treatment abolished the albuminuria elevation in diabetics.¹ Early diabetic nephropathy diagnosis is crucial and supports to decrease diabetic death. The current research designed to inspect the clinical implication of serum copeptin in patients of type II diabetes with and without nephropathy and to assess the relation of copeptin with other laboratory and clinical markers as a risk parameter for diabetic nephropathy prediction and also to examine serum copeptin association with elevating serum creatinine concentration risk in patients with DM type II and normoalbuminuria or macroalbuminuria from our study.

2. PATIENTS AND METHODS

2.1. Patients

Our study was conducted on type II diabetics presented to Diabetes and Endocrinology Unit, Internal Medicine Department, Tanta University Hospital, Egypt. The work involved 60 type II diabetic cases. The diagnosis of diabetes was considered as fasting blood glucose ≥ 126 mg/dL according to WHO.⁶ The exclusion criteria include patients with diabetes type I, type II diabetics with cancer, end-stage renal failure, liver disease or heart disease. The diagnosis of nephropathy was evaluated according to measuring albuminuria >300 mg/24 h in at least two of three successive assessments on 24-h sterile collected samples of urine. Urinary microalbumin was used to classify patients to type II diabetics without nephropathy (having normoalbuminuria <30 mg/24 h) and type II diabetics with nephropathy (having albuminuria >300 mg/24 h).⁷

The Control group consisted of fifteen healthy age-matched subjects. The history was engaged for participants with a precise recording of diabetes duration, urinary symptoms, therapeutic history and history of any other associated disorder. Table (1) illustrated the studied groups distribution regarding age, body mass index (BMI) and duration of diabetes.

2.2. Ethical statement

Informed consent was requested and collected from controls and patients. The study was approved by the Ethical Committee, Faculty of Medicine, Tanta University, Egypt.

2.3. Laboratory investigations

Early morning fasting blood samples were obtained. The collected blood was obtained by standard venipuncture in VACUETTE® blood collection tubes. Samples of serum were prepared by standing the samples at room temperature to clot for 5–10 minutes and were centrifuged at $1,000\times g$ for 10 minutes and were kept at -20°C till the time of biochemical analysis.⁸ Also, 24-hour urine samples were collected. Blood glucose, serum creatinine, and 24-hour urine albumin were assessed by commercial kits purchased from Biodiagnostic Co., Egypt, using Shimadzu® (Japan) Spectrophotometer. Hemoglobin A1c was determined for glycemic control by measuring the HbA1c% according to the method described by Hanas et al.,⁹ using a commercial kit obtained from Biosystems (Barcelona, Spain). Serum copeptin levels were assayed using human copeptin ELISA kit, obtained from Shanghai Sunred Biological Technology Co., China, using Awareness Technology® (USA) ELISA reader. Serum copeptin concentration was expressed as ng/mL.

2.4. Statistical analysis

Data were processed using SPSS statistical package version 22.0, IBM Corporation Software Group, USA. Quantitative results were examined for normality using one sample Shapiro-Wilk test. Normally distributed data as mean \pm SD. Analysis of variance (ANOVA) was used to compare normally distributed quantitative data. For non-normally distributed data; Mann-Whitney U test was performed to compare differences between groups. Spearman correlation coefficient was used to assess the strength and direction of association that exists between variables. All P values were two-tailed and $P<0.05$ was considered statistically significant. Receiver operating characteristic (ROC) curves were operated to evaluate the accuracy of copeptin and other biomarkers to diagnose diabetic nephropathy. The area under the receiver operating characteristic curve (AUC) is a summary measure over criteria and cut-point points.

3. RESULTS

3.1. Main findings

Table 1 displays the patient baseline data which include; age, body mass index (BMI), and duration of diabetes. The study involved 15 healthy volunteers and 60 type II diabetic patients. Thirty patients (50%) were diagnosed with diabetic nephropathy. Diabetic groups without and with nephropathy were age-matched in age compared to healthy control group. BMI exhibited a significant increase in both diabetic patient groups with and without nephropathy compared to control group ($P<0.001$), also, BMI showed a significant increase in diabetic group with nephropathy ($P<0.05$) compared to diabetic group without nephropathy. Moreover, the duration

of diabetes was significantly ($P < 0.05$) increased in diabetic patients with nephropathy compared to diabetic patient without nephropathy (**Table 1**).

Table 1: Baseline characteristics of healthy controls and diabetes mellitus groups

Characteristics	Control	DM without nephropathy	DM with nephropathy
N	15	30	30
Age (years)	56.20±1.78	56.63 ± 2.23	57.10 ± 2.94
Body mass index (BMI) (Kg/m ²)	19.17 ± 2.31	24.29 ^{***} ± 1.88	25.57 ^{***b*} ± 2.10
Duration of diabetes (years)	---	6.30 ± 1.68	9.09 ^{b*} ± 2.15

Data are presented as mean ± SD

Body mass index (BMI) was calculated as [mass (kg)]/[height (m)]²

***: significant $P < 0.001$, *: Significant $P < 0.05$

DM: Diabetes mellitus, N: number of subjects in each group

a: Significant versus the control group

b: Significant versus type II DM without nephropathy group

P values were compared by of analysis of variance (ANOVA) test

3.2. Relation between serum copeptin and blood glucose

We reported a significant increase in serum levels of copeptin in diabetic patients without nephropathy group compared to normal controls [7.10 (IQR, 6.69–7.20) ng/mL] vs. [5.99 (IQR, 3.99–6.81) ng/mL; $P < 0.001$; (**Table 2**) and (**Figure 1d**)]. The ROC curve analysis of serum copeptin levels (**Figure 2a**) showed a sensitivity of 90.0% and a specificity of 66.7%, with the area under the curve at 0.841 (95% CI, 0.708–0.974). As illustrated in (**Table 3**) and (**Figure 2**); measurement of serum copeptin levels exhibited a significantly higher discriminatory ability for diagnosis of hyperglycemia as compared with urinary microalbumin (AUC, 0.828; 95% CI, 0.703–0.953; $P < 0.001$, **Figure 2b**), HbA1c% (AUC, 0.803; 95% CI, 0.672–0.935; $P < 0.01$, (**Figure 2c**)), and FBG (AUC, 0.872; 95% CI, 0.773–0.971; $P < 0.001$).

Furthermore, in the present study, we found a significant positive correlation (non-parametric Spearman correlation test) between serum levels of copeptin and each of fasting blood glucose, HbA1c%, urinary microalbumin, and creatinine ($P < 0.001$ for each) which confirmed ROC-AUC results and indicated that an increased risk of DM was associated with increased serum levels of copeptin.

3.3. Serum copeptin for diagnosis of DM nephropathy

(**Table 2**) illustrated a significant increase in fasting blood glucose, HbA1c%, and urinary microalbumin among diabetic patients with and without nephropathy compared to control group, while a non-significant change in creatinine was observed in diabetic patients without nephropathy compared to normal controls. (**Figure 1**) shows the statistical differences between control group and diabetic patient groups for fasting

blood glucose, HbA1c%, urinary microalbumin, creatinine, and copeptin, which was analysed using Mann–Whitney test. As presented in (**Table 2**) and (**Figure 1d**) serum levels of copeptin in diabetic patients with nephropathy group shows a significant increase [10.06 (IQR, 9.94–10.63) ng/mL] compared to diabetic patients without nephropathy and control groups [7.10 (IQR, (6.69–7.20) and 5.99 (IQR, 3.99–6.81) ng/mL, respectively, $P < 0.001$].

Table 2: Biomarkers of healthy controls and diabetes mellitus groups

Biomarkers	Control	DM without nephropathy	DM with nephropathy
FBG (mg/dL)	104.20 (99.96-110.00)	116.52 ^a (110.1-151.02)	148.50 ^a (115.30-203.98)
Hb A1c%	5.16 (4.23-6.48)	7.11 ^a (5.39-7.64)	8.11 ^{ab} (8.40-8.69)
Urinary Microalbumin (mg/ 24 hr)	7.25 (5.36-8.69)	9.20 ^a (8.76-10.99)	235.69 ^{ab} (89.70-319.01)
Creatinine (mg/dL)	0.95 (0.63-0.98)	0.89 (0.70-1.10)	2.8 ^{ab} (2.61-3.14)
Copeptin (ng/mL)	5.99 (3.99-6.81)	7.10 ^a (6.69-7.20)	10.06 ^{ab} (9.94-10.63)

Data are presented as median (IQR), $P < 0.05$ was set as significant.

Statistical difference between groups was according to Mann–Whitney test.

FBG: fasting blood glucose, DM: diabetes mellitus

a: Significant versus the control group

b: Significant versus DM without nephropathy group

Table 3: Performance of copeptin, urinary microalbumin, and HbA1c compared to FBG as predictors of DM risk

Biomarker	AUC (95% CI)	P-value	Sensitivity	Specificity	Cut off point
Copeptin (ng/mL)	0.841 (0.708-0.974)	0.000	90.0%	66.7%	6.11
Urinary micro-albumin (mg/ 24 h)	0.828 (0.703-0.953)	0.000	80.0%	66.7%	8.17
HbA1c%	0.803 (0.672-0.935)	0.001	73.3%	73.3%	6.21
FBG (mg/dL)	0.872 (0.773-0.971)	0.000	---	---	---

Healthy controls and diabetic patients without nephropathy group are included to perform receiver operating curve (ROC) analysis. AUC: Area under curve, CI: Confidence interval, FBG: Fasting blood glucose

3.4. Diagnostic performance of copeptin for diabetic nephropathy detection

The ROC-AUC analysis for copeptin to predict diabetic nephropathy at the cut-off point of 6.40 ng/mL shows a sensitivity of 90.0% and a specificity of 73.3%, with the area under the curve (AUC) at 0.921 (95% CI, 0.851–0.991) (**Figure 3a**) which was almost comparable to urinary microalbumin (AUC, 0.914, 95% CI, 0.847–0.980) (**Figure 3b**) and higher than that of HbA1c (AUC, 0.899, 95% CI, 0.826–0.971) (**Figure 3c**) and serum creatinine (AUC, 0.760, 95% CI, 0.649–0.871) (**Figure 3d**). The ROC-AUC analysis,

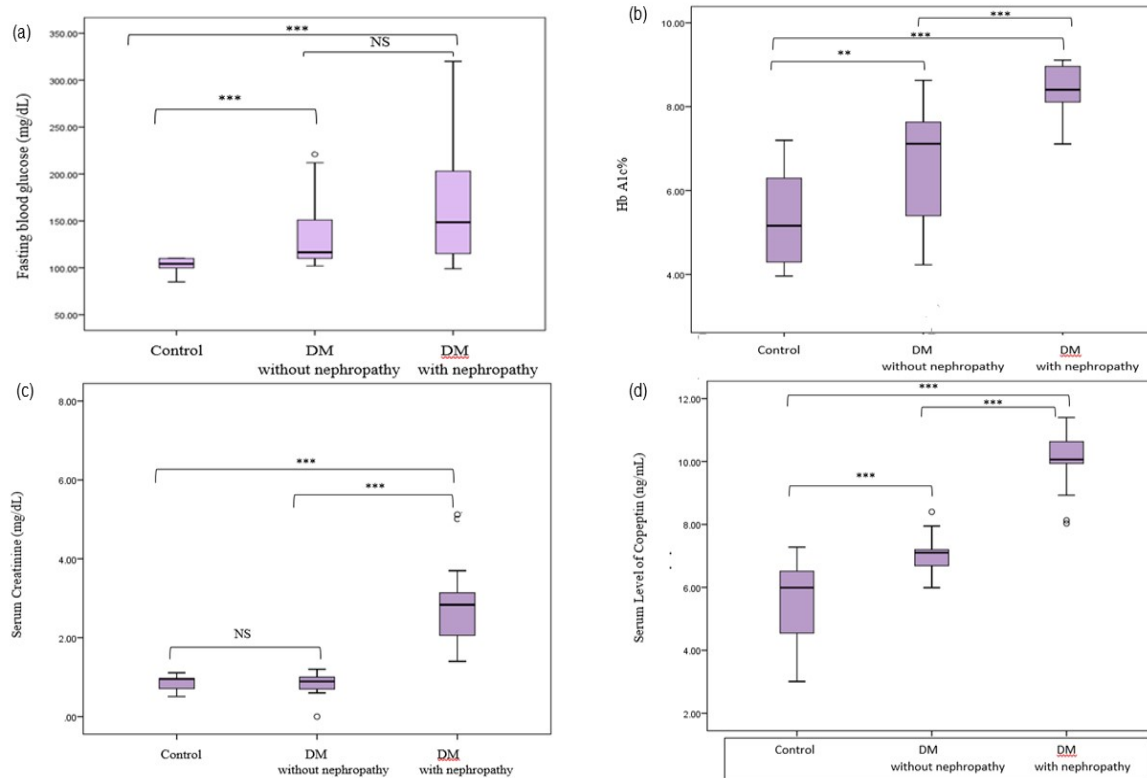


Figure 1: Levels of different biomarkers in different groups. (a) serum levels of fasting blood glucose, (b) HbA1c%, (c) serum levels of creatinine, (d) serum levels of copeptin. Mann–Whitney U test. All data are medians and interquartile ranges (IQR). DM: Diabetes mellitus. NS: non-significant;

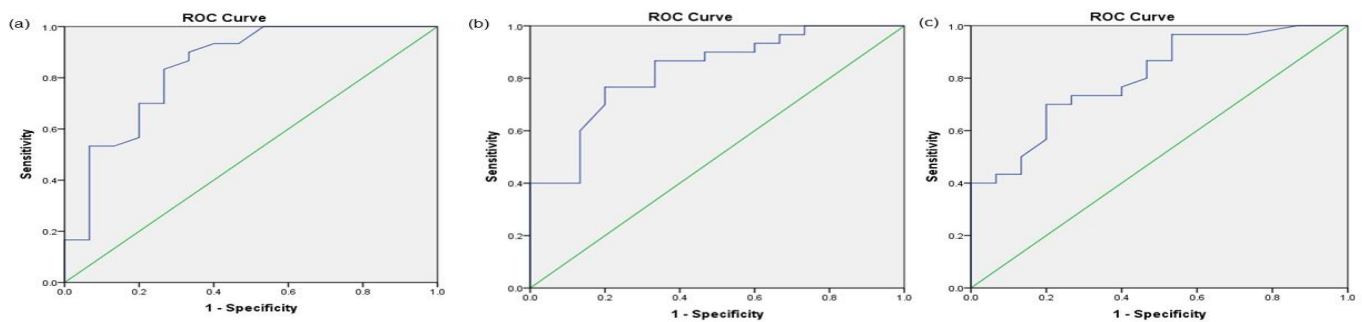


Figure 2: Comparison of diagnostic values of copeptin, urinary microalbumin, and HbA1c to discriminate Type II DM (without nephropathy) from healthy controls. (a) ROC curves of copeptin for differential diagnosis of Type II DM (without nephropathy) (n = 30) from healthy controls (n = 15). (b) ROC curves of urinary microalbumin for differential diagnosis of Type II DM (without nephropathy) (n = 30) from healthy controls (n = 15). (c) ROC curves of HbA1c for differential diagnosis of Type II DM (without nephropathy) (n = 30) from healthy controls (n = 15). DM: diabetes mellitus, AUC: area under curve, ROC: Receiver operating characteristic.

sensitivity, and specificity of measured parameters were summarized in (Table 4).

Moreover, we found that the serum copeptin improved the diagnostic performance of HbA1c as showed in the combined ROC curve model (Figure 4) (AUC of HbA1c in the combined model: 0.913, P<0.001).

3.5. Correlation of serum copeptin with the other biomarkers used for diabetic nephropathy detection

(Table 5) illustrated a significant positive correlation between serum copeptin and urinary microalbumin. Also, each of copeptin and urinary microalbumin had a significant positive correlation with fasting blood glucose, HbA1c, and creatinine. These results confirmed the ROC curve analysis of copeptin and indicated that measurement of serum copeptin could be a predictor of diabetes mellitus risk and a diagnostic for diabetic nephropathy (Figure 5). Also, measurement of serum copeptin have a better patient connivance compared to 24-h urine samples collection which needed for urinary microalbumin determination.

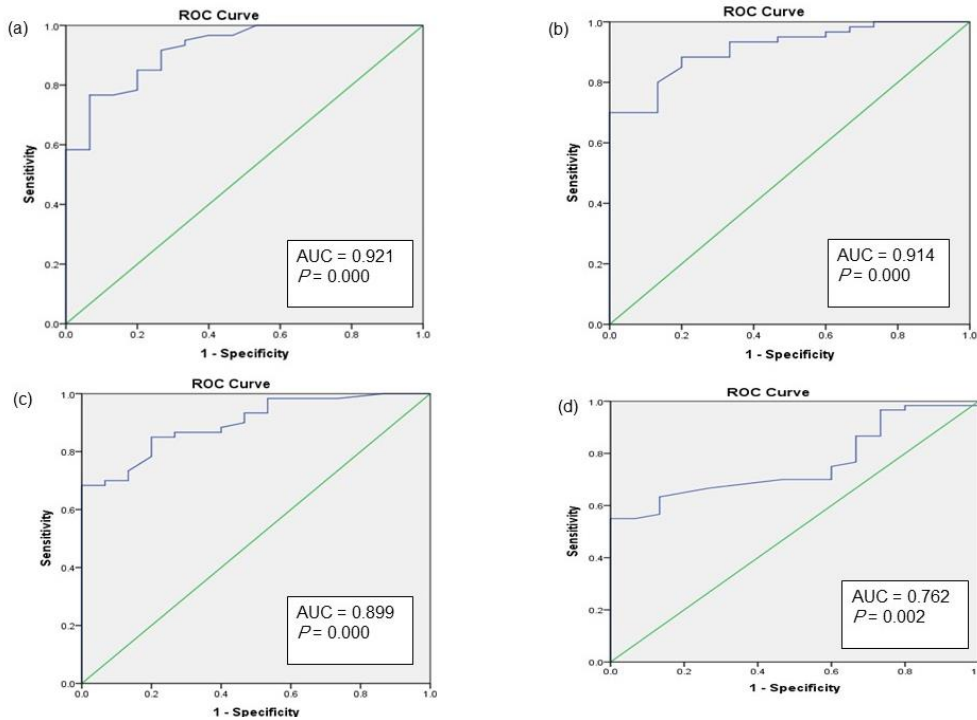


Figure 3: Performance of Copeptin, urinary microalbumin, HbA1c, and creatinine in diagnosis of Type II DM patients (with and without nephropathy). ROC curves of coceptin (a), urinary microalbumin (b), HbA1c (c), and creatinine (d), showing that coceptin had the highest ROC-AUC for diabetic nephropathy detection. AUC: Area under curve, ROC: Receiver operating characteristic.

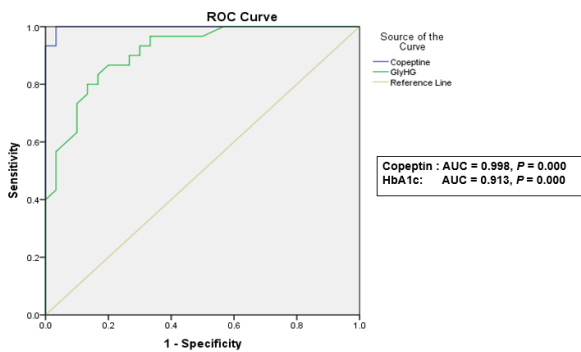


Figure 4: Combined ROC curve of coceptin and HbA1c for differential diagnosis of Type II DM complicated with nephropathy. Combined ROC curve of coceptin and HbA1c for differential diagnosis of Type II DM (with nephropathy) (n = 30) from Type II DM (without nephropathy) (n = 30). DM: diabetes mellitus, AUC: area under curve, ROC: Receiver operating characteristic.

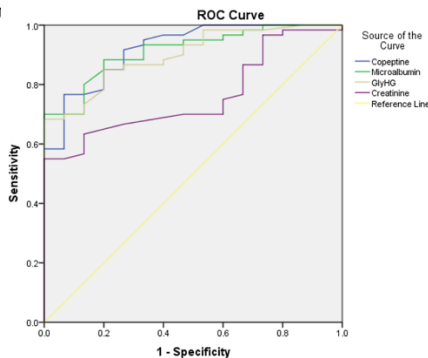


Figure 5: Combined ROC curve of coceptin, urinary microalbumin, HbA1c, and creatinine for differential diagnosis of Type II DM from healthy controls. DM: diabetes mellitus, AUC: area under curve, ROC: Receiver operating characteristic.

Table 4: Diagnostic performance of coceptin, urinary microalbumin, and HbA1c compared to creatinine in diagnosis of diabetic nephropathy

Biomarkers	AUC	P-value	Sensitivity	Specificity	Cut off point
Copeptin (ng/mL)	0.921 (0.851-0.991)	0.000	90.0%	73.3%	6.40
HbA1c%	0.899 (0.826-0.971)	0.000	86.7%	66.7%	5.94
Urinary microalbumin (mg/24 h)	0.914 (0.847-0.980)	0.000	90.0%	66.7%	8.17
Creatinine (mg/dL)	0.760 (0.649-0.871)	0.002	63.3%	86.70%	0.99

Healthy controls and diabetic patients without and with nephropathy groups are included to perform receiver operating curve (ROC) analysis. AUC: Area under curve, CI: Confidence interval.

Table 5: Correlation between measured biomarkers in different groups

Parameters	Copeptin level r values	Urinary microalbumin r values
FBG (mg/dL)	0.425*	0.433*
HbA1c%	0.712*	0.703*
Urinary Microalbumin (mg/24 hr)	0.772*	---
Creatinine (mg/dL)	0.712*	0.691*
Copeptin (ng/mL)	---	0.772*

FBG: fasting blood glucose, *: significant P<0.001. Non-parametric Spearman correlation analysis was performed

4. DISCUSSION

Diabetic nephropathy is one of the commonly occurring microvascular complications of DM and is considered the main cause of end-stage renal failure in Middle East countries.¹⁰ Protein glycosylation with advanced glycated end products (AGEs) is the main pathological source of elevated urinary albumin excretion, which resulted in hypertrophy of glomerular and renal systems. The continuous leakage of albumin and other proteins into urine in turn lead to diabetic nephropathy.¹¹

In our work, diabetic nephropathy was evident in Type II DM patients and characterized by a significant increase in serum creatinine as well as urinary microalbumin compared to DM patients without nephropathy. Our findings agreed with El-Ashmawy et al.¹¹ who reported a significant positive correlation between microalbuminuria and serum creatinine levels.

Diabetic nephropathy is associated with presence of large amount of urinary proteins, mainly albumin.¹² We reported a significant increase in microalbuminuria in diabetic patients with nephropathy, which was in line with Satchell and Tooke.¹³ Moreover, we reported a normoalbuminuric range in diabetic patients without nephropathy which was consistent with Viswanathan et al.,¹⁴ who suggested that the risk of diabetic nephropathy development starts even when urinary excretion of albumin is within the normoalbuminuric range, and the progression from normoalbuminuria into micro/macroalbuminuria occurs more frequently in type II DM patients with baseline urinary albumin > 2.5 mg/24 h.

In the present study, microalbuminuria showed a significant positive correlation with fasting blood glucose and HbA1c%. Furthermore, ROC curve analysis revealed that microalbuminuria has a greater efficacy as a biomarker of diabetic nephropathy (AUC; 0.914) compared to HbA1c% (AUC; 0.899) and serum creatinine (AUC; 0.760).¹⁵ So, the study of new diagnostic tools and markers for prediction and diagnosis of diabetic nephropathy is an urgent need.

Arginine vasopressin (AVP) has a significant role in the pathophysiology of DM and its associated complications such as diabetic nephropathy. Copeptin is an inactive analogue of AVP which secreted in an equimolar quantity to AVP and is considered one of the most reliable biomarkers of AVP as it has a relatively longer half-life and stable structure than AVP.¹⁶ Furthermore, copeptin; unlike other biomarkers such as creatinine, HbA1c, and urinary microalbumin excretion; is sensitive only to DM and its related complications.¹⁷

In this work, we reported for the first time a significant increase in serum levels of copeptin among Type II DM patients without and with nephropathy compared to healthy controls. Consistent with our findings, Bjornstad et al. (2016) reported that copeptin was strongly associated with diabetic kidney disease and coronary atherosclerosis in adults with Type I DM.¹⁸

High level of copeptin may play a critical role in the process of DM progression. Binding of AVP to vasopressin V1b receptor in the anterior hypophysis leads to release of adrenocorticotrophic hormone and increase the glucocorticoid levels in blood.¹⁹ Glucocorticoids are involved in the

regulation of inflammation, adipocyte development, and glucose homeostasis. Elevated glucocorticoid level in blood is clinically characterized by the development of diabetes, insulin resistance and visceral adiposity.²⁰

ROC curve analysis in the present study revealed that copeptin could be an excellent dependable predictor of DM risk with a sensitivity of 90.0% and specificity of 66.7% (AUC; 0.841) compared to fasting blood glucose and HbA1c (AUC; 0.872 and 0.803, respectively). These results were in line with Zhu et al.¹⁵ Moreover, copeptin shows high sensitivity and specificity (90.0% and 73.3%, respectively) (AUC; 0.921) for diagnosis of nephropathic complications of type II DM. while other biomarkers such as urinary microalbumin and HbA1c exhibited decreased diagnostic values (AUC; 0.914 and 0.899, respectively) compared to copeptin.

We also revealed that the addition of copeptin to HbA1c improved the diagnostic value of HbA1c as shown in the combined ROC-AUC curve which was consistent with the previous work.²¹

Moreover, we reported a significant positive correlation with urinary microalbumin as a gold standard biomarker of DM nephropathy.

In this study, the increased levels of serum copeptin in diabetic patients with/without nephropathy compared to controls strongly indicate the potential role of copeptin in the development of DM and progressive decline of renal functions.

5. CONCLUSIONS

The present study suggests the strong correlation of copeptin with DM development and declined renal functions in patients of Type II DM. Increased levels of copeptin in diabetic patients without nephropathy strongly indicates the potential use as an early predictor of diabetic nephropathy. Future studies are warranted to investigate the role of copeptin as early biomarker for diagnosis of diabetic nephropathy on larger sample size.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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