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**Original article**

# The Relation between Microvascular Complications of Type 2 Diabetic Patients and Plasma Copeptin Levels

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**Abstract**

**Background:** Diabetes mellitus (DM), commonest metabolic illness, is one of the major public health concerns worldwide. **Objectives:** To inspect the clinical importance of serum copeptin in patients of type 2 diabetes with and without nephropathy and to assess the relation between microvascular complication of type 2 diabetic patients and copeptin plasma levels. **Patients and Methods:** The study was conducted between November 2021 till May 2022, included 90 participants; 30 healthy age and sex matched control participants, 20 cases of DN with normoalbuminuria, 20 cases of DN with microalbuminuria, and 20 cases of DN with macroalbuminuria. Serum copeptin levels were measured by ELISA, Blood Urea Nitrogen (BUN), creatinine, Glycosylated Hemoglobin (HbA1c), and spot urinary albumin creatinine ratio (UACR) were done using spectrophotometry. **Results:** it was shown

that serum copeptin level in patients with diabetic nephropathy with macro albuminuria was significantly lower than in healthy control people. There was no significant difference in level of serum copeptin in normal or abnormal fundus examination, neurological examination. **Conclusion:** serum copeptin level in patients with diabetic nephropathy with macroalbuminuria is significantly lower than in normal healthy control. There was no significant association was found between serum copeptin level, diabetic retinopathy nor neuropathy.

## 1. Introduction

Diabetes mellitus (DM) is a disease characterized by hyperglycemia. Hyperglycemia is caused by a deficiency in insulin secretion or its biological action, or both. High blood glucose in DM has existed for a long time, resulting in chronic damage and dysfunction of various organs, mainly to eye, kidney, heart, blood vessels, and nerve. Diabetes can be associated with a variety of complications **(1).**

Diabetes mellitus (DM), commonest metabolic illness, is one of the major public health concerns worldwide **(2).**

Microvascular complications are sequels of diabetes mellitus following uncontrolled chronic hyperglycemia which includes diabetic nephropathy, neuropathy and retinopathy that are caused by pathological changes in capillaries **(3).**

The time to develop microvascular complications is much faster and common than macrovascular complication **(4).**

Diabetic nephropathy (DN) is the most common and serious microvascular complications caused by diabetes. With the increasing incidence of diabetes mellitus (DM), the morbidity of DN is increased year by year, and it has become the main cause of end-stage renal disease **(5).**

Copeptin, the COOH-terminal stable part of vasopressin precursor, is a simply quantifiable substitute biomarker of vasopressin **(6).**

Researches on healthy subjects have reported that plasma vasopressin and copeptin levels strongly correlate over a different osmolalities range **(7).**

Although, there is a strong correlation between copeptin and AVP concentrations but their relationship gets distorted in chronic kidney diseases suggesting incomplete clearance of peptide, whenever the renal function is impaired. Therefore, copeptin is preferred over AVP **(8).**

## 2. Patients And Methods

This study is a Case-Control study conducted from November 2021 to December 2022 in the Internal medicine department at Beni-Suef University Hospital.

( Approval No: FMBSUREC/05122021/Mostafa).

**Sample size**: calculation was done using an estimated effect size of 0.7. Accordingly, sample size was calculated with G*Power (3.1.9.4) software using a priori analysis for difference between two independent means (two groups) independent sample t-test

A total sample size of 90 participants (60 cases and 30 matched controls) was estimated for 90% power, α- error probability 0.05 and 10% dropout rate during follow up.

The (60) Diabetic patients were divided into three subgroups according to albuminuria: a normoalbuminuric diabetic group with 24-hr urinary albumin excretion (UAE) < 30mg, (20 patients), a microalbuminuric diabetic group with a 24-hr UAE in the range 30-299mg, (20 patients) and an overt proteinuria group with proteinuric diabetic patients defined as having a 24-hr UAE ≥ 300mg, (20 patients).

The current research is designed to inspect the clinical importance of serum copeptin in patients of type 2 diabetes with and without nephropathy and to assess the relation between microvascular complication of type 2 diabetic patients and copeptin plasma levels.

**Inclusion criteria:** Diabetic patients according to American diabetic association criteria 2015 as followings: Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L) Fasting is defined as no caloric intake for ≥8 hours**,** 2 Hours plasma glucose (2-hr PG) ≥200 mg/dL (11.1 mmol/L), Hemoglobin A1C ≥6.5% (48 mmol/l) and random plasma glucose (PG) ≥200 mg/dL (11.1 mmol/L) in individuals with symptoms of hyperglycemia.

**Exclusion criteria:** Type 1 DM, patients with malignancy, patients with other endocrine diseases which affect glucose metabolism and lipid metabolism, people with chronic hepatitis, pregnancy, and history of drug abuse and the presence of

hematuria, renal insufficiency of unexplained origin, Urinary tract infection, history of rapidly progressive renal failure, polycystic kidney disease and glomerulonephritis.

**Statistical analysis:** The collected data were coded then entered and analyzed using the SPSS version 25 (Statistical package for social science) for windows 10.

**Ethical considerations**: The study was approved by the ethical committee of the Faculty of Medicine, Beni-Suef University**.** Informed written consent was obtained from all participants before recruitment in the study, after explaining the objectives of the work**.** Confidentiality was guaranteed on handling the data base.

## 3. Results:

**Table (1): Comparison between different groups regarding demographic and baseline characteristics**

| | Group | | | | | | | | p-value |
|---|---|---|---|---|---|---|---|---|---|
| | Control (A) | | DN with normoalbuminuria (B) | | DN with microalbuminuria (C) | | DN with macroalbuminuria (D) | | |
| | Mean | ±SD | Mean | ±SD | Mean | ±SD | Mean | ±SD | |
| **Age** | 46 | 5 | 52 | 7 | 56 | 10 | 62 | 7 | 0.768 |
| **Sex** | N | % | N | % | N | % | N | % | p-value |
| **(Male)** | 17 | 44.7% | 3 | 7.9% | 11 | 28.9% | 7 | 18.4% | 0.987 |
| **(Female)** | 13 | 25.0% | 17 | 32.7% | 9 | 17.3% | 13 | 25.0% | |
| | Mean | ±SD | Mean | ±SD | Mean | ±SD | Mean | ±SD | p-value |
| **BMI** | 22 | 2 | 24 | 2 | 23 | 3 | 25 | 3 | 0.876 |
| **HB** | 12.3 | 1.0 | 10.9 | 1.0 | 11.5 | 1.1 | 9.9 | 1.9 | 0.089 |
| **NA** | 138 | 4 | 137 | 3 | 136 | 3 | 138 | 3 | 0.987 |
| **K** | 3.9 | .4 | 4.4 | .5 | 4.0 | .6 | 4.3 | .8 | 0.456 |
| **Platelets** | 269 | 86 | 327 | 157 | 276 | 103 | 268 | 92 | 0.632 |
| **Total leucocytic count** | 6.7 | 2.1 | 9.1 | 4.4 | 8.0 | 2.6 | 8.2 | 2.6 | 0.082 |

This table showed that there was no significant difference between the studied groups in the base line characteristics including age and gender.

**Table (2): Comparison between different groups regarding kidney functions, albumin level and copeptin level**

| | Group | | | | | | | | P-value |
|---|---|---|---|---|---|---|---|---|---|
| | Control (A) | | DN with normo-albuminuria (B) | | DN with microalbuminuria (C) | | DN with macroalbuminuria (D) | | |
| | Mean | ±SD | Mean | ±SD | Mean | ±SD | Mean | ±SD | |
| **UREA** | 30 | 11 | 41 | 7 | 41 | 29 | 120 | 75 | <0.05 [a.b.c] |
| **Creatinine** | 0.8 | 0.2 | 0.9 | 0.2 | 1.2 | 1.4 | 5.0 | 4.3 | <0.05 [a.b.c] |
| **albumin** | 3.8 | 0.2 | 3.9 | 0.3 | 3.7 | 0.3 | 3.2 | 0.4 | <0.05 [a,b,c] |
| **A/C Ratio** | 15 | 7 | 24 | 5 | 147 | 65 | 3222 | 2873 | <0.05 [a.b.c] |
| **GFR** | 95 | 20 | 71 | 21 | 79 | 32 | 28 | 25 | <0.05 [a,b.c] |
| **copeptin** | 2.96 | .66 | 2.82 | .61 | 2.76 | 0.92 | 2.42 | 0.54 | <0.05 [a] |

This table showed that level of urea, creatinine, A/C ratio, was significantly higher in group D than other groups. While albumin and GFR was significantly lower in group D than other groups. Copeptin level in group D was significantly lower than group A.

**Table (3): comparison copeptin level regarding fundus examination, neurological examination, and ultrasound findings**

| | | Copeptin level | | p-value |
|---|---|---|---|---|
| | | Mean | Standard Deviation | |
| **Fundus Ex.** | **Normal** | 2.81 | 0.73 | 0.345 |
| | **NPDR** | 2.50 | 0.42 | |
| | **PDN** | 2.69 | 1.12 | |
| **Neuro** | **Normal** | 2.81 | 0.73 | 0.176 |
| | **Abnormal** | 2.54 | 0.57 | |
| **US** | **Normal** | 2.80 | 0.73 | 0.309 |
| | **Abnormal** | 2.58 | 0.61 | |

This table showed that there was no significant difference in level of copeptin in normal or abnormal fundus examination, neurological examination or ultrasound examination.

**Table (4): Correlation between copeptin and studied parameters**

| | | UREA | Creatinine | GFR | HBA1C | A/C Ratio | Albumin |
|---|---|---|---|---|---|---|---|
| Copeptin | Pearson Correlation | -.013- | -.063- | .111 | -.195- | -.054- | 0.257* |
| | p-value | .287 | .554 | .297 | .065 | .611 | 0.014 |
| | N | 90 | 90 | 90 | 90 | 90 | 90 |

This table showed that there a weak negative correlation between copeptin and (urea, creatinine, HbA1C and A/C ratio) and weak positive correlation between copeptin and GFR but P-value were not significant. But there was a positive weak correlation between copeptin and albumin and p- value was significant (P-value 0.014).

**Table (5): Analysis of serum Copeptin levels with different demographic and clinical parameters by using univariate linear regression**

| | Unstandardized Coefficients | | Standardized Coefficients | t | p-value | 95.0% Confidence Interval for B | |
|---|---|---|---|---|---|---|---|
| | B | Std. Error | Beta | | | Lower Bound | Upper Bound |
| (Constant) | 0.088 | 3.547 | --- | 0.025 | 0.980 | -6.972 | 7.147 |
| Age | -0.006 | 0.009 | -0.085 | -0.703 | 0.484 | -0.025 | 0.012 |
| BMI | -0.021 | 0.030 | -0.084 | -0.676 | 0.501 | -0.081 | 0.040 |
| NA | 0.017 | 0.022 | 0.086 | 0.806 | 0.423 | -0.026 | 0.061 |
| K | -0.232 | 0.138 | -0.200 | -1.676 | 0.098 | -0.507 | 0.043 |
| UREA | -0.002 | 0.004 | -0.175 | -0.568 | 0.572 | -0.011 | 0.006 |
| Creatinine | 0.077 | 0.075 | 0.291 | 1.027 | 0.308 | -0.072 | 0.226 |
| HBA1C | -0.009 | 0.104 | -0.012 | -0.087 | 0.931 | -0.217 | 0.199 |
| A/C Ratio | 4.189 | 0.000 | 0.111 | 0.637 | 0.526 | 0.000 | 0.000 |
| Albumin | 0.558 | 0.292 | 0.289 | 1.913 | 0.059 | -0.023 | 1.138 |
| GFR | 0.000 | 0.004 | 0.012 | 0.073 | 0.942 | -0.007 | 0.007 |
| a. Dependent Variable: copeptin | | | | | | | |

This table showed that the independent variable (age, BMI, Na, K, urea, create, HbA1C, A/C ratio, albumin and GFR) cannot predict copeptin level.

## 4. Discussion:

Although, there is a strong correlation between copeptin and AVP concentrations but their relationship gets distorted in chronic kidney diseases suggesting incomplete clearance of peptide, whenever the renal function is impaired. Therefore, copeptin is preferred over AVP **(8).**

This study aimed to inspect the clinical importance of copeptin level in patients with type 2 diabetes mellitus with and without nephropathy and to assess the relation between microvascular complications of type 2 diabetic patients and copeptin plasma levels.

This study included 90 participants; 30 healthy control participants, 20 cases of DN with normoalbuminuria, 20 cases of DN with microalbuminuria, and 20 cases of DN with macroalbuminuria. The study was conducted between November 2021 till May 2022.

In our study we found that serum copeptin level was lower in diabetic patients with macroalbuminuria than in normal control.

The study by **Meijer et al., (9)** found that vasopressin might contribute to the progression of kidney damage and plasma copeptin could be a good candidate for the identification of subjects at high risk for progression of nephropathy and also found that Vasopressin is elevated in diabetes and associated with albuminuria in a recent, cross-sectional, population-based study.

copeptin was positively associated with urinary albumin/protein excretion Population-based studies have shown copeptin to be strongly associated with microalbuminuria. It was suggested that increased AVP might have albuminuric effect **(10)** but these findings disagree with our study**.**

Reverse findings that appeared in the our study can be explained by the lack of adjustment of other factors like blood glucose level and history of hypertension and this may highlight the importance of considering such factors when using copeptin as a biomarker for renal affection .

Velho and his colleagues found that Copeptin, a surrogate marker for arginine vasopressin, independently associated with progression to ESRD in patients with T2DM and normal renal function, copeptin also predicted an early eGFR decline leading to CKD **(7).**

In our study we found that there was a weak positive correlation between

copeptin and GFR but P -value was not significant.

In the study by **Wen et al., (11)** they found Decline in GFR was found in 6.1% of patients in normal UAE group and 26.4% in microalbuminuria group. However, serum copeptin was comparable between two groups. Serum copeptin was negatively related to GFR (r=-0.586, P<0.001). Serum copeptin is an independent risk factor of decline in renal function of T2DM patient but this result disagrees with our study.

Our study showed that there was no significant difference between the studied groups in the base line characteristics including age and gender.

In PREVEND study as reported by Meijer et al., they found that copeptin levels is higher in males than females corresponding with lower urine volumes and higher urinary osmolarity in males versus females. In both males and females, high copeptin concentration is associated with low 24-h urinary volume and high 24-h urinary osmolarity **(9)**.

Regarding the relation between copeptin level and microvascular complications, our study showed that there is no association between copeptin level and retinopathy and neuropathy.

One of the major complications in patients with diabetes mellitus (DM) is diabetic retinopathy (DR), a leading cause of blindness worldwide. DR causes visual impairment as a result of long-term accumulated damage to the small blood vessels in the retina **(12).**

In a chinease study by **Zhao, et al. (13)** showed that increased plasma copeptin levels were considered as an independent marker of diabetic retinopathy in patients with T2DM, suggesting a possible role of copeptin in the pathogenesis of diabetic retinopathy complications.

Increased plasma copeptin concentrations were an independent marker of DR in Chinese patients with T2DM, suggesting a possible role of copeptin in the pathogenesis of DR complications **(14)** but in our study there was no significant difference in level of serum copeptin in normal or abnormal fundus examination,

## 5. Conclusion:

It was shown that serum copeptin level was significantly lower in diabetic patients with macroalbuminuria than in normal healthy control. There was no significant association was found

between serum copeptin level, diabetic retinopathy nor neuropathy.

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