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Original Article

Correlation of copeptin with osmolarity and electrolytes in diabetes Mellitus: A tertiary center outpatient experience.

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Abstract

Background: Arginine Vasopressin (AVP) plays a significant role in the pathophysiology of Diabetes Mellitus (DM) and its related nephropathy. Timely detection of copeptin, a surrogate biomarker of AVP, would help in minimizing the osmoregulatory complications secondary to DM. The study aimed to correlate serum copeptin levels with serum osmolarity and electrolytes in subjects with progressive stages of DM.

Methodology: A total of 120 patients were recruited as controls, pre-diabetes, DM without nephropathy, and nephropathy. Serum copeptin levels were measured by Enzyme-Linked Immunosorbent Assay. At the same time, routine biochemical tests for diabetes and renal function were done from the affiliated diagnostic laboratory.

Results: The mean copeptin and osmolarity levels were 207.74 ± 192.08 pg/ml and 302.29 ± 18.13 mOsm/kg, respectively. Both, the copeptin and osmolarity levels raises progressively from controls to various stages of DM and share significant positive correlation (r=0.214, p=0.019). Osmolarity was also correlated significantly with RBS (r=0.262), BUN (r=0.844), Na+ (r=0.210) and K+ (r=0.461).

Conclusion: The significant correlation of copeptin with osmolarity highlights the importance of the AVP system in regulating body fluid equilibrium in diabetic patients progressing towards nephropathy. Timely detection of copeptin can play an important role in the early management of the disease.

Keywords

Arginine Vasopressin, Copeptin, Electrolytes, Osmolarity, Diabetes Mellitus.

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Introduction

Serum or plasma osmolarity is one of the vital survival parameters for any organism[1]. Any change in the body's fluid homeostasis, electrolyte equilibrium, or metabolic balance may disturb the body's osmolarity. Increased osmolarity in blood drags the water extracellular; this, in turn, increases the glomerular filtrate in the kidneys, thus damaging the glomerular membranes and initiating the cycle of declining renal functions[2]. This, in turn, activates various physiological systems to bring them towards normal. AVP, also known as Antidiuretic Hormone (ADH), is one of them[3].

AVP causes arteriolar constriction mediated through AVP receptor 1a (V1a) receptors and anti-diuresis via AVP receptor 2 (V2) receptors. AVP also regulates Adrenocorticotropic hormone (ACTH) secretion, insulin, or glucagon release from the pancreatic islet cells of Langerhans through V1b receptors. It also supports glycogen lysis and gluconeogenesis in the liver by V1a receptors[4,5].

Besides the role of AVP as an endocrine hormone and neurotransmitter, AVP is also a novel stress biomarker. It is increased in patients with stroke[6], acute myocardial infarction[7], metabolic syndrome, and Diabetes mellitus (DM)[8]. Higher levels of AVP have been documented from the studies done on humans and in streptozotocin-induced rodents[9,10]. But the mechanism of the rise in AVP levels in DM is still not fully elucidated. It is assumed that the initial rise in AVP levels is beneficial due to its role in water reabsorption from the medullary and cortical collecting ducts, thereby decreasing the osmolarity and restoring the homeostasis which was produced secondary to hyperglycemia and glycosuria[11]. However, the prolonged rise in AVP levels can have detrimental effects and be associated with the worst cardiovascular and renal outcomes[7,11].

Regardless of the cause, most importantly, the release of AVP is mainly stimulated by increased osmolarity[2]. These factors are dependent on each other and disturbed by metabolic disorders such as DM[11]. Hospital admissions secondary to osmotic disturbances in DM are not uncommon.

A study at Civil Hospital Karachi revealed that diabetes with complications is the fourth most common cause of hospital admission[12]. Another study in Canada also revealed that hospital admission secondary to DM is greater than in non-diabetic individuals. The same study found that electrolyte disturbance secondary to DM has a 1.11 prevalence ratio of hospital admission[13]. This is indeed a very alarming situation, and it is important to rule out electrolyte and osmotic imbalances at the initial stages to combat the progressively increasing rate of morbidity and mortality secondary to the homeostatic disturbance in DM. For this purpose, increased osmolarity among outpatient subjects with DM needs to be ruled out first.

Since people with DM are at risk of osmotic and electrolyte irregularities, particularly hypernatremia and hyperkalemia[14], at critical levels[15], levels of AVP and its relation with electrolytes could be an early diagnostic, and therapeutic target as successful trials have been done using AVP antagonists (vaptans) in subjects with DM[16]. However, AVP has a relatively shorter half-life than its carboxyl-terminal glycopeptide, copeptin, which is released in an equimolar amount to that of AVP. It has been found that the concentration of AVP and copeptin correlated well over the vast range of plasma osmolarity. Therefore, it is considered a good diagnostic marker for AVP function[17,18] and is usually preferred in studies when the AVP system is being investigated.

This study was planned to identify the effects of AVP in regulating body osmolarity and electrolyte equilibrium in subjects with DM. For this purpose, the trend of changes in AVP levels and the coherent alteration of body osmolarity and electrolytes at various stages of DM from pre-diabetes to DM and further DM with associated nephropathy were investigated. It would eventually help in the early diagnosis of electrolyte disturbance among susceptible patients, which may reduce hospital admissions and timely management of fluid disorders.

Methodology

Study design & subject selection

It was a comparative cross-sectional study and the sample size was measured through Open Epi.com, keeping 90% power at a 95% Confidence Interval[19]. The required sample size was 108 subjects; however, it was rounded up to 120 individuals. Sampling was done in a non-probability and purposive manner from the outpatient department of nephrology and endocrinology, Dow University of Health Sciences (DUHS). A complete evaluation was done through their laboratory reports based on American Diabetes Association (ADA) 2018 and National Kidney Foundation/Kidney Disease Outcome Quality Initiative (NKF/KDOQI) 2018 guidelines[20,21].

Ethical consideration

This study followed Helsinki's principle and was registered in the research directory of the ethical review board of Dow University of Health Sciences (IRB-1145/DUHS/Approval/2018). An Informed consent was taken from each participant during the data collection. It was made sure that the identities of the study participants and data remained confidential throughout the study.

Inclusion and exclusion criteria

A total number of 120 adults (aged between 18-70 years) who controlled hypertensive (i.e., target BP < 140/90 mmHg on anti-hypertensive drugs) were included in the survey. Patients with diabetes were also compared with controls. The recruited study participants were stratified into controls, pre-diabetes, DM without nephropathy, and DM with nephropathy based on their random blood sugar, which was later on confirmed by glycosylated hemoglobin levels from the diagnostic laboratory of the affiliated institute. Patients with DM were also tested for Urinary Albumin Creatinine Ratio (UACR) for advancing albuminuria and Glomerular Filtration Rate (GFR) for declining renal function to differentiate between diabetic individuals with and without nephropathy. The findings were published earlier in a separate paper[22].

Subjects with any renal or endocrine comorbidity other than hypertension and diabetes mellitus were excluded from the survey. Pregnant and lactating mothers were also not included in the study.

Demographic details

After giving their written consent, the study participants were inquired about their basic demographic details regarding their age, gender, ethnicity, occupation, residential area, and substance abuse. They were also interrogated about any other associated medical disorder, duration of diabetes, treatment history of DM, and any other associated comorbidity and family history of diabetes. All this information was noted in a formally designed proforma.

Clinical variables and vital examination

After filling up the proforma, body weight and height were taken, blood pressure was measured following the standard protocols, and random blood sugar (RBS) was measured by the capillary dipstick method. Body Mass Index (BMI) was also calculated later.

Laboratory procedures for biochemical parameters

After this procedure, peripheral venous blood was collected by a trained phlebotomist in properly labeled (marked with patients'/ controls' identity as per their proforma) EDTA (Ethylene Diamine Tetra Acetate) and gel tubes and 50 ml of spot urinary sample in urine specimen collection container respectively. All the procedures were carried out under sterile conditions, and tubes were then inverted 6-8 times to ensure proper mixing of anti-coagulant with blood. One EDTA and Gel tube of each patient, along with a urine specimen, was immediately sent to the diagnostic lab for the assessment of Glycosylated Hemoglobin (HbA1c) by spectrophotometric method, serum Blood Urea Nitrogen (BUN) by kinetic assay, serum Creatinine by Jaffe's principle, serum Electrolytes (NA^+, K^+, and Cl^-) by Ion-Selective electrode method.

Serum copeptin measurement via ELISA

The sample in one remaining gel tube was then taken to the Dow University of Health Sciences research lab for serum separation and subsequent

storage at – 80°C until further use for copeptin measurement through sandwich Enzyme-Linked Immunosorbent Assay (ELISA) of Cloud Clone Corp. The USA, according to the manufacturer's protocol. The detection range of this kit for copeptin was 15.6 – 1000 pg/ml. The loss rate of this kit is less than 5% before the date of expiry if stored in a suitable environment.

Measurement of serum osmolarity

Serum osmolality was measured using the following formulae and expressed in mOsm/kg;

$$\text{Calculated serum osmolality} = 2 \times Na^{+} + \text{Glucose}/18 + \text{BUN}/2.8$$

Statistical analysis

Data were analyzed through SPSS version 21.0. All data analysis was carried out at a 95% confidence interval. Mean ± standard deviation (SD), frequency (n), and percentage (%) were used to present quantitative and qualitative data. An independent sample t-test was applied to compare individuals who had raised levels of copeptin versus those who did not have raised levels of copeptin. Analysis of Variance (ANOVA) was applied between different study groups. Pearson correlation was used to show the strength of relation of serum copeptin with different clinical variables. Affected factors were controlled by univariate and multivariable linear regression.

Results

Baseline characteristics of the study population

A total number of 120 individuals were recruited for our study. At the time of diagnosis of DM and pre-diabetes, the average age was 45.56 ± 8.9 years and 53.3 ± 9.7 years, respectively. Out of 16.6% of pre-diabetics, 11.8% were drug naïve. Table 1 describes all the basic characteristics, including demographic features and medical and drug history of the study population.

Raised Serum Copeptin levels in the study population

The mean copeptin level found in this study was 207.74 ± 192.08 pg/ml. The serum copeptin levels were insignificantly (p=0.131) raised among individuals with pre-diabetes (252.84 ± 169.1 pg/ml), followed by subjects with nephropathy secondary to DM (230.72 ± 226.75 pg/ml). Out of 120 study participants, 85.8% (n=103) of them had raised levels of serum copeptin i.e., ≥ 45.2 pg/ml [29]. Among that 85.8%, 56.3% were females (X^2=2.590, p=0.108), 51.5% were the subjects with nephropathy secondary to DM (X^2=10.760, p=0.013), 70% of subjects were above 50 years of age (X^2=17.385, p=0.002), and 57.3% of them had a positive family history of DM.

Serum osmolarity & other biochemical variables

The mean serum osmolarity found among the study population was 302.29 ± 18.13 mOsm/ kg. The levels of serum osmolarity were significantly raised among the diabetic patients with nephropathy, i.e., 311.03 ± 19.2 mOsm/kg (p≤0.001), however, it ranges between 271.0 mOsm/kg to 358.0 mOsm/kg. Levels of serum osmolarity were raised among subjects with raised serum copeptin levels compared to individuals with normal copeptin levels (302.84 versus 298.82 mOsm/kg) with an insignificant difference between (Independent sample t-test, F=0.967, p=0.398). The details of serum copeptin, serum osmolarity, and other biochemical variables, including the electrolytes, are given in table 2.

Table 1: Basic characteristics of the study population.

Variables		N(%)
Study population	Controls	20(16.6)
	Pre-diabetes	20(16.6)
	DM without nephropathy	20(16.6)
	DM with nephropathy	60(50)

Gender	Male	56(46.7)
	Female	64(53.3)
Family History of DM	Yes	65(54.16)
	No	55(45.8)
Comorbidity	Hypertension (HTN)	64(53.4)
	Benign Prostate Hyperplasia (BPH)	10(8.3)
	Ischemic Heart Disease (IHD)	6(5)
	Others	17(14)
Drug History (Anti-hypertensive drugs)	ACE inhibitors/ARB	16(13.33)
	Ca+2-channel blocker	13(10.83)
	Beta blocker	12(10)
	Diuretics	12(10)
	Centrally acting anti-hypertensive	6(4.93)
Anti-diabetic drugs	Oral hypoglycemic	33(27.5)
	Insulin	38(31.6)
	Both	11(9.1)
	None	38(31.0)
Age (years); Mean±SD		52.53±11.4
Height (meters); Mean±SD		1.66±0.08
Weight (kg) ; Mean±SD		72.42±12.8
BMI (kg/m^2) ; Mean±SD		26.47±4.7
SBP (mmHg); Mean±SD		135.45±23.9
DBP(mmHg); Mean±SD		79.93±13.15
Mean Arterial Pressure (MAP); Mean±SD		107.69±16.85

Table 2: Biochemical parameters with their mean and standard deviation among different study population groups.

Variables	C (n=20)	PD (n=20)	DM (n=20)	DN (n=60)	Total (n=120)	F	p-value
RBS (mg/dl)	103.75±7.56	125.25±6.9	194.9±42.14***	200.55±56.72***	170.93±18.13	33.62	<0.001
HbA1c (%)	5.25±0.26	5.99±0.24	8.41±1.47***	8.63±1.95***	7.59±2.06	34.41	<0.001
BUN (mg/dl)	23.33±15.07	26.43±16.46	24.20±8.45	77.23±54.84***	50.94±47.75	17.05	<0.001
Na^+ (mEq/L)	138.75±4.27	138.35±4.9	137.25±4.1	136.2±3.9	137.58±4.3	2.54	0.600
K^+ (mEq/L)	4.23±0.36	4.18±0.29	3.93±0.35	4.64±0.70**	4.38±0.62	10.22	<0.001
Cl^- (mEq/L)	107.05±4.1	107.65±4.9	104.25±5.3	105.05±5.9	105.68±5.5	2.1	0.107
Osmolarity (mOsm/kg)	291.20±8.94	292.85±12.42	296.55±13.5	311.03±19.2***	302.29±18.13	12.37	<0.001
Copeptin (pg/ml)	139.72±112.34	252.84±169.12	161.71±138.75	230.72±226.75	207.74±192.08	1.91	0.131

C-Control; PD-Pre-diabetes; DM-Diabetes Mellitus; DN-Diabetic nephropathy; RBS-Random Blood Sugar; HbA1c-Glycosylated Hemoglobin; BUN-Blood Urea Nitrogen.

When serum copeptin was correlated with serum osmolarity, a significant positive but statistically weak trend was found. The details of the Pearson correlation coefficient alongside with p-value of both copeptin and osmolarity with other biochemical variables are given in Table 3.

Table 3: Pearson correlation coefficient along with the level of significance of serum copeptin and serum osmolarity with different biochemical variables evaluated among the study population.

Variables	Copeptin (pg/ml)		Osmolarity (mOsm/kg)	
	Pearson correlation coefficient	p-value	Pearson correlation coefficient	p-value
RBS (mg/dl)	0.154	0.093	0.262	0.004
HbA1c (%)	0.151	0.101	0.26	0.004
Serum BUN (mg/dl)	0.244	0.007	0.844	≤0.001
Serum Na^+ (mEq/L)	0.022	0.809	0.210	0.021
Serum K^+ (mEq/L)	0.056	0.544	0.461	≤0.001
Serum Cl^- (mEq/L)	0.124	0.176	-0.042	0.650
Serum Osmolarity (mOsm/kg)	0.214	0.019	--	--

RBS-Random Blood Sugar; HbA1c-Glycosylated Hemoglobin; BUN-Blood Urea Nitrogen.

Because it has been hypothesized that serum osmolarity is affected by the changes in copeptin levels and diabetic patients are more prone to it, the predictive model was assessed initially by univariable linear regression and later by multivariable linear regression keeping osmolarity as the dependent variable and serum copeptin as an independent variable. This model has 96.4% predictivity (R^2=0.964) at a 6.96 standard error of the estimate. The association was found to be significant with serum BUN (p-value ≤ 0.001), RBS (p-value ≤ 0.001) and Na+ (p-value ≤ 0.001). The control population was used as a reference. The univariable and multivariable regression details with all the confounding factors are given in Tablestables 4 and 5.

Table 4: Association between serum copeptin and serum osmolarity with clinical biomarkers using univariate linear regression.

Variables	β	Standard Error Coefficient	t	p-value	95% CI	
					Lower Bound	Upper Bound
Age	0.097	0.165	0.589	0.557	-0.23	0.424
Gender	-5.772	2.915	-1.98	-0.05	-11.547	0.002
PD	1.65	5.055	0.326	0.745	-8.363	11.663
DM	5.35	5.055	1.058	0.292	-4.663	15.363
DN	19.833	4.128	4.805	≤ 0.001	11.658	28.009
Serum BUN	0.315	0.022	14.028	≤ 0.001	0.271	0.36
RBS	-0.012	0.034	-.0.342	0.733	-0.078	0.055
Serum Na+	1.483	0.327	4.533	≤ 0.001	0.835	2.132

PD-Pre-diabetes; DM-Diabetes Mellitus; DN-Diabetic nephropathy

Table 5: Association between serum copeptin and serum osmolarity with different clinical biomarkers using multivariate linear regression.

Variables	β	Standard Error Coefficient	t	p-value	95% CI	
					Lower Bound	Upper Bound
Age	-0.056	0.52	-1.072	0.286	-0.159	0.047
Gender	-0.663	0.937	-0.707	0.481	-2.52	1.195
PD	0.761	1.792	0.425	0.672	-2.79	4.312
DM	2.725	1.969	1.384	0.169	-1.176	6.627
DN	0.164	2.08	0.079	0.937	-3.958	4.287
Serum BUN	0.36	0.012	29.558	≤0.001	0.336	0.384
RBS	0.064	0.011	5.974	≤0.001	0.043	0.085
Serum Na+	1.94	0.112	17.291	≤0.001	1.718	2.162

PD-Pre-diabetes; DM-Diabetes Mellitus; DN-Diabetic nephropathy

Discussion

In this cross-sectional study, there is a coherent change observed in serum copeptin levels and serum osmolarity with the advancing disease, as the least levels were found in controls and the highest among subjects with diabetic nephropathy.

Our study's mean serum copeptin levels were 207.74 ± 192.08 pg/ml, which is considerably higher than normal levels of copeptin[22]. It could be due to the reason that most of the study participants were diabetic patients either with or without nephropathy, and previous studies have reported the raised levels of AVP in subjects with DM and its associated nephropathy[23-25]. However, mean copeptin levels were found least in the control group but still much higher than the normal range of copeptin. The raised BMI levels of the study population could be one of the most relatable factors according to the studies published previously[23]. But most importantly, more studies are needed to find out the normal levels of copeptin among the local population.

The raised levels of copeptin found in our study population with compromised renal function, positive family history of DM, and advancing age are similar findings reported in the literature[24-27]. However, the levels of copeptin were found to be higher in females in our study than in the data published previously[26-28]. Although Abbasi et al. have reported the role of copeptin as a predictive biomarker in females for incident DM[25], some studies suggest the modulatory role of estrogen on the release and response of the AVP system[29].

Our study also observed progressively increased osmolarity levels from controls to pre-diabetes to DM without nephropathy and then DM with nephropathy. Moreover, there is also a significant correlation of osmolarity found in our study with blood glucose levels, HbA1c, serum BUN, Sodium, and Potassium (Table 3). According to the internationally reported data, these findings are where raised osmolarity is associated with compromised renal functions[30]. However, many studies have described osmotic disturbances in diabetic patients secondary to acute complications[31]. And the role of the AVP system in osmotic modulation in subjects with DM is even further less explained[32]. Fortunately, our study found a significantly positive correlation of osmotic balance with serum copeptin, a novel finding across the spectrum of glucose perturbance in patients with diabetes, contributing to the existing knowledge about the AVP system osmotic equilibrium and DM. In our study, serum copeptin was found to not correlate with electrolytes (Sodium, Potassium, and Chloride). To the best of our knowledge, this is the first study comparing

serum copeptin levels with different electrolytes of the human body.

As people with diabetes mellitus are more prone to electrolyte imbalance, however, it is least likely due to the involvement of AVP or copeptin[33]. Although interventional studies have been done evaluating the role of different AVP agonists or antagonists on electrolytes of the body[34], the comparison of serum electrolytes with the endogenous secretion of AVP/copeptin needs more attention.

Moreover, the lowest and highest levels of Potassium in this study were recorded in the diabetic nephropathy group but had no significant correlation with Copeptin levels. It could be due to the reason that some of the patients with diabetic nephropathy were dialysis-dependent, as Potassium is the most vulnerable ion to be disturbed in dialysis-dependent patients[35].

Several studies of variable ethnicity and study parameters have reported a significant association of copeptin with DM and renal outcomes[19,23-25]. Moreover, to the best of our knowledge, this is the first study reporting pattern of change in copeptin levels with osmolarity in each stage of diabetes mellitus (i.e., from healthy controls to pre-diabetic stage to the development of DM and then the onset of renal complications). Further, our study also correlated the copeptin level with most of the major electrolytes of the body, trying to find out the role of copeptin in regulating body electrolytes with progressive worsening renal functions.

There are some limitations of the study, such as lack of data regarding dialysis history, pre and post-dialysis status of the participants, and estimated urine osmolarity. Also, this study should be done prospectively on a larger sample size, but due to constraints in budget and time frame, a retrospective study was conducted.

Nevertheless, the local data concerning the copeptin levels in Type 2 DM patients is also lacking. Being a lower socioeconomic country with a higher prevalence of DM, this data is important from both diagnostic and therapeutic points of view. Further, copeptin being one of the modifiable risk factors for worsening renal outcomes can be a potential target of further research in this domain. These findings would help clinicians modulate DM's treatment strategy and its associated homeostatic complications.

Conclusion

The findings of our study suggested a significantly positive correlation between copeptin and osmolarity. Also, the change in the levels of copeptin and osmolarity correspond to each other in each stage of DM, highlighting the role of copeptin in regulating body fluid equilibrium in diabetic patients with worsening renal outcomes. Based on the outpatient diabetes population, this study possesses limelight importance concerning the role of copeptin in the early detection and management of the disease. It will eventually delay the progression of DM-related renal outcomes and their consequences.

Conflicts of Interest

The authors have declared that no competing interests exist.

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