The Correlation Between Copeptin and Volume Status in Chronic Hemodialysis Patients

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Introduction. Currently There is no noninvasive chemical biomarker, available for evaluating volume status, in individuals with end-stage kidney disease (ESKD). This study aimed to determine the relationship between copeptin level and volume status in hemodialysis patients.

Methods. This clinical trial enrolled 84 patients with ESKD (Mean age ± SD: 54.31 ± 15.47) on maintenance hemodialysis (3-times weekly, 4h /session). Plasma levels of Hb, copeptin, HCT, Na, and BUN, patients' weight, systolic and diastolic blood pressure and mean arterial pressure were measured, before and after hemodialysis. Age, sex, etiology of kidney failure, and duration of dialysis were also recorded., and the correlation between copeptin level and all variables was evaluated.

Results. There was a significant positive correlation between copeptin level and Hb (r = 0.313, $P < .05$), and HCT (r = 0.25, $P < .05$), while a negative association was found between copeptin level and Na (r = -0.051, $P > .05$) and IDWG (r = -0.05, $P > .05$). Although copeptin concentration was higher in females before (929.23 pmol/L) and after dialysis (783.3 pmol/L) than male patients (657.05 and 697.45 pmol/L), the mean copeptin changes was higher in male (205 pmol/L) than female (197 pmol/L) ($P > .05$). The level of copeptin decreased ($P > .05$) but the level of Hb ($P < .05$), HCT ($P < .05$), and Na ($P > .05$) were increased after dialysis compared to pre-dialysis period.

Conclusions. Copeptin could be used as a surrogate marker for the diagnosis of volume status in hemodialysis patients.

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Original Paper

INTRODUCTION

Kidney function can be impaired in different circumstances; Diabetes and hypertension are among the most common causes. . Although dialysis and kidney transplantation are employed as accepted renal replacement therapies, complications such as renal allograft rejection and volume overload put the patients at great risks.[1,2,3] Regulation of volume status, to prevent volume overload or dehydration, is of great importance among dialysis patients. Fluid imbalance may result in volume overload, leading to hypertension and ventricular hypertrophy or dehydration, resulting in hypotension and muscle cramps.[4] However, there is no appropriate noninvasive biochemical marker available for evaluation of volume status, in dialysis patients. Current methods used for the evaluation of volume status include measurement of blood pressure, physical examination and calculation of dry weight. Dry weight is the minimum weight

that a patient would be able to tolerate without hypotension, after dialysis. Obtaining the optimal dry weight with dialysis requires time and skill.[5,6] Pro-brain natriuretic peptide (Pro-BNP), sodium (Na), hematocrit (HCT), and plasma hemoglobin (Hb) are among biochemical markers, used in the clinical evaluation of dry weight, but none of them meet the criteria for a favorable marker.[8] Body fluid homeostasis is regulated by various factors, including arginine vasopressin (AVP).[9,10] AVP, along with neurophysin II and copeptin, are stored in the posterior pituitary vesicles and released into the bloodstream, in response to changes in blood pressure, volume contraction, or stress.[11] AVP has very short half-life (between 27-69 minutes), and its plasma level could not be measured easily, so a longer-lasting surrogate marker should be used instead of AVP.[12] Copeptin is a glycopeptide with 35 amino acids, which is isolated from the C-terminal of the AVP precursor, and has been demonstrated to be stable for seven days at room temperature and fourteen days at 4 °C.[13] It is a stable molecule, with a longer half-life (86 min) compared to AVP, and is easily measurable.[14,15] Studies have shown that copeptin is elevated in patients with end-stage kidney disease (ESKD), and can be used as an alternative marker to vasopressin, for predicting cardiovascular diseases and mortality in ESKD patients.[16] Other studies have reported that copeptin is correlated with chronic kidney disease (CKD), renal cystic disease, diabetes insipidus, diabetes mellitus, cardiovascular, and metabolic disorders.[17-20]

There are several studies which have suggested bioimpedance, as one of the best methods to assess volume status in ESKD patients, although it is not the gold standard method In general, one of the reasons for conducting this study, was to establish an accurate and effective method, for evaluation of volume status, by the use of copeptin, in ESKD patients. This study aimed to determine the relationship between copeptin level and volume status in hemodialysis patients.

MATERIAS AND METHODS

In this study 90 ESKD patients on routine hemodialysis (3 times a week, 4h /session), who were referred to our hospital between 2016 and 2017, were enrolled. This study was approved by Tehran University of Medical of Science Research Ethics Committee in 2016 (ethical code 9511402002, grant number 960414637161). An informed written consent was obtained from all patients. Patients with age > 18 years old and ESKD, on routine hemodialysis, for at least 90 days, were included in this study. Exclusion criteria were pregnancy, breastfeeding, myocardial infarction (MI) / stroke during the last 6 months, deep vein thrombosis (DVT), low serum albumin, and history of psychiatric problems. Hemodialysis was performed in all patients with a low-flux polysulfone dialyzer, blood flow rate of 250 to 350 mL/min and dialysate flow rate of 500 mL/min. All patients were dialyzed in a supine position, to prevent the effect of body posture on blood volume. Weight, age, sex, and duration on dialysis were recorded in the first visit (Table 1). Two blood samples were obtained, before and after dialysis, for the measurement of copeptin level (ELISA Kit assay, Bioassay Technology Laboratory, China), HCT, Na, blood urea nitrogen (BUN), and Hb (Biochemical, Pars azmun, Iran). Additionally, systolic and diastolic blood pressures, as well as mean arterial pressure (MAP) were measured, before and after dialysis. Bioimpedance was used to measure the patients' weight before and after dialysis. In addition, volume status was calculated based on patients' weight before and after dialysis and the fluid overload of all patients was evaluated by bioimpedance spectroscopy method (bioimpedance analysis; BIA, InBody S10) before and after dialysis. Finally, the relationship between copeptin level and Hb, HCT, Na, BUN, dry weight, systolic and diastolic blood pressure, MAP, volume overload, age, sex, etiology of kidney failure, interdialytic weight gain (IDWG), and duration on dialysis was analyzed.

Table 1. Patients' Demographic Data

	ESRD (n = 84)
Male / Female (n)	52 / 32
Age, y	54.48 ± 15.56
Male	54.3 ± 15.55
Female	
Etiology (n)	
HTN	52
Diabetes	48
ADPKD*	10
Glomerulonephritis	6
Obstruction and Nephrolithiasis	6
Others	9

*Adult Polycyctic Kidney Disease

Statistical Analysis

Data were expressed as mean ± SD and analyzed with SPSS statistical software. *P* value of < .05 was considered significant. Pearson correlation analysis was used to evaluate the correlations between copeptin level and other variables.

RESULTS

Totally, 84 patients were enrolled in this study, four patients passed away and two other experienced an episode of heart attack, during the study period, and therefore were excluded from the study. The mean concentrations of copeptin ($P > .05$), Hb ($P < .05$), HCT ($P < .05$), and Na ($P > .05$) were increased after dialysis compared to pre-dialysis values (Table 2). Dry weight, BUN, MAP, systolic and diastolic BP were all significantly lower after dialysis than before. The findings also revealed that, copeptin level had positive significant relationships with Hb (r = 0.313, $P < .05$) and HCT (r = 0.25, $P < .05$). There were also an inverse correlation between copeptin level and IDWG (r = -0.05, $P > .05$), and Na (r = -0.051, $P > .05$). However, no significant correlation was found between copeptin and other variables before and after dialysis. Table 2 demonstrates the changes in copeptin level, IDWG, HCT, Hb, Na, BUN, MAP, systolic and diastolic blood pressure, and before and after dialysis. The mean changes of copeptin concentration were higher in males (205 pmol/L) than in females (197 pmol/L) ($P > .05$), despite the fact that the absolute copeptin concentration were higher in females than males, before and after dialysis, (929.23 pmol/L and 783.3 pmol/L) and (657.05 pmol/L and 697.45) ($P > .05$), respectively. We did not find any significant correlation between copeptin level and age. Also, no significant correlation was found between the levels of copeptin, and type 2 diabetes, as a cause of ESKD, neither there was a significant change before and after dialysis ($P > .05$ and $P > .05$, respectively) (Furthermore, in diabetic patients, pre-dialysis levels of copeptin were higher than its post-dialysis levels. There was also no association between copeptin level and the duration on dialysis ($P > .05$). Our study

Table 2. The Copeptin and Biomarkers Concentrations in Pre-dialysis and Post-dialysis

Variables	Median	IQR	*P*
Weight, kg			
Before Dialysis	68.5	(60 to 80)	< .05
After Dialysis	66	(56 to 76)	
Copeptin, pm/mL			
Before Dialysis	405.8	(321.6 to 992.4)	> .05
After Dialysis	449.4	(303.05 to 1005.25)	
HCT, %			
Before Dialysis	33.5	(28.37 to 37.95)	< .05
After Dialysis	33.6	(29.5 to 38.6)	
Hb, g/dL			
Before Dialysis	10.5	(8.85 to 12.2)	< .05
After Dialysis	10.8	(9.5 to 12.7)	
Na, meq/L			
Before Dialysis	131	(131 to 138)	< .05
After Dialysis	136	(133 to 142)	
Mean Arterial Pressure, mmHg			
Before Dialysis	113.3	(102.7 to 130)	< .05
After Dialysis	103.3	(95 to 116)	
BUN			
Before Dialysis	123	(100 to 140)	< .05
After Dialysis	41	(31 to 50)	
Systolic Blood Pressure, mmHg			
Before Dialysis	130	(120 to 150)	< .05
After Dialysis	120	(110 to 140)	
Diastolic Blood Pressure, mmHg			
Before Dialysis	77.5	(70 to 80)	< .05
After Dialysis	70	(65 to 80)	

Table 3. The Copeptin Levels and Congestive Heart Failure (CHF)

	n	Mean	SD	*P*
CHF	73	356.52	1098.61	> .05
Copeptin	10	220.83	283.20	

Table 4. The Copeptin Levels and Interdialytic Weight Gain (IDWG)

IDWG	n	Mean	SD	*P*
Copeptin				
< 3.5	73	356.52	1098.61	> .05
> 3.5	10	220.83	283.20	

showed that, the copeptin changes were decreased in patients with CHF and only patients with IDWG more than 3.5% of body weight, had substantially lower copeptin levels (Table 3, 4).

DISCUSSION

In this study, we investigated the association between volumetric and osmotic variables (blood pressure, hematocrit, hemoglobin, and Na), and copeptin level in hemodialysis patients. We found a positive correlation between copeptin level and HCT and Hb, and a negative correlation with IDWG and Na. It has been shown that chronic volume overload is associated with an increased risk of cardiovascular diseases and death in ESKD patients.[8,19] Assessment of biomarkers, dry weight and blood volume, lung ultrasonography, and use of bioimpedance, are all appropriate approaches, for detecting volume overload, in dialysis patients.[8] These methods have some advantages and limitations for determination of volume status in dialysis patients. Ettema *et al.* conducted a study in 2015, and showed that the copeptin level was significantly higher in males (161.1 pmol/L) than in females (107 pmol/L), before dialysis. They also reported a significant correlation between copeptin level and age in pre-dialysis period, and showed that diabetic patients had higher copeptin levels, compared to non-diabetic patients, before dialysis. They could not demonstrate any correlation between copeptin level and plasma Na level, MAP and dry weight, before dialysis.[21] Another study conducted by Bhandari *et al.* on 706 healthy volunteers, in 2009, showed a significantly higher median copeptin levels in male patients compared to females (4.3 vs. 3.2 pmol/L). They also defined a link between copeptin levels in men and eGFR. In brief, they illustrated that gender, eGFR, left atrial size could all independently predict the plasma levels of copeptin.[22] However, our findings contradict those of Ettema *et al.* and Bhandari *et al.*, regarding higher copeptin levels in females, while they support their results regarding higher levels of copeptin in diabetic patients.

Kim *et al.*, conducted a study to assess the concentration of copeptin, in 41 hemodialysis patients. They reported that the level of copeptin (171.4 pg/mL) increased before hemodialysis and decreased after dialysis. Their findings suggest a correlation between copeptin level and pre- and post-dialysis total body volume. Furthermore, copeptin level was considerably higher in patients with left ventricular dysfunction, compared to those with normal left ventricular function. They proposed copeptin as a good marker for the diagnosis of left ventricular failure, in ESKD patients.[23]

In a cohort study conducted in Sweden, which enrolled two independent groups, a strong association was found between increased copeptin levels and increased risk of kidney disease. The authors suggested that, copeptin could be used to identify patients at risk for developing progressive kidney disease.[24] Another cohort study, which included 3186 participants, followed for 16.6 ± 1.5 years, showed that high copeptin levels could predict the decline in eGFR.[25] Our results illustrated that, copeptin was not significantly associated with the etiology of kidney failure and duration of dialysis. We demonstrated that the mean copeptin concentrations, Hb, HCT, and Na increased after dialysis (($P > .05$, $P < .05$, $P < .05$, and $P > .05$; respectively). High copeptin levels in hemodialysis patients, was an important finding of our investigation.

One limitation of this research was the small sample size. Another limitation was the effect of some chronic diseases, such as heart failure, on copeptin level, which should be considered as a confounding factor. Also, we did not have a normal control group. We recommend more detailed studies, with larger sample sizes, to examine the copeptin level in different clinical and etiologic settings.

Some studies demonstrated that, high copeptin level is directly linked to volume overload, hypertension and increased mortality. Another study showed that, copeptin indirectly increased

blood pressure. Copeptin and AVP are secreted simultaneously, and AVP causes vasoconstriction and diastolic hypertension. On the other hand, some studies showed no correlation between copeptin levels and systolic or diastolic HTN.

CONCLUSION

We demonstrated that copeptin level had significant positive association with Hb, HCT, and negative correlation with IDWG and Na in ESKD patients. Therefore copeptin could be used, as an alternative surrogate marker, for estimation of volume status, and help to prevent volume overload in hemodialysis patients. As volume overload is the most common cause of hypertension in ESKD patients, its management helps to control the blood pressure.

ETHICAL APPROVAL

All procedures performed in this study including data mining from existing information, were in accordance with the ethical standards of the Tehran University of Medical Science Research Committee and compatible with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Ethics Committee of Tehran University of Medical Science approved this study (ethical cod 29518, grant number 960414637161).

CONFLICT OF INTEREST

The authors declare that there was no conflict of interest

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