Section A -Research paper

Role of Plasma Copeptin as a Diagnostic biomarker for Diabetic Nephropathy and Different Diseases: Review Article

Abdel Monem Fathy Zeid [1], Atef Gouda Hussien [2] , Ahmed Mohamed Ramadan Mesalam[3], Alhoussein Alsayed Abdelaal [1]

[1] Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt
[2] Medical Biochemistry Department, Faculty of Medicine, Zagazig University, Egypt
[3] Internal medicine department, National Institute of Diabetes and Endocrinology, Egypt

Corresponding author: Ahmed Mohamed Ramadan Mesalam
Email: ahmedramadan1492@gmail.com , **Tel**: 01019852993

Article History: Received: 16.05.2023 **Revised:**04.06.2023 **Accepted:** 28.06.2023

Abstract:

Diabetic nephropathy (DN) accounts for 50% of end stage renal diseases (ESRD). It is mandatory to search for new prognostic markers like plasma copeptin that could facilitate early diagnosis, treatment and wise planning of treatment strategy. Little studies were performed on the relation between Plasma copeptin and diabetic nephropathy, yet this relationship is unclear and needs further investigations.

Keywords: Copeptin, biomarker, Diabetic, Nephropathy.

DOI: 10.53555/ecb/2023.12.1090

Introduction:

Copeptin (also known as CT-pro AVP) is a 39-amino acid-long peptide derived from the C-terminus of pre-pro-hormone of arginine vasopressin, neurophysin II and copeptin (Land H, et al., 1982). Arginine vasopressin (AVP), also known as the antidiuretic hormone (ADH), is encoded by the AVP gene and is involved in multiple cardiovascular and renal pathways and abnormal level of AVP are associated with multiple diseases **(1).** So, measurement of AVP is useful, but is not commonly used in clinical practice because of its very short half-life making it difficult to quantify. In contrast, copeptin can be immunologically tested easily and therefore can be used as a vasopressin surrogate bio-marker **(2).**

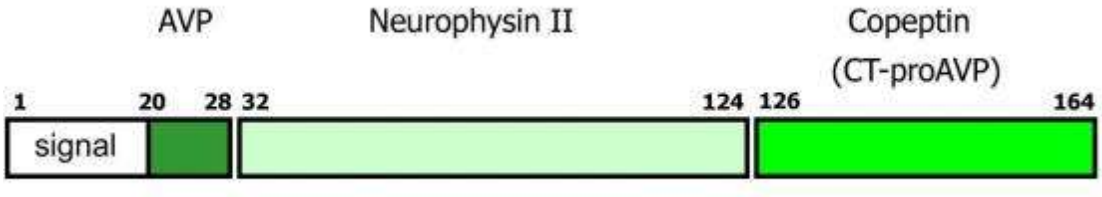

Figure (1): Cartoon of the 164-amino acid peptide precursor, preprovasopressin. Shows the signal sequence (white), AVP (dark green), neurophysin II (pale green) and copeptin (light green). Copeptin (CT-proAVP) is the C-terminal part of proAVP. Numbers indicate amino acids of the human protein. AVP: arginine vasopressin; CT-proAVP: C-terminal proAVP; signal: signal peptide. **(3).**

Synthesis and secretion:

Copeptin is a 39-amino acid-long, glycosylated peptide **(3).** It is synthesized mainly in the paraventricular neurons of the hypothalamus and in the supra optic nucleus**(1).**

During axonal transport, pre-pro-AVP is proteolytically cleaved into vasopressin, neurophysin II and copeptin **(4).** These molecules are then stored in secretory granules in the posterior pituitary and released upon osmotic or non-osmotic (hemodynamical; stress-related) stimuli **(1).**

Function:

Once secreted into the bloodstream, there is no known biological role for copeptin. However, when pre-pro-vasopressin is processed during the axonal transport, copeptin may contribute to the 3D folding of vasopressin **(1).**

Surrogate vasopressin marker:

The size and half-life of copeptin allow an easier immunological testing, compared to vasopressin, and so copeptin is proposed as a reliable AVP surrogate **(2).** The clinical interest in copeptin testing is closely linked to the pathophysiological pathways in which vasopressin is involved: polydipsia-polyuria syndrome, hyponatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH) as well as heart failure and acute coronary syndrome **(5).**

In blood:

The concentration of copeptin in the blood circulation ranges from 1 to 12 pmol/L in healthy individuals **(5).** The levels of copeptin are slightly higher in men than in women regardless of the age **(5).** In response to serum osmolality fluctuations, the kinetics of copeptin are comparable to those of vasopressin **(5).**

For example, patients with an electrolyte disorder such as diabetes insipidus with very low vasopressin concentrations also have very low copeptin concentrations in blood plasma **(6).** On the other hand, patients with syndrome of inappropriate antidiuretic hormone secretion have high concentrations of both vasopressin and copeptin **(7).**

Diabetic Nephropathy:

Arginine vasopressin (AVP) is one of the main hormones of the hypothalamic–pituitary–adrenal axis, and it is mainly stimulated by hyperosmolarity. AVP plays deleterious renal effects, inducing hypertension, glomerular hyperfiltration, albuminuria, and glomerulosclerosis, whereas its inhibition, by drinking water or by V2 antagonism, led to a renoprotection. The direct measurement of AVP in humans is problematic, due to its bond with platelets and its instability in isolated plasma **(8).**

Copeptin, the stable COOH-terminal portion of the precursor of AVP, is an easily measurable surrogate marker of vasopressin. Copeptin is released into the circulation from the posterior pituitary gland in equimolar amounts with AVP. In many studies copeptin mimed AVP levels and its behavior, modified by plasma osmolality, stress, and various disease states, revealing some of the various physiologic and pathophysiologic conditions associated with increased or decreased AVP **(8).**

It was demonstrated that high copeptin concentration was strongly associated with the risk of severe renal outcomes (doubling of plasma creatinine concentration and/or end-stage renal disease) in DM patients, independently of relevant covariates such as age, duration of diabetes, blood pressure and baseline levels of glycated haemoglobin, urinary albumin excretion (UAE), and eGFR**(9).**

An increasing body of experimental, pharmacological and epidemiological data supports a causal role of vasopressin (or antidiuretic hormone) in the development and progression of chronic kidney disease (CKD) **(10).** Plasma copeptin, the COOH-terminal portion of pre-pro vasopressin and a surrogate bio-marker of vasopressin, was shown to be positively associated with the decline in kidney function in the general population **(11).**

In different diseases:

Cardiogenic shock:

High concentrations of vasopressin during cardiogenic shock have been widely described. It has been shown that the kinetics of copeptin are similar to vasopressin in that context **(12).**

Heart failure:

The prognostic value of vasopressin for prediction of outcome in patients with heart failure has been known since the 1990s. Patients presenting with high levels of vasopressin have a worsened outcome**(13).**

Acute coronary syndrome:

One of the most common and deadly health problems in the world is acute coronary syndromes (ACS), which occur when the blood flow to the heart is blocked**(14).**

To diagnose acute myocardial infarction (AMI), which is a type of ACS, doctors use ECG and cardiac biomarkers, mainly troponins **(15).** However, this method is not very fast or accurate, because troponins take time to appear in the blood

after the heart is damaged **(16)** and they can also be elevated for other reasons **(17).**

Therefore, there is a need for a better marker of AMI that can help doctors decide who needs urgent treatment. Some recent studies have suggested that copeptin, which is a part of a hormone called arginine vasopressin (AVP), could be such a marker.

Several studies have shown that copeptin is released very early during the onset of an acute myocardial infarction (AMI) **(18),** raising the question of its potential value in the diagnosis of AMI and particularly in ruling-out AMI **(19).**

Indeed, copeptin is released much earlier than troponin, given that copeptin is actively released from the hypothalamus, while troponin occurs in the bloodstream as a breakdown product from dying cardiomyocytes, **(20),** making the interpretation of their complementary kinetics a useful tool to rule-out AMI **(21).**

It has been shown that the combination of a negative result of troponin together with a negative result of copeptin can rule out AMI at emergency department presentation with a negative predictive value ranging from 95% to 100% **(19).**

Copeptin rises quickly in the blood within 30 minutes of chest pain in AMI patients **(22)** because it is released by the body as a stress response **(23).** Unlike troponin, copeptin does not require repeated blood tests to confirm or rule out AMI **(24)** and it may have higher sensitivity and specificity for diagnosing AMI in people who come to the emergency department.

Using copeptin to diagnose AMI could save lives and money by reducing the mortality rate and the cost of treatment. Copeptin also has a prognostic role after AMI, as it can predict the risk of death in AMI patients, independently of other factors such as cortisol and NT-proBNP **(25).**

Liver cirrhosis:

Cirrhosis is a condition that causes the liver to scar and malfunction. When cirrhosis gets worse, it can lead to serious complications and death **(26).** These complications are mainly caused by increased pressure in portal vein and abnormal blood circulation.

In the early stages of cirrhosis, when there are no symptoms, the blood pressure and blood volume are normal, but the resistance of the blood vessels is slightly lower **(27).** As cirrhosis progresses, symptoms appear and the blood circulation gets worse. In this stage, the blood vessels in the abdomen (splanchnic) become very dilated, which reduces the blood volume and pressure.

To compensate for this, the body activates hormones and nerves that constrict the blood vessels, such as renin-angiotensin-aldosterone system, and sympathetic nervous system.

In more advanced stages, another hormone called vasopressin (AVP) is also released. These hormones help maintain the blood pressure, but they also damage the

kidneys by making them retain salt and water, which leads to ascites and low sodium levels in the blood (hyponatremia). Eventually, the kidneys become very constricted and stop working properly (hepatorenal syndrome) **(28)**.

Therefore, AVP could be a potential marker of how severe cirrhosis is, how likely it is to cause symptoms and complications, and how long the patient will survive. However, measuring AVP levels in the blood is difficult because AVP is unstable and hard to detect **(29).**

Copeptin is a part of a larger molecule that contains AVP and is released from the brain along with AVP **(30).** Copeptin does not have any function in the body, but it is stable and easy to measure **(5).**

There is evidence that copeptin levels reflect AVP levels well, as they are correlated with each other **(31).** By measuring copeptin levels in the blood, we can estimate AVP levels and study their role in cirrhosis and its complications. We can also understand why AVP is released more in cirrhosis and what effects it has on the body.

Copeptin has been found to be related to survival in many diseases such as heart failure, chronic respiratory diseases and critically-ill patients **(32).**

Polycystic kidney disease:

The most prevalent hereditary kidney disorder and a major cause of kidney failure around the world is autosomal dominant polycystic kidney disease (ADPKD). The disease is influenced by vasopressin signaling, which regulates the growth and fluid accumulation of cysts in the kidneys through the activation of a cellular messenger called cAMP **(33).**

However, measuring vasopressin levels is challenging due to its instability and rapid degradation in blood. Therefore, a more reliable marker is copeptin, which is derived from the same precursor molecule as vasopressin and is released in equal amounts**(34).**

Previous studies with small sample sizes suggested that higher plasma copeptin levels are linked to worse outcomes and faster progression of ADPKD **(35, 36).**

More recently, a large-scale analysis of data from the TEMPO 3:4 trial confirmed that copeptin levels are associated with kidney function decline, kidney volume enlargement, and the efficacy of tolvaptan treatment **(37).**

Ischemic stroke:

Stroke is a major cause of death and disability worldwide **(38).** However, there is still no reliable blood test that can help diagnose and predict the outcome of stroke patients, despite the advances in clinical care and imaging techniques **(39).**

Several biomarkers have been proposed to help assess the risk of stroke patients **(40).** These include markers of inflammation (such as procalcitonin and mannose-binding lectin), atherosclerosis (such as adipocyte fatty acid-binding protein), stress response (such as copeptin

and cortisol), and heart function (such as the natriuretic peptide).

These markers have been consistently linked to worse outcomes after stroke and have added value to the existing risk factors. However, the quality and validity of these studies are questionable, and their results are not yet applicable to clinical practice **(40).**

Therefore, more research is needed on the most promising markers. Copeptin is one of them, as it has been shown to be useful for distinguishing stroke, TIA, and stroke-like conditions **(41).**

Moreover, high copeptin levels have been associated with poor prognosis after stroke and higher risk of TIA or stroke recurrence after a TIA episode **(39).**

Covid-19:

A new infectious disease called COVID-19, caused by a virus named SARS-CoV-2, emerged in China in late 2019 and spread around the world, becoming a global health crisis with high death rates and huge impacts on health care systems **(42).**

This virus belongs to the coronavirus β-family and can cause respiratory problems ranging from mild to severe in humans **(43).** Some people with COVID-19 have mild symptoms at first, but they can quickly deteriorate and develop life-threatening complications such as acidosis, breathing difficulties, sepsis and ARDS (acute respiratory distress syndrome), which can lead to death **(44).**

A new blood marker that can help evaluate the severity of COVID-19 could improve the management of symptoms, provide appropriate support and reduce mortality.

COVID-19 infection leads to stress, inflammation and pain. These conditions trigger the release of a hormone called arginine vasopressin (AVP) through the activation of the brain or the pituitary gland **(45).**

In addition, lung damage can cause low oxygen levels in the blood vessels of the lungs, which can reduce the blood flow to the heart and increase AVP levels **(46).**

Furthermore, inflammatory molecules such as IL-6 can stimulate the secretion of AVP without changes in blood osmolarity **(47).**

AVP is involved in stress adaptation, blood vessel constriction and blood volume regulation. It is also released in response to high blood osmolarity, low blood pressure, low oxygen levels, low blood volume, infections and acidosis **(48).**

Many hormones are involved in the stress adaptation process, including AVP and cortisol, which are activated by the brain and the pituitary gland. Copeptin is a good indicator of AVP levels because it is produced from the same precursor molecule as AVP and released in equal amounts. It is also more stable and easier to measure in blood samples **(49).**

The inflammation, pain, lung damage, changes in blood osmolarity and psychological stress associated with COVID-19 activate the stress adaptation

system and increase the levels of AVP/copeptin in the blood **(45).**

There is a significant difference in serum copeptin levels between severe and mild to moderate COVID-19 cases **(48),** as well as other respiratory infections such as pneumonia **(50),** where high copeptin levels are related to worse outcomes and prognosis**(51).**

The mechanism behind the syndrome of inappropriate antidiuretic hormone secretion in pneumonia and COVID-19 is not fully understood, but it may be due to a non-osmotic release of AVP caused by low blood volume, which activates the rennin–angiotensin–aldosterone system **(52).**

People infected with SARS-CoV-2 usually experience emotional, psychological and physical changes along with stress and pain**(52).** These changes can stimulate AVP/copeptin release through two pathways: one involving the brain and the pituitary gland and another involving the brain and CRH (corticotropin-releasing hormone) **(53).**

References:

1. **Acher R, Chauvet J, Rouille Y (2002):** "Dynamic processing of neuropeptides: sequential conformation shaping of neurohypophysial preprohormones during intraneuronal secretory transport". *Journal of Molecular Neuroscience. 18 (3): 223–8*
2. **Robertson GL, Mahr EA, Athar S, et al. (1973):** Development and clinical application of a new method for the radioimmunoassay of arginine vasopressin in human plasma. *The Journal of Clinical Investigation. 52(9):2340-2352. DOI: 10.1172/jci107423. PMID: 4727463; PMCID: PMC333039.*
3. **Land H, Schütz G, Schmale H, et al. (1982):** "Nucleotide sequence of cloned cDNA encoding bovine arginine vasopressin-neurophysin II precursor". Nature. 295 (5847): 299–303
4. **Repaske DR, Medlej R, Gültekin EK, et al. (1997):** Heterogeneity in clinical manifestation of autosomal dominant neurohypophyseal diabetes insipidus caused by a mutation encoding Ala-1-->Val in the signal peptide of the arginine vasopressin/neurophysin II/copeptin precursor. J Clin Endocrinol Metab. 82(1):51-6. doi: 10.1210/jcem.82.1.3660. PMID: 8989232.
5. **Morgenthaler LG, Struck J, Jochberger S, et al. (2008):** Copeptin: clinical use of a new biomarker. Trends Endocrinol Metab; 19:43–49.
6. **Katan M, Morgenthaler NG, Dixit KC, et al. (2007):** "Anterior and posterior pituitary function testing with simultaneous insulin tolerance test and a novel copeptin assay"
7. **Fenske W, Störk S, Blechschmidt A, et al. (2009):** "Copeptin in the differential diagnosis of hyponatremia"
8. **Lacquaniti A, Chirico V, Cernaro V, et al. (2016):** Apelin and Copeptin as Biomarkers of Kidney Disease. In: Patel V., Preedy V. (eds) Biomarkers in

Kidney Disease. Biomarkers in Disease: Methods, Discoveries and Applications. Springer, Dordrecht.

9. **Velho G, Bouby N, Hadjadj S, et al. (2013):** Plasma copeptin and renal outcomes in patients with type 2 diabetes and albuminuria. Diabetes Care. 36:3639–45.
10. **Roussel R, Matallah N, Bouby N, et al. (2015):** Plasma copeptin and decline in renal function in a cohort from the community: the prospective D.E.S.I.R. study. Am J Nephrol. 42(2):107–114. doi: 10.1159/000439061.
11. **Roussel R, Velho G, Bankir L (2017):** Vasopressin and diabetic nephropathy. Curr Opin Nephrol Hypertens.;26(4):311-318. doi: 10.1097/MNH.0000000000000335. PMID: 28403013.
12. **Arnauld E, Czernichow P, Fumoux F, et al. (1977):** "The effects of hypotension and hypovolaemia on the liberation of vasopressin during haemorrhage in the unanaesthetized monkey (Macaca mulatta)". Pflügers Archiv. 371 (3): 193–200
13. **Rouleau JL, Packer M, Moyé L, et al. (1994):** "Prognostic value of neurohumoral activation in patients with an acute myocardial infarction: effect of captopril". Journal of the American College of Cardiology. 24 (3): 583–91.
14. **Lüscher TF (2017):** Outcomes of acute coronary syndromes: Clinical presentation, gender, inflammation, and cell therapy. Eur. Heart J., 38, 125–129.
15. **Willemsen RT, Kietselaer BL, Kusters R et al. (2014):** Diagnostic tools for acute coronary syndrome (ACS): A challenge for general practitioners and cardiologists. Ned. Tijdschr. Geneeskd. 158, A8078.
16. **Bozkurt S, Kaya EB, Okutucu S, et al. (2011):** The diagnostic and prognostic value of first hour glycogen phosphorylase isoenzyme BB level in acute coronary syndrome. Cardiol. J., 18, 496–502.
17. **Shah ASV, Anand A, Strachan FE, et al. (2018):** High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: A stepped-wedge, cluster-randomised controlled trial. Lancet, 392, 919–928.
18. **Reichlin T, Hochholzer W, Stelzig C, et al. (2009):** "Incremental value of copeptin for rapid rule out of acute myocardial infarction". Journal of the American College of Cardiology. 54 (1): 60–8
19. **Maisel A, Mueller C, Neath SX et al. (2013):** "Copeptin helps in the early detection of patients with acute myocardial infarction: primary results of the CHOPIN trial (Copeptin Helps in the early detection Of Patients with acute myocardial INfarction)". Journal of the American College of Cardiology. 62 (2): 150–160.
20. **Boeckel JN, Oppermann J, Anadol R, et al. (2016):** "Analyzing the Release of Copeptin from the Heart in Acute Myocardial Infarction Using a

Transcoronary Gradient Model". Scientific Reports. 6: 20812

21. **Keller T, Tzikas S, Zeller T, et al. (2010):** "Copeptin improves early diagnosis of acute myocardial infarction". Journal of the American College of Cardiology. 55 (19): 2096–106
22. **Möckel M, Searle J (2014):** Copeptin-marker of acute myocardial infarction. Curr. Atheroscler. Rep., 16, 421.
23. **Katan, M., Christ-Crain, M. (2010):** The stress hormone copeptin: A new prognostic biomarker in acute illness. Swiss Med. Wkly. 140, w13101.
24. **Yang Y, Gao S, Fang Q, et al. (2021):** Diagnostic value of copeptin combined with hypersensitive cardiac troponin T detection in early acute myocardial infarction: A prrotocol of randomized double-blind diagnostic trial. Medicine, 100, e23949.
25. **Smaradottir MI, Andersen K, Gudnason V, et al. (2021):** Copeptin is associated with mortality in elderly people. Eur. J. Clin. Investig. 51, e13516.
26. **Ginès P, Quintero E, Arroyo V, et al. (1987):** Compensated cirrhosis: natural history and prognostic factors. Hepatology;7:122–128.
27. **Ginès P, Cárdenas A, Solà E, et al.(2012):** Liver Disease and the Kidney. In: Schrier RW, editor. Schrier´s Diseases of the kidney. Coffman TM, Falk RJ, Molitoris BA, Neilson EG, Schrier RW, Eds. 9th ed. Lippincott Williams &Wilkins.
28. **Schrier RW, Arroyo V, Bernardi M, et al. (1988):** Peripheral arterial vasodilatation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology;8: 1151–1157.
29. **Kluge M, Riedl S, Erhart-Hofmann B, et al. (1999):** Improved extraction procedure and RIA for determination of arginine8-vasopressin in plasma: role of premeasurement sample treatment and reference values in children. Clin Chem.; 45(1):98-103. PMID: 9895344.
30. **Holwerda DA (1972):** A glycopeptide from the posterior lobe of pig pituitaries. I. Isolation and characterization. Eur J Biochem; 28:334–339.
31. **Morgenthaler LG, Struck J, Alonso C, et al. (2006):** Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. Clin Chem;52:112–119.
32. **Miller WL, Hartamn KA, Grill DE, et al.(2012):** Serial measurements of midregion proANP and copeptin in ambulatory patients with heart failure: incremental prognostic value of novel biomarkers in heart failure. Heart;98:389–394.
33. **Rinschen MM, Schermer B, Benzing T. (2014):** Vasopressin-2 receptor signaling and autosomal dominant polycystic kidney disease: from bench

to bedside and back again. J Am Soc Nephrol; 25(6): 1140-7.

34. **Christ-Crain M, Fenske W (2016):** Copeptin in the diagnosis of vasopressin-dependent disorders of fluid homeostasis. Nat Rev Endocrinol; 12(3): 168-76.
35. **Meijer E, Bakker SJ, Halbesma N, et al. (2010):** Copeptin, a surrogate marker of vasopressin, is associated with microalbuminuria in a large population cohort. Kidney Int; 77(1): 29-36.
36. **Boertien WE, Meijer E, Li J, et al. (2013):** Relationship of copeptin, a surrogate marker for arginine vasopressin, with change in total kidney volume and GFR decline in autosomal dominant polycystic kidney disease: results from the CRISP cohort. Am J Kidney Dis; 61(3): 420-9.
37. **Gansevoort RT, van Gastel MDA, Chapman AB, et al. (2019):** Plasma copeptin levels predict disease progression and tolvaptan efficacy in autosomal dominant polycystic kidney disease. Kidney Int; 96(1): 159-69.
38. **Feigin VL, Stark BA, Johnson CO, et al. (2021):** Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol; 20(10): 795–820
39. **De Marchis GM, Weck A, Audebert H, et al. (2014):** Copeptin for the prediction of recurrent cerebrovascular events after transient ischemic attack: results from the CoRisk study. Stroke;45(10): 2918–2923
40. **Montellano FA, Ungethüm K, Ramiro L, et al. (2021):** Role of blood based biomarkers in ischemic stroke prognosis: a systematic review. Stroke; 52(2): 543–551
41. **Wang CW, Wang JL, Zhang Yi, et al. (2014):** Plasma levels of copeptin predict 1-year mortality in patients with acute ischemic stroke. Neuroreport; 25(18): 1447–1452
42. **Elshafei A, Khidr EG, El-Husseiny AA, et al. (2021):** RAAS, ACE2 and COVID-19; a mechanistic review. Saudi J. Biol. Sci. 28(11), 6465–6470.
43. **Pal M, Berhanu G, Desalegn C, et al. (2020):** Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): an update. Cureus 12(3), e7423.
44. **Wang D, Li R, Wang J, et al. (2020):** Correlation analysis between disease severity and clinical and biochemical characteristics of 143 cases of COVID-19 in Wuhan, China: a descriptive study. BMC Infectious Diseases 20(1), 1–9.
45. **Jezova D, Skultetyova I, Tokarev D, et al. (1995):** Vasopressin and Oxytocin in Stress a. Annal. N.Y. Acad. Sci. 771(1), 192–203.
46. **Dunham-Snary KJ, Wu D, Sykes EA, et al. (2017):** Hypoxic pulmonary vasoconstriction: from molecular mechanisms to medicine. Chest 151(1), 181–192.
47. **Park SJ, Shin JI (2013):** Inflammation and hyponatremia: an underrecognized

condition? Korean J. Pediatr. 56(12), 519–522.

48. **Gregoriano C, Molitor A, Haag E, et al. (2021):** Activation of vasopressin system during COVID-19 is associated with adverse clinical outcomes: an observational study. J. Endocrin Soc. 5(6), bvab045.
49. **Christ-Crain M, Fenske WK (2020):** Copeptin in the differential diagnosis of hypotonic polyuria. J. Endocrin. Invest. 43(1), 21–30.
50. **Kuluozturk M, ˙In E, Telo S, Karabulut E, et al. (2021):** Efficacy of copeptin in distinguishing COVID-19 pneumonia from community-acquired pneumonia. J. Med. Virol. 93(5), 3113–3121 (2021).
51. **Christ-Crain M (2019):** Vasopressin and Copeptin in health and disease. Rev. Endocrin. Metabol. Disord. 20(3), 283–294.
52. **Yousaf Z, Al-Shokri SD, Al-Soub H, et al. (2020):** COVID-19-associated SIADH: a clue in the times of pandemic! Am. J. Physiol. Endocrinol. Metab. 318(6), E882–E885.
53. **Elshafei A, Abdalla G, Abd El-Motaal O, et al. (2013):** Copeptin: a neuroendocrine biomarker in acute myocardial infarction. Annual Research & Review in Biology 3(4), 1040–1054.