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ORIGINAL ARTICLE.

Value of Serum Copeptin Estimation in the Diagnosis of Kidney Injury in Preeclampsia

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ABSTRACT

Background: Copeptin is a peptide secreted from the hypothalamus, with the arginine vasopressin (AVP). Also, as copeptin is excreted by the kidneys and is stable in plasma, it can be used as a biomarker for AVP secretion. This study aims to evaluate the role of serum copeptin in the diagnosis of kidney injury in pregnant females with preeclampsia. **Methods:** This study included a total of 60 women; 20 pregnant with preeclampsia, 20 with normal pregnancy, and 20 healthy non-pregnant control. The following investigations had been made; HbA1C, blood urea, serum creatinine, serum uric acid, creatinine clearance, glomerular filtration rate (GFR), urinary protein, urinary sodium (Na), liver function tests, and serum copeptin levels were measured by an enzyme-linked immunoassay(ELISA). **Results:** Serum copeptin levels in pg/ml mean±SD were significantly higher in preeclampsia (3778.5±265.45) than in normal pregnancy (1452.9±397.81), and non-pregnant control (253.88±294.6) ($p<0.05$) (S). Serum copeptin showed a positive correlation with the blood pressure, HbA1C, serum creatinine, uric acid, bilirubin, ALT and AST, urin ary Na, blood urea, and urinary proteins ($p<0.05$) (S), and a negative correlation with the GFR and creatinine clearance ($p<0.05$) (S). Receiver Operating Characteristic (ROC) curve for serum copeptin as a marker for kidney injury in preeclampsia; at a cutoff point 3100 pg/ml, showed 95.0% sensitivity, 85.0% specificity ($p<0.05$) (S) .

Conclusiosn: Serum copeptin can be used as a marker forthe diagnosis of kidney injury in preeclampsia, with high sensitivity and specificity.

Keywords: Serum copeptin, preeclampsia, kidney injury, arginine vasopressin,AVP.

INTRODUCTION

During pregnancy, all aspects of kidney function are widely affected. The glomerular filtration rate (GFR) increases about 50% with a decrease in serum creatinine, blood urea nitrogen (BUN), and serum uric acid[1].

For the assessment of renal function in pregnancy, serum creatinine measurement is better than the estimated glomerular filtration rate (eGFR), and proteinuria is quantified using the urinary albumin creatinine ratio (UACR), or urinary protein creatinine ratio (UPCR)[2].

In preeclampsia, the renal blood flow and the glomerular filtration rate (GFR) are reduced, and urinary excretion of protein is increased [3].Rarely in severe preeclampsia, prolonged renal hypoperfusion may result in acute tubular necrosis, but the BUN and serum creatinine often remain in the normal range. Proteinuria usually accompanies hypertension, and after the termination of pregnancy, it usually disappears within weeks [4].

Anti-diuretic hormone (ADH), also known as arginine vasopressin (AVP), maintains vascular tone and fluid balance [5].Copeptin is an inactive pro-segment, that is co-secreted from the hypothalamus, with the AVP, and as it is stable in plasma, it can be used as a marker for AVP secretion [6].

Serum copeptin levels are increased in preeclampsia, as the AVP stimulates cortisol release, resulting in salt and water retention. In addition, the AVP increasesthe release of epinephrine, causing vasoconstriction and hypertension[7].

Plasma copeptin levels were found to be independently associated with progression to CKD, and high AVPshowed a harmful effect on renal health in patients with CKD and the general population[8].In addition, water ingestion decreases circulating AVP and copeptin levels and could modify CKD progression [9].Thus, copeptin is considered a promising diagnostic and prognostic marker in preeclampsia [10].

This study was conducted to evaluate the role of serum copeptin in the diagnosis of kidney injury in patients with preeclampsia.

METHODS

This case-control study included 60 women and was carried out in the inpatient wards, and the outpatient clinics, at the Internal Medicine Department and Nephrology Unit, the Gynecology and Obstetrics Department and the Biochemistry Department, Faculty of Medicine, Zagazig University Hospitals, Egypt, during the period from 2015-2019.

The case group included a total of age-matched 40 pregnant women; 20 with normal pregnancy, and 20 pregnant with preeclampsia. The diagnosis of preeclampsia was made according to the criteria of the Preeclampsia Community Guidelines (PRECOG) [11].

Control group included a total of age-matched 20 healthy non-pregnant females par ticipated as healthy control.

Patients with sepsis, malignancy, chronic obstructive pulmonary disease (COPD), S-T elevation-myocardial infarction, or cerebrovascular stroke were excluded.

Informed consent had been taken from participants, with approvals taken on (May 4th, 2014) from the Ethical Committee, the Institutional Research Board (IRB) of the Faculty of Medicine, Zagazig University, Egypt, according to the declaration of Helsinki.

The following had been studied: History taking, physical examination, and investigations; serum creatinine, blood urea, serum uric acid, calculated creatinine clearance, by Cockcroft-Gault equation[12], calculated glomerular filtration rate (GFR), by the Modification of Diet in Renal Disease (MDRD) calculator[13], liver function tests (LFT), complete blood count (CBC), urine analysis, urinary protein, serum and urinary sodium (Na), glycosylated hemoglobin (HbA1C) and fasting blood sugar (FBS).

Serum copeptin level was measured by an enzyme-linked immunosorbent assay (ELISA), using Human Vasopressin-neurophysin 2-Copeptin, ELISA Kit; Catalog No: E0462h, manufactured by EIAab, China.

STATISTICAL ANALYSIS

Data were analyzed, using SPSS 20.0 for windows. Quantitative; mean ± SD andmedian (range), and qualitative; absolute frequencies (number) & relative frequencies (percentage). Independent samples Student's t-test was used to compare two groups of normally distributed variables, while the Mann-Whitney U test was used for non-normally distributed variables.

A one-way ANOVA test was used for differencesamong three variables. Chi-square or Fisher's test was used when appropriate. Spearman's rank correlation coefficient was calculated to assess the relationship between variables. Multivariate regression analysis was used when appropriate.

The Receiver operating characteristic (ROC) curve, with the cutoff point, the area under the curve (AUC), positive predictive value (PPV), and negative predictive value (NPV), were calculated for specificity and sensitivity of serum copeptin levels.

All tests were two-sided. The results were considered statistically non-significant (NS), andsignificant (S), when the significant probability (p-value) was >0.05, and< 0.05,respectively.

RESULTS

As regards the baseline characteristics, all studied groups were age-matched, with a statistically significant difference as regards the body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP) ($p<0.05$) (S) (Table 1).

There was a significant difference as regards the serum creatinine, blood urea, serum uric acid, fasting blood sugar (FBS), Hb%, platelets count, AST, ALT, total bilirubin, serum albumin, serum total proteins, creatinine clearance, and urinary Na, glomerular filtration rate (GFR), and 24-hours urinary proteins ($p<0.05$) (S), with no significant difference as regards HbA1C, white blood cells (WBCs) count, or serum sodium ($p>0.05$)(NS) (Table 1).

There was a statistically significant differenceas regards serum copeptin levels mean±SD in pg/ml, with higher levels in pregnant women with preeclampsia (3746.7±780.3) than in normal pregnancy (2615.7±980.2), than non-pregnant

healthy females (253.88±294.6)($p<0.05$) (S) (Table 1 and Figure1).

There was a positive correlation between serum copeptin levels andBMI, SBP, DBP, HbA1C, serum creatinine, uric acid, bilirubin, ALT and AST, urinary Na, blood urea, and 24 hours urinary proteins ($p<0.05$) (S), and a negative correlation with the GFR and creatinine clearance ($p<0.05$) (S), but no correlation with age, fasting blood sugar, or serum sodium ($p>0.05$) (NS) (Table 2).

The receiver operating characteristic (ROC) curve for serum copeptin level in pg/ml, as a marker for kidney injury in preeclampsia was studied;area under the curve (AUC) was (0.90), 98% confidence interval (CI%) (0.87-1.0), cutoff point (3100 pg/ml), sensitivity (95.0%), specificity (85.0%), positive predictive value (PPV) (86.3%),negative predictive value (NPV) (94.4%), and accuracy (90.0%),($p<0.05$) (S) (Figure 2).

Using the multivariate regression analysis for serum copeptin levels versus laboratory investigations (quantitative) showed that serum copeptin is independently correlated to BUN, urinary protein, urinary sodium, FBS, and HbA1C ($p<0.05$) (S), but not with serum creatinine, total serum protein, serum albumin, creatinine clearance or GFR ($p>0.05$) (NS), (Table 3).

Using the multivariate analysis for serum copeptin levels as an independent variable (Qualitative, divided at the cutoff) showed that serum copeptin is independently correlated to serum creatinine, BUN, urinary protein, urinary sodium, GFR, serum albumin, and HbA1C ($p<0.05$) (S), but not with total serum protein, creatinine clearance, or FBS ($p>0.05$) (NS), (Table 4).

Table 1: Comparison of the studied groups (n=60), as regards the mean±SD of the demographic data, laboratory investigations, and serum copeptin levels in pg/ml.

Variables	Preeclampsia (n=20)	Normal preg (n=20)	Control (n=20)	F	P-value
Age (years)	27.3±4.52	25.23±3.95	25.62±5.43	1.1	0.33
BMI	32.8±2.89	29.15±1.48	29.3±2.05	17.3	0.001*
SBP (mmHg)	140.0±15.64	113.25±8.92	114.7±13.3	27.09	0.001*
DBP (mmHg)	89.25±12.59	69.0±10.83	71.0±12.6	17.1	0.001*
FBS (mg/dl)	101.5±35.4	147.89±45.5	88.85±4.4	17.34	0.001*
HbA1C (%)	5.52±0.69	5.39±0.29	5.3±0.31	1.118	0.33
Hb (mg/dl)	9.61±0.87	10.23±0.88	11.2±0.92	16.2	0.001*
WBCs (10^3/dl)	5.86±2.28	5.98±1.61	5.8±1.9	0.044	0.95
Platelets (10^3/dl)	159.85±53.6	245.15±51.73	240.75±85.1	10.82	0.001*
S. Na (mmol/l)	135.3±2.4	135.8±3.0	135.5±6.1	0.073	0.93
Bl. urea (mg/dl)	29.15±4.92	19.5±4.54	19.9±9.5	13.24	0.001*
S. creat. (mg/dl)	1.07±0.33	0.66±0.2	0.74±0.16	16.24	0.001*
S. alb. (gm/dl)	3.53±0.35	3.84±0.35	3.8±0.36	4.55	0.015*
S. prot. (mg/dl)	7.11±0.42	7.39±0.38	7.3±0.36	3.2	0.048*
Uric acid (mg/dl)	5.08±1.23	4.12±0.35	3.7±0.12	18.19	0.001*
S. ALT (mg/dl)	19.34±8.09	13.3±5.72	11.78±4.04	8.38	0.001*
S. AST (mg/dl)	30.12±16.3	23.6±5.98	19.31±3.81	5.62	0.001*
S. bil. (mg/dl)	1.09±0.61	0.73±0.06	0.29±0.18	23.6	0.001*
GFR (ml/min)	101.5±35.4	147.89±45.5	145.7±40.9	8.22	0.001*
Ccr (ml/min)	140.25±49.2	170.5±24.5	176.2±39.6	4.88	0.011*
U. Na (mmol/l/day)	36.15±9.44	29.95±8.95	30.4±9.2	3.04	0.049*
U. proteins (gm/l/day)	0.73±0.28	0.03±0.004	0.04±0.06	117.8	0.001*
S. copeptin (pg/ml)	3746.7±780.3	2615.7±980.2	253.88±294.6	115.04	0.001*

*Statistically significant difference ($p<0.05$). Preg (pregnancy), BMI (Body mass index), SBP (Systolic blood pressure), DBP (Diastolic blood pressure), FBS (Fasting blood sugar), HbA1C (Hemoglobin A1C), Hb (Hemoglobin), WBCs (White blood cell count), S. (serum), Na (Sodium), bl. (blood), creat. (creatinine), alb. (albumin), prot. (protein), ALT (alanine aminotransferase), AST (aspartate aminotransferase), bil. (bilirubin), GFR (glomerular filtration rate), min (minute), Ccr (creatinine clearance), U (urinary).

Table 2: Correlation between serum copeptin levels in pg/ml and other parameters in the studied groups (n=60).

Laboratory investigations	Copeptin in pg/ml	
	R	P-value
Systolic blood pressure (SBP) in mmHg	0.574	0.001*
Diastolic blood pressure (DBP) in mmHg	0.534	0.001*
Fasting blood sugar (FBS) in mg/dl	0.219	0.175
Hemoglobin A1C (HbA1C) (%)	0.464	0.003*
Serum sodium (Na) in mmol/l	0.226	0.161
Blood urea in mg/dl	0.591	0.001*
Serum creatinine in mg/dl	0.368	0.019*
Glomerular filtration rate (GFR) in ml/minute	-0.312	0.04*
Creatinine clearance in ml/minute	-0.225	0.012*
24 Hours urinary sodium (Na) in mmol/l	0.327	0.018*
24 Hours urinary protein in gm/l	0.659	0.001*

*Statistically significant difference (p<0.05).

Table 3: Multivariate regression analysis for serum copeptin levels versus laboratory investigations (Quantitative):

Model	Unstandardized Coefficient		Standard. Coefficient	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	-295.046	3340.916		-0.088	0.930	-7127.986	6537.894
S. creatinine	484.576	757.994	0.125	0.639	0.528	-1065.696	2034.849
Bl. Urea	49.163	15.220	0.362	3.230	0.003*	18.035	80.291
U. Protein	2177.968	440.376	0.626	4.946	0.001*	1277.297	3078.638
Urinary Na	-76.057	16.301	-0.483	-4.666	0.001*	-109.396	-42.718
T. protein	-428.057	373.280	-0.125	-1.147	0.261	-1191.500	335.387
S. albumin	642.362	453.715	0.170	1.416	0.167	-285.589	1570.314
HbA1c	1344.453	458.333	0.523	2.933	0.006*	407.057	2281.850
Ccr	-2.861	9.294	-0.102	-0.308	0.760	-21.869	16.147
GFR	17.183	9.739	0.627	1.764	0.088	-2.737	37.102
FBS	-62.979	24.161	-0.430	-2.607	0.014*	-112.395	-13.564

a. Dependent Variable: serum copeptin. *Statistically significant difference (p<0.05), S. (serum), Bl. (blood), U. (urinary), Na (sodium), T. (total), HbA1C (Hemoglobin A1C), Ccr (creatinine clearance), GFR (glomerular filtration rate), FBS (fasting blood sugar).

Table 4: Multivariate analysis for serum copeptin levels as an independent variable (Qualitative, divided at the cutoff):

Items	Type III Sum of Squares	Df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[k]
S. creat.	0.885[a]	1	0.885	7.313	0.010	0.161	7.313	0.750
Bl. urea	1503.43[b]	1	1503.43	19.24	0.001*	0.336	19.245	0.990
U. protein	2.677[c]	1	2.677	24.63	0.001*	0.393	24.639	0.998
Urinary Na	428.082[d]	1	428.082	5.621	0.023	0.129	5.621	0.637
T. protein.	0.311[e]	1	0.311	1.773	0.191	0.045	1.773	0.255
S. albumin	0.725[f]	1	0.725	5.502	0.024	0.126	5.502	0.628
HbA1c	2.924[g]	1	2.924	11.68	0.002	0.235	11.680	0.915
Ccr	6309.46[h]	1	6309.46	2.461	0.125	0.061	2.461	0.334
GFR	12940.5[i]	1	12940.5	5.092	0.030	0.118	5.092	0.595
FBS	148.558[j]	1	148.558	1.534	0.223	0.039	1.534	0.227

a. Dependent Variable: serum copeptin. *Statistically significant difference ($p<0.05$), S. (serum), Bl. (blood), U. (urinary), Na (sodium), T. (total), HbA1C (Hemoglobin A1C), Ccr (creatinine clearance), GFR (glomerular filtration rate), FBS (fasting blood sugar).

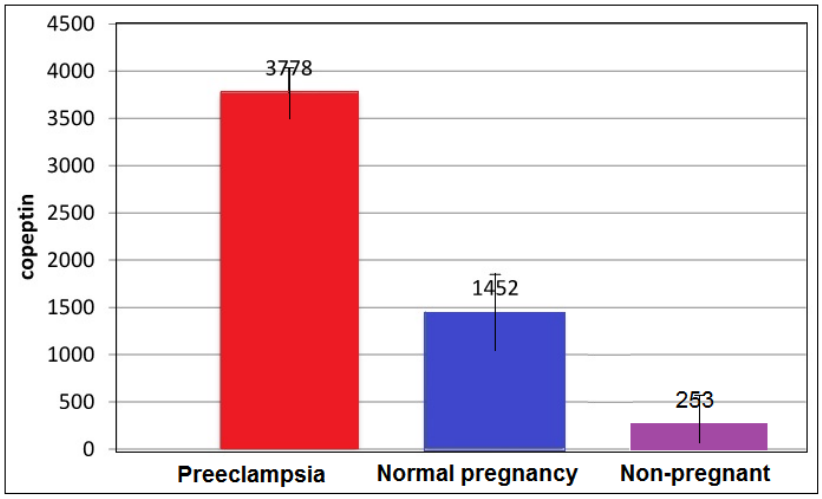

Figure 1: Serum copeptin levels in pg/ml means±SD in the studied groups (n=60).

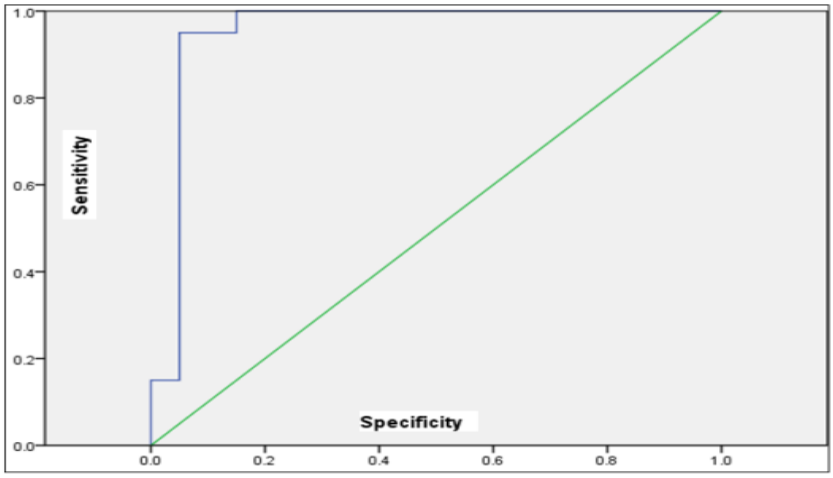

Figure 2: Receiver operating characteristic (ROC) curve for serum copeptin levels in pg/ml, as a marker for kidney injury in preeclampsia.

DISCUSSION

Copeptin is a peptide, that is co-secreted with the anti-diuretic hormone (ADH), also known as arginine vasopressin (AVP), from the hypothalamus upon hemodynamic or osmotic stimuli. Unlike the AVP, copeptin is stable in serum and plasma and can easily be measured as a marker for AVP secretion[14].

This case-control study was conducted to evaluate the role of serum copeptin in the diagnosis of kidney injury in pregnant women with preeclampsia.The sample included 60 women: 20 pregnant with preeclampsia, 20 with normal pregnancy, and 20 healthy non-pregnant control.We observed that serum copeptin levels were significantly higher in pregnant women with preeclampsia than in females with normal pregnancy than in healthy non-pregnant females.

This is in agreement with[7], who found that the plasma copeptin level was higher in women with preeclampsia compared to normotensive women, and this increase was related to the severity of the disease. The chronic psychological stress that causes activation of the hypothalamic-pituitary-adrenal axis, may explain the association between serum copeptin levels and preeclampsia.

This is also in line with[15], who mentioned that the mean copeptin level was more than three

times higher in women with preeclampsia than in the control. Other researchers [11] found that serum copeptin was higher in pregnant women with preeclampsia, but not elevated in other pregnancy complications, such as gestational diabetes mellitus, gestational hypertension, or preterm birth.

Chronic infusion of AVP during pregnancy leads to the development of pre-eclampsia [6]and AVP secretion is increased from the 6th week of pregnancy in women who develop preeclampsia later[16].

The increased levels of serum copeptin in normal pregnant women, who are not hypertensive raises questions as regards its other possible roles, apart from those related to AVP. The levels of circulating platelet-bound-AVP in normal pregnancy are normal or decreased, which may be explained by sodium retention, increased metabolic clearance by vasopressinase, or absence of non-osmotic stimulation[17].

Other researchers [18]concluded that serum copeptin is increased in pregnant women who may develop preeclampsia, but not with other pregnancy complications; gestational diabetes, hypertension, and preterm labor.This may make it important to measure the serum copeptin routinely and regularly throughout any pregnancy, to detect early pre-eclampsia, especially when it keeps rising. We still need to answer a question, whether serum copeptin measurement early in pregnancy, could detect kidney injury even when serum creatinine is still normal or before it starts to increase or not?

We observed that serum copeptin levels have a positive correlation with the body mass index (BMI), blood pressure, HbA1C, serum creatinine, uric acid, bilirubin, ALT and AST, urinary Na, blood urea, and 24 hours urinary proteins, and a negative correlation with the GFR and creatinine clearance.

This is in agreement with[15]who found that in women with preeclampsia, copeptin correlated positively with systolic and diastolic blood pressure, proteinuria, creatinine, AST, ALT, and total bilirubin.An explanation for the increased urine albumin in the preeclamptic group was suggested by[19],who stated that renal vasospasm in preeclampsia leads to decreased renal perfusion, which leads to decreased glomerular filtration rate and glomerular lesion.

The strong correlation of serum copeptin with many other tests for kidney function, strongly suggests the role of serum copeptin in kidney injury. This cannotbe explained by its co-secretion with the AVP alone, because in normal pregnancy serum copeptin increases, while the AVP is supposed to be normal or even decreased. Thus, we suggest another possible role for serum copeptin in kidney injury or preeclampsia, other than its co-secretion with the AVP.

Other studies showed that serum copeptin is increased with the reduction of the GFR[20].This is in line with the current study, as regards the increased serum copeptin in preeclamptic patients, with decreased GFR. But this does not explain the reason why despite the slight increase in the GFR in normal pregnancy, serum copeptin levels increased in normal pregnancy than normal control. Why serum copeptin levels do not decline in normal pregnancy, with the supposed increased excretion due to the high GFR?

The receiver operating characteristic (ROC) curve for serum copeptin level in pg/ml, as a marker for kidney injury in preeclampsia was studied; area under the curve (AUC) was (0.90), 98% confidence interval (CI%) (0.87-1.0), cutoff point (3100 pg/ml), sensitivity (95.0%), specificity (85.0%), positive predictive value (PPV) (86.3%), negative predictive value (NPV) (94.4%), and accuracy (90.0%).

Using the multivariate regression analysis for serum copeptin levels versus laboratory investigations (quantitative) showed that serum copeptin is independently correlated to BUN, urinary protein, urinary sodium, FBS, and HbA1C, but not with serum creatinine, total serum protein, serum albumin, creatinine clearance or GFR.

Using the multivariate analysis for serum copeptin levels as an independent variable (Qualitative, divided at the cutoff) showed that serum copeptin is independently correlated to serum creatinine, BUN, urinary protein, urinary sodium, GFR, serum albumin, and HbA1C, but not with total serum protein, creatinine clearance, or FBS.

This is in agreement with[7], who found that copeptin is a predictive biomarker for preeclampsia, as early as the first trimester, and it might be useful in the assessment of the severity of the disease. Other studies showed that copeptin is a potent predictor of preeclampsia and may play a role in its pathogenesis [21]

In addition, [18]found that increased copeptin levels were higher in severe preeclampsia than mild preeclampsia, and when they infused AVP throughout pregnancy it caused preeclampsia. Thus, AVP and copeptin may play a role in the pathogenesis of preeclampsia [16].

Previous studies concluded that a higher baseline concentration of plasma copeptin predicts kidney function decline in patients with autosomal

dominant polycystic kidney disease [22],while other studies have linked copeptin to the development of end-stage kidney disease [23].

Other researchers[8]found that the plasma copeptin level was independently and positively associated with chronic kidney disease progression and that a deleterious effect of high vasopressin on renal health is suggested.Recent studies showed that an increased level of copeptin independently predicts kidney injury and the risk of progression of chronic kidney disease (CKD) and other renal diseases [24].

The GFR increases by 40%-50% in normal pregnancy, and normal-range serum creatinine could reflect a significant decline in renal function in a pregnant woman[25] .Copeptin is stable both in serum and plasma at room temperature, can be easily measured, and its results can be available within an hour [26]

Increased water intake caused a significant decrease in plasma copeptin concentration, and this may cause improvement in renal functions[27].Increased serum copeptin and AVP may increase GFR and proteinuria, leading to a deterioration of kidney function, and their blockage may be beneficial in preventing the development of CKD [28].

Thus, serum copeptin can predict the outcome, and serve as a sensitive indicator of early decline in renal function, particularly when combined with the GFR estimation, or other screening methods. Serum copeptin is an independent risk factor of the reduction in renal function, and when combined with microalbuminuria, they are useful for early diagnosis of diabetic nephropathy [29]&[30].

This study showed that serum copeptin is independently related to other markers of kidney injury. The increase of serum copeptin in normal pregnancy raises questions as regards other possible functions apart from the AVP. The cause of increased serum copeptin should be studied, whether it is related to its increased secretion with the AVP or decreased excretion due to decreased GFR. Early assessment of serum copeptin, with follow up of its level, could predict preeclampsia. Further studies are required to assess the possibility of preventing or improving preeclampsia with medications blocking serum copeptin harmful effects.

CONCLUSION

Serum copeptin can be used as a marker for the diagnosis of kidney injury in preeclampsia, with high sensitivity and specificity. Also, serum copeptin is independently related to BUN, urinary protein, and urinary sodium, and can be used as an early indicator for deterioration of kidney function.

Conflicts of Interest: Nothing to declare.

Financial Disclosures: Nothing to declare.

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