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EVALUATION OF COPEPTIN HORMONE FUNCTION IN CHRONIC RENAL FAILURE STAGES AND DIALYSIS

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ABSTRACT

The predominance of constant kidney infection (CKD) is expanding around the world. The identification of variables contributing to its movement is critical for planning preventive measures. Past ponders have proposed that chronically high vasopressin is pernicious to renal function. Here, we assessed the affiliation of plasma copeptin, a surrogate of vasopressin, with the rate of CKD within the common populace. CPP increased in CRF, and more deterioration directly related to the degree of renal failure. Conclusions: rise copeptin levels are connected with the development and the progression of CKD in the general population. Interferences studies are needed to assess the potential beneficial effect on kidney health in the general population of decrease vasopressin secretion or action

Keywords: CKD (chronic kidney disease), CPP (copeptin)

Introduction

The predominance of ceaseless kidney malady (CKD) is expanding around the world (Levin *et al.,.;* 2017.). It influences the same number of as 10%–15% of the populace and is currently perceived as a worldwide general medical issue. CKD is related with weakened personal satisfaction, decreased future, and expanded danger of end-stage renal sickness (ESRD) and extreme cardiovascular occasions (Clark WF *et al.,* 2016). The consideration for patients with CKD improved particularly in the most recent decades, however there is as yet a critical need to recognize modifiable elements that are driving the expansion of CKD frequency and commonness. It is currently perceived that satisfactory hydration is basic to kidney wellbeing (Levin A, *et al.,* 2017.). Repetitive parchedness and warmth stress coming about because of outrageous word related conditions were appeared to cause subclinical kidney, prompting perpetual kidney harm after some time (Glaser J *et al.,* 2016). This clinical condition known as Mesoamerican nephropathy was reported among youthful horticultural specialists in Central America (Glaser *et al.,* 2016). Results from a couple of observational examinations in everyone recommend that high water admission may effectsly affect restricting the decrease of kidney work after some time (Wesseling *et al.,* 2014). Lack of hydration and a humble height of plasma osmolality are significant boosts for vasopressin (or antidiuretic hormone) emission by the neurohypophysis (Strippoli *et al.,* 2011) .Vasopressin is cosecreted into the blood in an equimolar sum with copeptin, the C-terminal part of the pre-favorable to vasopressin peptide. Copeptin is simpler to measure (Sontrop JM *et al.,* 2013) and is a satisfactory substitute of vasopressin (Szinnai G, *et al.,* 2007). Exploratory proof backings a causal and direct function of vasopressin in the turn of events and exacerbation of CKD through V2 receptor initiation (Roussel *et al.,* 2014). As vasopressin emission can be adjusted by water admission, and its activities hindered by nonpeptide specific receptor opponents (vaptans), (Morgenthaler *et al.,* 2006) the vasopressin framework could be a likely remedial objective for the counteraction and treatment of CKD (Bankir *et al.,* 2013) Positive relationship of copeptin with markers of kidney work or with kidney work decrease were seen in populaces with CKD or at high danger of CKD, for example, individuals with diabetes (Boertien *et al.,* 2013, patients with autosomal prevailing polycystic kidney malady (ADPKD) (Boertien *et al.,* 2013), and kidney relocate beneficiaries. Nonetheless, just restricted planned information are accessible on the relationship of plasma copeptin with the danger of new-beginning CKD in everyone (Heida *et al.,* 2017). Consequently, we attempted an individual-level pooled examination of 3 European partners from everybody to survey the relationship of copeptin with the frequency of different kidney work related results. As circling levels of vasopressin and copeptin (Roussel *et al.,* 2014) are as much as half higher in men than in ladies, we likewise evaluated collaborations of sex and copeptin in these affiliations.

Material and Methods

The study was case – controlled in design .We selected the patients as they presented 176 patients with undergoing chronic kidney disease mean age of the sample was 64.86 (±14.89) years with minimum and maximum values of 30 and 60 years.

Stage I : 20 patients (7 male, 13 female), Stage II : 32 patients (21 male, 11 female), Stage III : 32 patients (20 male, 12 female), Stage I V :32 patients (20 male, 12female), Dialysis : 44 patients (30 male , 14 female), Control : 16 patients (10 male, 6 female)

Compared with 16 healthy subjects (10 male and 6 female) as control group. Were all admitted to the Ibn Sina center for dialysis in Baquba teaching hospital for the period. Fully informed consent was obtained from patients and controls. Copeptin was determined in serum of all subjects by using a commercially ELISA Micro wells kit (from LDN, Germany).

Statistical analysis

Analysis of data was carried out using the available statistical package of SPSS-25 (Statistical Packages for Social Sciences-version 25). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values). The significance of difference of different means (quantitative data) were tested using Students-t-test for difference between two independent means or Duncan test for difference of any two independent means, or ANOVA test for difference among more than two independent means. The significance of difference of different percentages (qualitative data)

Results

The study showed that the stage III was the highest rang compared to the rest of the stages (61.85±41.09) pg /ml), During hemodialysis, copeptin decreased the rate was (37.38±14.23) pg /ml .As for the stage IV(30.67±12.51 pg /ml) and stage I (30.70 ± 12.65 pg /ml)), whilst the stage II was (26.83±3.00 pg /ml). The copeptin showed Significant (P<0.01) difference when compared it with dialysis and when compared with healthy control too, Figure 4.

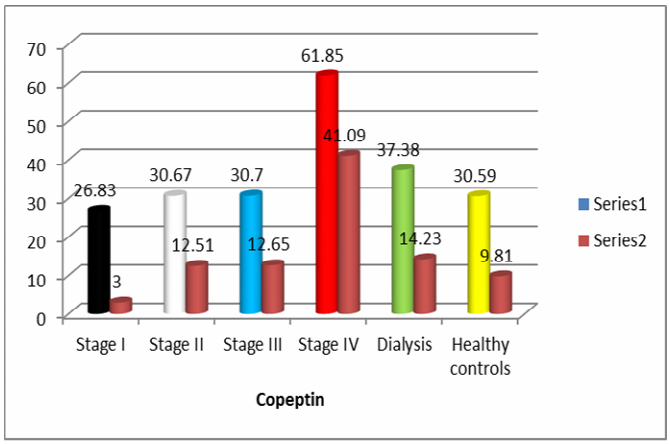

Fig. 4: Copeptin levels in all subgroups

Table 1: Comparison between difference groups in copeptin and kidney function

Groups	Mean ± SD			
	Copeptin (pg/ml)	Urea (mMol/L)	GFR (ml/min)	Creatinine (mMol/L)
Stage I	30.70±12.65 bc	4.54±1.56 d	104.00±27.26 b	60.82±7.34 de
Stage II	26.83±3.00 c	7.27±2.95 cd	75.71±8.35 c	92.55±15.28 d
Stage III	61.85±41.09 a	10.27±4.08 c	40.71±9.35 d	157.56±25.60 c
Stage IV	30.67±12.51 bc	18.60±9.70 b	22.15±4.21 de	263.80±48.77 b
Dialysis	37.38±14.23 b	22.57±9.73 a	9.83±2.43 e	547.44±105.50 a
Controls	30.59±9.81 bc	3.87±1.23 d	210.58±121.06 a	43.37±13.37 e
LSD value	9.291 **	3.704 **	31.954 **	31.954 **
Means having with the different letters in same column differed significantly. ** (P≤0.01).				

Urea level was higher in dialysis (22.57±9.73 mMol/L), than in control group (3.87±1.23 mMol/L) but it was higher than the control group in stage IV and III, II (18.60±9.70 mMol/L), (10.27±4.08 mMol/L), (7.27±2.95 mMol/L), Urea levels showed significant difference (p<0.01) amid two groups. The levels of Urea are shown in Fig. 1

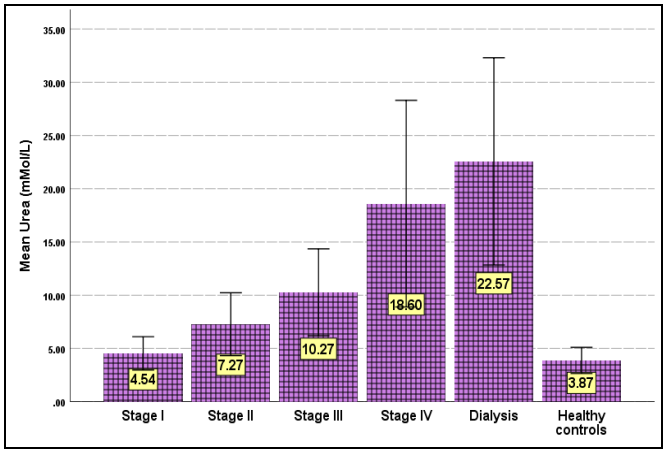

Fig. 1: Urea levels in all subgroups

Creatinine level was higher in dialysis (547.44±105.50 mMol/L), than in control group(43.37±13.37 mMol/L) but it was higher than the control group in stage IV and III, II (263.80±48.77 mMol/L), (157.56 ± 25.60 mMol/L), (92.55±15.28 mMol/L), Creatinine levels showed significant difference (p< 0.01) amid two groups. The levels of Creatinine are shown in Fig. 2.

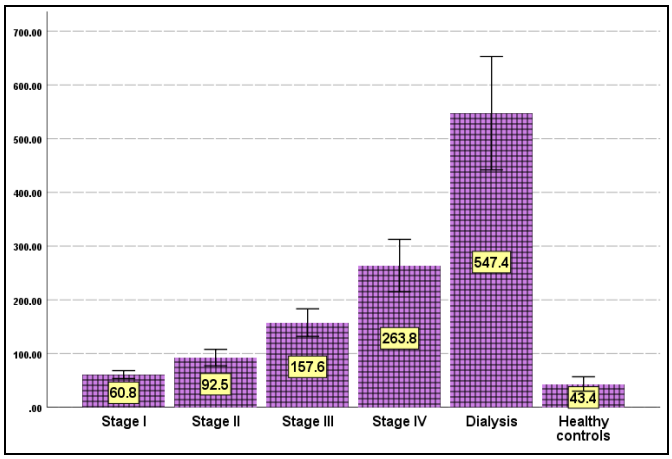

Fig. 2: Creatinine levels in all subgroups

The glomerular filtration rate GFR was the lowest in the dialysis group (9.83±2.43 mMol/L), and in the stage IV(22.15 ± 4.21 mMol/L) compared to the control group (210.58 ± 121.06 mMol/L) GFR levels showed significant difference (p< 0.01) amid two groups. The levels of GFR are shown in Fig. 3

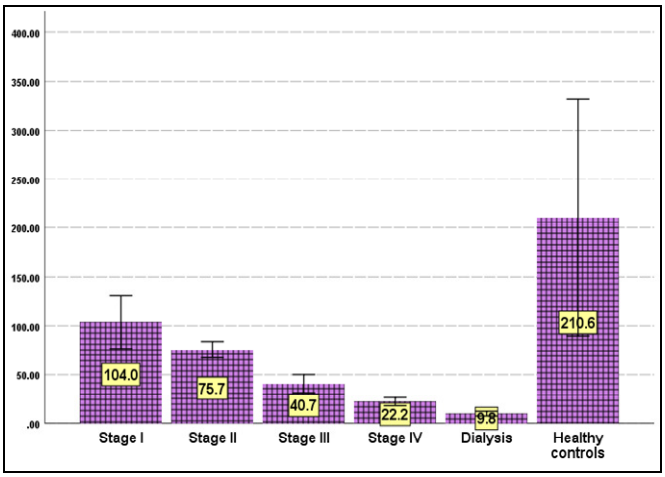

Fig. 3: GFR levels in all subgroups

Discussion

Our current data extend our previous finding that increased levels of **copeptin** independently predict decline in eGFR (Tasevska *et al.,* 2016) and suggest that copeptin can be used to identify individuals at higher risk for development of CKD. Whether the relationship between VP (measured as copeptin) and disease development is causal or due to covariation is unknown. Together with previous experiments in humans and animals, showing progressive renal function decline during VP exposure (Bouby *et al.,* 1999) as well as beneficial effects on kidney function as a result of genetic lack of VP(Bardoux .P *et al.,* 1999), VP receptor antagonism , and increased water intake (Perico *et al.,* 2009), our current data point at a possible causal role of elevated VP in the progression of CKD. Assuming causality between VP and CKD development, lowering of circulating VP level, for example by increased water intake or pharmacological manipulation, would represent a promising treatment target.

Our data further implicate beneficial effects of lower circulating VP concentrations/ increased hydration in the progression of specific other renal diseases. The exact mechanisms regarding the relationship between copeptin, albuminuria and GFR are not known but two mechanisms were suggested. First, as copeptin is cleared by kidney excretion, copeptin levels would tend to increase as kidney function decreases. Second, in patients with lower kidney function, more copeptin is released, because the AVP system is activated due impaired urine concentrating capacity to maintain water homeostasis (Zittema *et al.,* 2012). Longitudinal studies in humans have shown that plasma copeptin levels increase before eGFR decreases (Ponte *et al.,* 2015). Studies in the 5/6 nephrectomized rat model suggested that increased water intake decreases circulating AVP levels and slows down the progression of kidney disease (Bouby *et al.,* 1990). The relationship between copeptin and hypertension is also worth to mention. Most of the studies have shown a positive association with copeptin and hypertension recent evidence suggests that elevated blood pressure is associated with increased copeptin levels. For example, in hypertensive adolescents, copeptin levels were higher in normotensive adulterants. Not only office blood pressure but ambulatory blood pressures (both systolic and diastolic) were associated with copeptin levels (Tenderenda-Banasiuk *et al.,* 2014). In another recent study, the relationship between copeptin and resistant hypertension were investigated. Baseline plasma copeptin concentration was positively associated with male sex, plasma osmolality, BP, and negatively with glomerular filtration rate. It was higher in the resistant hypertension than in the controlled blood pressure group [geometric mean 5.7 (confidence interval 95% 5.1–6.4) vs. 2.9 (2.3–3.9) fmol/ml, adjusted $P < 0.0001$) (Mendes *et al.,* 2016) In fact older studies have already suggested that AVP may have a role in development of hypertension (Bakris *et al.,* 1997). Several lines of evidence suggest a role of copeptin in hypertension. One of the suggested mechanisms is the local tissue Renin Angiotensin Aldosterone System (RAAS) activation in supraoptic and paraventricular nuclei which stimulates the production and release of arginine vasopressin. Second mechanisms involve the vasoconstriction. This vasoconstriction is due to both direct effects on smooth muscle cells and by indirectly increasing renin secretion (Tenderenda-Banasiuk *et al.,* 2014). Third mechanism is the effect of copeptin on increased tubular sodium retention (Perucca *et al.,* 2008) Thus copeptin may be common marker for essential hypertension and kidney disease. In conclusion, our study demonstrates that high copeptin levels are associated with the development and the progression of CKD in the general population. Our results argue for the relevance in human pathology of the experimental data obtained in animal models, suggesting a causal link between vasopressin and kidney disease. Together, they provide a strong basis to design future intervention studies that assess the effect of reducing vasopressin secretion, and the potential role of high water intake, in the prevention of kidney disease in the general population. Our study demonstrates that high copeptin levels are associated with the development and the progression of CKD in the general population. A few studies investigated the impact of high copeptin levels on renal function in people with diabetes (Velho *et al.,* 2016), (Boertien *et al.,* 2013), and co-workers analysed data from 1328 patients with type 2 diabetes of relatively recent onset (4 years of median duration of diabetes) from the Dutch ZODIAC prospective study (Boertien *et al.,* 2013).

They reported the higher quartile of baseline plasma copeptin to be associated with a faster decline in eGFR during a follow-up of 6.5 years. In a Swedish study of people with newly diagnosed type 2 diabetes from the Skaraborg Diabetes Register, plasma copeptin was positively associated with eGFR decline at re-examination after 12 years of follow-up (Pikkemaat *et al.,* 2015). So It has been suggested that high copeptin levels observed in people with CKD might merely reflect a decline in GFR. Both vasopressin and copeptin are small-sized molecules and thus could be subjected to renal clearance. However, results from a recent investigation suggest that renal clearance is not the predominant factor in the degradation of circulating copeptin (43). Moreover, strong experimental data have been accumulated in the last decades supporting a direct causal role for vasopressin in the pathogenesis of CKD (Bankir *et al.,* 2013). Moreover, copeptin is also known as a stress hormone and may serve as a marker of individual stress. Copeptin is even more reliable for the stress level determination than cortisol, due to its higher stability (Katan *et al.,* 2008). In one of the largest studies conducted by (Enho¨ rning *et al.,* 2010) copeptin was the independent predictor for future risk of diabetes mellitus (DM). In conclusion the authors also suggest that their findings may be relevant for risk evaluation and contribute to a new

therapeutic approach in the prevention and treatment of diabetes. Similar results were also reported with respect to metabolic syndrome (MetS), where elevated plasma copeptin concentration have significantly correlated with MetS independently, as well as with high fat intake and low physical activity (Enho¨ rning *et al.,* 2011). Several publications have appeared in recent years documenting the relation between copeptin and renal outcomes in patients with type 2 diabetes. As reported by (Boertien *et al.,* 2013). baseline copeptin levels have correlated with albumin/creatinine ratio and eGFR in patients with type 2 diabetes mellitus. This relation was only observed among patients not treated with renin–angiotensin– aldosteron system inhibitors. Similar results have been also revealed by (Velho *et al.,* 2016). in the long term follow-up study concerning patients with type 2 diabetes. In this cohort plasma copeptin was significantly associated with severe renal outcome and albuminuria, independently of age, duration of diabetes, hypertension and baseline levels of eGFR

Conclusion

In this study CPP hormone was increased in chronic renal failure disease and more elevation was seen at the end stage of renal disease and

References

Levin A, *et al.,* Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. Lancet. 2017; 390(10105): 1888– 1917.

Clark, W.F.; Sontrop, J.M.; Huang, S.H.; Moist, L.; Bouby, N.; Bankir, L. (2016). Hydration and Chronic Kidney Disease Progression: A Critical Review of the Evidence. Am J Nephrol. 43(4):281–292.

Glaser, J. *et al.* (2016). Climate Change and the Emergent Epidemic of CKD from Heat Stress in Rural Communities: The Case for Heat Stress Nephropathy. Clin J Am Soc Nephrol. 11(8): 1472–1483.

Wesseling C. *et al.* (2014). Resolving the enigma of the mesoamerican nephropathy: a research workshop summary. Am J Kidney Dis. 63(3): 396–404.

Strippoli, G.F.; Craig, J.C.; Rochtchina, E.; Flood, V.M.; Wang, J.J.; Mitchell, P. (2011). Fluid and nutrient intake and risk of chronic kidney disease. Nephrology (Carlton) 16(3): 326–334.

Sontrop, J.M. *et al.,* (2013). Association between water intake, chronic kidney disease, and cardiovascular disease: a cross-sectional analysis of NHANES data. Am J Nephrol. 37(5): 434–442.

Morgenthaler, N.G.; Struck, J.; Alonso, C.; Bergmann, A. (2006). Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. Clin Chem.; 52(1):112–119.

Heida, J.E. *et al.,* (2017). Comparison of ex vivo stability of copeptin and vasopressin. Clin Chem Lab Med.; 55(7): 984–992.

Szinnai, G. *et al.,* (2007). Changes in plasma copeptin, the c-terminal portion of arginine vasopressin during water deprivation and excess in healthy subjects. J Clin Endocrinol Metab. 92(10): 3973–3978

Roussel, R. *et al.,* (2014). Comparison between copeptin and vasopressin in a population from the community and in people with chronic kidney disease. J Clin Endocrinol Metab. 99(12): 4656–4663.

Bankir, L.; Bouby, N.; Ritz, E. (2013). Vasopressin: a novel target for the prevention and retardation of kidney disease? Nat Rev Nephrol. 9(4): 223–239.

Wang, C.J.; Grantham, J.J. and Wetmore, J.B. (2013). The medicinal use of water in renal disease. Kidney Int.; 84(1): 45–53.

Boertien, W.E. *et al.,* (2013). Copeptin, a surrogate marker for arginine vasopressin, is associated with declining glomerular filtration in patients with diabetes mellitus (ZODIAC-33). Diabetologia. 56(8):1680–1688.

Bouby, N.; Hassler, C. and Bankir, L. (1999). Contribution of vasopressin to progression of chronic renal failure: study in Brattleboro rats. *Life sciences*, 65(10): 991-1004.

Tasevska, I.; Enhörning, S.; Christensson, A.; Persson, M.; Nilsson, P.M. and Melander, O. (2016). Increased levels of copeptin, a surrogate marker of arginine vasopressin, are associated with an increased risk of chronic kidney disease in a general population. American Journal of Nephrology, 44(1): 22–28.

Bardoux, P.; Martin, H.; Ahloulay, M.; Schmitt, F.; Bouby, N.; Trinh-Trang-Tan, M. M.; and Bankir, L. (1999). Vasopressin contributes to hyperfiltration, albuminuria, and renal hypertrophy in diabetes mellitus: study in vasopressin-deficient Brattleboro rats. Proceedings of the National Academy of Sciences, 96(18): 10397-10402.

Perico, N.; Zoja, C.; Corna, D.; Rottoli, D.; Gaspari, F.; Haskell, L. and Remuzzi, G. (2009). V1/V2 Vasopressin receptor antagonism potentiates the renoprotection of renin–angiotensin system inhibition in rats with renal mass reduction. Kidney international, 76(9): 960-967.

Zittema, D.; Boertien, W.E.; van Beek, A.P.; Dullaart, R.P.F.; Franssen, C.F.M.; de Jong, P.E.; Meijer, E. and Gansevoort, R.T. (2012). Vasopressin, copeptin, and renal concentrating capacity in patients with autosomal dominant polycystic kidney disease without renal impairment. Clinical Journal of the American Society of Nephrology, 7(6): 906–913.

Ponte, B.; Pruijm, M.; Ackermann, D.; Vuistiner, P.; Guessous, I.; Ehret, G.; Alwan, H.; Youhanna, S.; Paccaud, F.; Mohaupt, M.; Péchère-Bertschi, A.; Vogt, B.; Burnier, M.; Martin, P.Y.; Devuyst, O. and Bochud, M. (2015). Copeptin is associated with kidney length, renal function, and prevalence of simple cysts in a population-based study. Journal of the American Society of Nephrology, 26(6): 1415–1425.

Bouby, N.; Bachmann, S.; Bichet, D.; & Bankir, L. (1990). Effect of water intake on the progression of chronic renal failure in the 5/6 nephrectomized rat. American Journal of Physiology-Renal Physiology, 258(4): F973-F979.

Tenderenda-Banasiuk, E.; Wasilewska, A.; Filonowicz, R.; Jakubowska, U. and Waszkiewicz-Stojda, M. (2014). Serum copeptin levels in adolescents with primary hypertension. Pediatric Nephrology, 29(3): 423–429.

Bakris, G.; Bursztyn, M.; Gavras, I.; Bresnahan, M.; & Gavras, H. (1997). Role of vasopressin in essential hypertension: Racial differences. Journal of Hypertension, 15(5): 545–550.

Perucca, J.; Bichet, D.G.; Bardoux, P.; Bouby, N. and Bankir, L. (2008). Sodium excretion in response to vasopressin and selective vasopressin receptor

antagonists. Journal of the American Society of Nephrology, 19(9): 1721–1731.

Velho, G.; El Boustany, R.; Lefèvre, G.; Mohammedi, K.; Fumeron, F.; Potier, L.; Bankir, L.; Bouby, N.; Hadjadj, S.; Marre, M.; & Roussel, R. (2016). Plasma copeptin, kidney outcomes, ischemic heart disease, and all-cause mortality in people with long-standing type 1 diabetes. *Diabetes Care*, 39(12): 2288–2295.

Boertien, W.E.; Riphagen, I.J.; Drion, I. and Alkhalaf, A. (2013). Copeptin , a surrogate marker for arginine vasopressin , is associated with declining glomerular filtration in patients with diabetes mellitus (ZODIAC-33). 1680–1688.

Pikkemaat, M.; Melander, O. and Bengtsson Boström, K. (2015). Association between copeptin and declining glomerular filtration rate in people with newly diagnosed diabetes. the Skaraborg Diabetes Register. Journal of Diabetes and Its Complications, 29(8): 1062–1065.

Bankir, L.; Bouby, N. and Ritz, E. (2013). Vasopressin: A novel target for the prevention and retardation of kidney disease? Nature Reviews Nephrology, 9(4): 223–239.

Katan, M.; Morgenthaler, N.; Widmer, I.; Puder, J. J.; Konig, C.; Muller, B.; & Christ-Crain, M. (2008). Copeptin, a stable peptide derived from the vasopressin precursor, correlates with the individual stress level. Neuroendocrinology Letters, 29(3): 341-346.

Enhörning, S.; Wang, T.J.; Nilsson, P.M.; Almgren, P.; Hedblad, B.; Berglund, G. and Groop, L. (2010). Plasma copeptin and the risk of diabetes mellitus. Circulation, 121(19): 2102.

Enho, S.; Struck, J.; Wirfa, E.; Hedblad, B.; Morgenthaler, N.G. and Melander, O. (2011). Plasma Copeptin , A Unifying Factor behind the Metabolic Syndrome. 96(July), 1065–1072.

Mendes, M.; Dubourg, J.; Blanchard, A.; Bergerot, D.; Courand, P.Y.; Forni, V.; Frank, M.; Bobrie, G.; Menard, J.; Azizi, M. (2016). Copeptin is increased in resistant hypertension. J Hypertens. 34: 2458–64.