Novel insights into the diagnostic and prognostic function of copeptin in cardio-metabolic disorders

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Research Article

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Abstract

As is shown in previous reports, arginine vasopressin, as one of the most important hormones within circulation in human beings, is of great clinically significance given that it could maintain the body fluid balance and vascular tone. However, the laboratory measurements arginine of vasopressin in daily clinical practice are shown to be difficult and with low accuracy. Concerning on this notion, it is unpractical to use the serum levels of arginine vasopressin in diagnosing multiple diseases. On the other hand, another key serum biomarker, copeptin, is confirmed as the C-terminal of the arginine vasopressin precursor which could be released in equal amounts with arginine vasopressin, resultantly making it as a sensitive marker of arginine vasopressin release. Notably, emerging recent evidence has demonstrated the critical function of copeptin as a clinical indicator, especially in the diagnosis and prognosis of several diseases in diverse organs, such as cardiovascular disease, kidney disease, and pulmonary disease. In addition, copeptin was recently verified to play an important role in diagnosing multiple acute diseases when combined it with other gold standard serum biomarkers, indicating that copeptin could be recognized as a vital disease marker. Herein, in the current review, the functions of copeptin as a new predictive diagnostic and prognostic biomarker of various diseases, according to the most recent studies, are well summarized. Furthermore, the importance of using copeptin as a serum bio-marker in diverse medical departments and the impact of this on improving healthcare service is also summarized in the current review.

Highlights

1. Copeptin and arginine vasopressin are released from the pituitary gland in equimolar amounts in response to stress.

2. Copeptin is a surrogate marker of arginine vasopressin.

3. Copeptin could predict clinical outcomes in several critical diseases.

4. Copeptin appears to play an important role as a prognostic marker in some acute diseases.

1. Introduction

As is well-reported in previous studies, hormones are complex chemical substances which could be secreted into circulation by the endocrine system. The most important functions of hormones are regulating biological metabolism and physiological processes [1]. Concerning on this notion, diverse hormones might act different functions as the chemical messengers which maintains the body catabolism and homeostasis. Furthermore, hormones could affect almost all the essential life processes, including cell growth, metabolism, development, immune defense, reproduction, behavior, and adaptation to the conditions of existence [2]. The mechanisms of action of hormones depends on the different locations of receptors. As shown, diverse receptors could interact with different hormones which
subsequently affects the metabolic process of different target cells and presents different physiological effects.

Among several different hormones within circulation, arginine vasopressin and copeptin are identified as two vital hormones released in equal amounts from the posterior pituitary gland into the systemic circulation, as a response to osmotic and hemodynamic stimulants in daily clinical practice. Notably, in the healthy individuals, the arginine vasopressin could modulate the vascular tone and the fluid homeostasis which resultantly maintaining the equilibrium of the cardiovascular system. Moreover, the arginine vasopressin is also confirmed to embrace an essential function in affecting multiple systems, including endocrine, hemostatic, and central nervous systems, besides the direct renal and vasoconstrictor effects [3]. It is well-established that the serum concentrations of arginine vasopressin are highly important in prognosis and diagnosis of multiple diverse diseases, however, the measurements of serum arginine vasopressin concentrations in daily clinical practice are limited since several reasons. For instance, the short half-life time of arginine vasopressin, the low molecular stability of arginine vasopressin even if stored at -20°C, also almost all of the serum arginine vasopressin is bound to platelets within circulation, which leads to under-estimation of the actual arginine vasopressin concentrations [4].

Given that arginine vasopressin and copeptin are released together in equimolar amounts, copeptin was recently approved to be used for mirroring the existence of arginine vasopressin. Importantly, this was due to its high molecular stability compared to arginine vasopressin and its high serum concentrations which could be easily determined by diverse easy assays in daily clinical practice. Currently, the main function of copeptin is as a stable surrogate biomarker of arginine vasopressin concentration in human beings, where it was approved to be a biomarker for prognosis of several diseases, such pulmonary diseases, cardiovascular diseases, and kidney diseases [3]. Herein, in the current review, the functions of copeptin as a new predictive diagnostic and prognostic biomarker of various diseases, according to the most recent studies, are well summarized. Furthermore, the importance of using copeptin as a serum biomarker in diverse medical departments and the impact of this on improving healthcare service is also summarized in our review.

2. Basic Characteristics Of Arginine Vasopressin And Copeptin

2.1 Basic characteristics of arginine vasopressin

According to the published literatures, arginine vasopressin, also known as anti-diuretic hormone or argipressin, is the most important form of vasopressin in human beings and most mammals. As shown, it is a synthetic non-peptide composed of nine amino acids with arginine at residue eight and two cysteines at residues 1 and 6 linked together by a disulfide bond [5]. The structure arginine vasopressin is shown in Fig. 1. Furthermore, the arginine vasopressin hormone is produced as a part of 164 amino acid precursor protein, as pro-arginine vasopressin, in the hypothalamus. This precursor is composed of signal peptide, arginine vasopressin moiety, neurophysin-2 protein, and copeptin [3].
Pro-arginine vasopressin precursor is produced in the hypothalamus (as shown in Fig. 3) and released through two diverse mechanisms, as one for the posterior pituitary, the other for the anterior pituitary. As for the first release mechanism, pro-arginine vasopressin is produced in the magnocellular neurons of the supraoptic (SON) and paraventricular (PVN) hypothalamic nuclei, after that it is treated in the endoplasmic reticulum where the signal peptide is removed and carbohydrate chain is added [6]. This process is followed by axonal transport to the posterior pituitary gland where pro-arginine vasopressin is subjected to enzymatic cleavages producing three diverse peptides, copeptin, arginine vasopressin, and Neurophysin-2, as shown in Fig. 2.

In addition, the three diverse peptides are subsequently stored in the neurohypophysis and secreted in case of hemodynamic or osmotic stimuli. Concerning on the second mechanism, pro-arginine vasopressin is synthesized and processed in the parvocellular neurons of hypothalamus, where corticotropin-releasing hormone is also synthesis and release [7]. The arginine vasopressin is subsequently transported to the pituitary portal system where it acts co-operatively with corticotropin-releasing hormone stimulating the adrenocorticotropic hormone release from the anterior pituitary gland, resulting in cortisol secretion from the adrenal gland.

Importantly, this backup system of arginine vasopressin and corticotropin-releasing hormone which further facilitate the release of adrenocorticotropic hormone reflects how the endocrine stress response is physiologically important, additionally it gives indication about the ability of using arginine vasopressin and copeptin, as potential biomarkers in determining stress levels [7]. Arginine vasopressin is considered to have three main physiological functions, including maintaining the fluid balance homeostasis, modulating the endocrine stress response, and influencing the vascular tone regulation. Clinically, arginine vasopressin presents an essential function in affecting the osmotic balance, blood pressure, sodium homeostasis, and kidney function, which explains the high clinical importance of arginine vasopressin. On the other hand, the functions of arginine vasopressin are mediated by three G-protein coupled receptors, including the vascular receptor (V_{1a}R), the anterior pituitary receptor (V_{1b}R), and the anti-diuresis-mediating receptor (V_{2}R) [8]. Nevertheless, the measurement of arginine vasopressin as a clinical biomarker showed a lot of difficulties and inaccuracy in daily clinical practice. For instance, the measurement of arginine vasopressin started since 19th century using radio-immuno-assay (RIA), after that measurement of arginine vasopressin exhibited several limitations. Notably, the key limitations is the long-timed assays due to complicated pre-analytical requirements which is not suitable in clinical diagnosis. Also, the instability of arginine vasopressin in isolated serum even if stored at -20°C, besides its short half-life (less than 30 minutes) made it more difficult for arginine vasopressin to be used as a biomarker. This was in addition to the fact that a huge amount of arginine vasopressin is bound to platelets in the blood circulation which affects the actual determination of arginine vasopressin concentration [9]. Finally, the amount of serum required in arginine vasopressin measurement is actually large as greater than 1ml. All those limitations led to much more researches about the probability of using copeptin as an alternative biomarker for arginine vasopressin as they are both released in equimolar amounts in response to stress [3].
1.2 Basic characteristics of copeptin

Copeptin was first described in 1972 by Holwerda and colleagues, where it was first detected in the pigs’ posterior pituitary [10]. It is a 39-amino acid glycosylated peptide containing a leucine rich core region, found in the C-terminal part of pro-arginine-vasopressin. The molecular mass of copeptin is approximately 5 kDa.

According to the reports, copeptin is released into the blood stream in equivalent amounts to arginine vasopressin, thus reflecting its presence and activity. However, unlike arginine vasopressin, the physiological function of copeptin within circulation is not yet clarified. After description of copeptin in 1972, several early basic experiments demonstrated that copeptin might act as a prolactin releasing factor, but this function could not be confirmed as other experiments denied it [11]. Recently, copeptin was presumed to act as a chaperone protein in the folding and proteolytic maturation of arginine vasopressin [12]. As copeptin is assumed to be strictly regulated in circulation, it might have a specific peripheral function. Accordingly, much more experiments are needed to find out copeptin’s specific role in circulation. At present, as copeptin was proved to show same respond as arginine vasopressin to stress, osmotic and hemodynamic stimuli, and as it is produced in equimolar quantities together with arginine vasopressin, the main and most important role of copeptin is giving indication about the amount of arginine vasopressin in the circulation which in turn reflects its importance in prognosis and diagnosis of arginine vasopressin disorder-related diseases. As for copeptin elimination, no specific mechanism was approved, whereas emerging evidence shows that it could eliminated via kidney relying on the fact that it could be measured in kidney [13]. It has been discussed before the difficulties in using arginine vasopressin as a clinical biomarker, the following table will show the advantages of using copeptin, as a clinical biomarker, over arginine vasopressin, as shown in Table 1.
Table 1  
Advantages of copeptin over arginine vasopressin

<table>
<thead>
<tr>
<th></th>
<th>Copeptin</th>
<th>Arginine vasopressin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assay</strong></td>
<td>Sandwich immunoassay</td>
<td>Radio immunoassay</td>
</tr>
<tr>
<td><strong>Duration of assay</strong></td>
<td>30 minutes to 2 hours</td>
<td>Usually more than 48 hours</td>
</tr>
<tr>
<td><strong>Amount of serum or plasma</strong></td>
<td>50 µL serum or plasma</td>
<td>≥ 1 mL plasma</td>
</tr>
<tr>
<td><strong>Sensitivity of the assay</strong></td>
<td>Sandwich immunoassay is highly sensitive (1.7 pmol/L)</td>
<td>Arginine vasopressin must be measured using low sensitive immunoassays because of its small size.</td>
</tr>
<tr>
<td><strong>Pre-analytical steps</strong></td>
<td>None</td>
<td>- Extraction step is needed.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Addition of protease inhibitor.</td>
</tr>
<tr>
<td><strong>Half-life time</strong></td>
<td>Long half life time (≈ 86 minutes)</td>
<td>Short half life time (≈ 44 minutes)</td>
</tr>
<tr>
<td><strong>Stability</strong></td>
<td>In both serum and plasma, it is stable for 7 days at room temperature, and for 14 days at 4 °C</td>
<td>Unstable in isolated plasma even if stored at -20 °C</td>
</tr>
</tbody>
</table>

According to the mechanism of arginine vasopressin production discussed before, it has been well-reported that after cleavage of the pro-arginine vasopressin precursor, arginine vasopressin, neurophysin-2, and copeptin are produced [14]. Concerning on this notion, the current question is why copeptin is preferred to be the perfect fragment to reflect the release of arginine vasopressin and not neurophysin-2. The complicated structure of neurophysin-2 (approximately seven intramolecular disulfide bonds), and its ability to bind to arginine vasopressin denies the possibility of being an ideal arginine vasopressin alternative target. Nonetheless, in case of copeptin such limitations are absent. Concerning on this notion, it is suitable as an arginine vasopressin alternative target in clinical practice [15].

The circulating concentrations of copeptin respond, similar to arginine vasopressin, to blood pressure, stress, and osmolality changes. It was observed that copeptin is more associated with serum osmolality compared with the arginine vasopressin in healthy individuals. Where in healthy controls concentrations of copeptin are shown to be closely correlated to osmolality alterations with a rapid rise in copeptin concentrations during thirsting and a rapid drop after fluid intake. Copeptin might be also better than cortisol in physiological stress levels determination, as it is difficult to measure cortisol as a free hormone, given that it has a strong circadian rhythm, and it is downstream during stress response [16]. Normal serum copeptin concentrations in healthy controls have been found to be approximately 1.70 to 11.25 pmol/L. In normal situations, the serum concentrations of copeptin were observed to be higher in men compared to those in women. The reason of higher serum copeptin concentrations in males is
unknown, but it was proposed that this might be due to higher osmolar intake in men [17]. Similar with these findings, the serum concentrations of copeptin are significantly higher in men compared with those in women. Nonetheless, gender differences in serum concentrations of arginine vasopressin were not approved to be correlated with the differences in plasma sodium concentration, blood pressure, or plasma volume. It was reported that copeptin has no regular variability in circadian rhythm, whereas the serum concentrations of arginine vasopressin present a diurnal rhythm where its levels increase at nighttime in both males and females. In addition, the age differences do not seem to affect copeptin concentrations. On the other hand, it was observed that the serum concentrations of copeptin might increase by physical exercise. For instance, in a large general-population cohort study which enrolled approximately 6,801 participants, it was found that life-style and diet-related factors, such as smoking, alcohol use, and sodium intake were strongly associated with the serum copeptin concentration. Recently, it is also confirmed that the serum concentrations of copeptin were closely associated with higher systolic blood pressure, lower 24-hour urine volume, and higher renal sodium in healthy individuals, indicating that copeptin could be identified as an essential biomarker in cardio-metabolic disorders [18].

Introducing copeptin in daily clinical practice gave the evidence which copeptin could act as a promising serum biomarker for diagnosing arginine vasopressin-dependent fluid homeostasis disorders, such as hyponatremia and diabetes insipidus. Despite the fact that copeptin serum concentrations are quite variable and more related to osmolality, copeptin demonstrated significantly higher concentrations in different cases including myocardial infarction, type 1/2 diabetes mellitus, kidney diseases, acute and chronic heart failure, severe hypertension, stroke, pulmonary diseases, psychological stress, birth stress, sepsis, neurological stress and critical conditions, which in turn increases the probability of depending on copeptin as an effective prognostic biomarker of diverse diseases [19]. The functions of copeptin as a biomarker in daily clinical practice is being highlighted through the following pages according to results obtained from recent studies.

3. Functions Of Copeptin In Cardiovascular Diseases

It is well-established that the cardiovascular diseases term refers to all types of diseases affecting the heart or blood vessels, such as atherosclerosis, hypertension, and valvar heart disease. According to the World Health Organization (WHO), the cardiovascular diseases are the leading cause of death worldwide, posing serious to the human health all over the world. In 2019, approximately 17.9 million deaths were due to the cardiovascular diseases, which represents about 32% of the whole global deaths [20]. Concerning on this notion, early diagnosis of cardiovascular diseases might significantly facilitate disease control and early treatment. Indeed, the diagnosis of cardiovascular diseases depends on both laboratory assessments and symptoms. As a biomarker, copeptin has been studied in many clinical cases especially diagnosis of myocardial infarction and heart failure, and prognosis of chronic stable heart failure, in which the results were highly satisfying [21].
3.1 Evidence of copeptin in modulating the risk of myocardial infarction

Recently, several studies demonstrated the relationship between copeptin and the risk of acute myocardial infarction. Several cardiac troponins, including troponin T (TnT), troponin C (TnC), and troponin I (TnI), have been firmly demonstrated as the gold standard serum biomarkers for diagnosing acute myocardial infarction together with electrocardiography [22]. Despite being the most important methods in diagnosis of acute myocardial infarction, perfect diagnosis is still under challenging, this is due to the fact that levels of troponins take time to increase in the circulation (approximately 6 to 9 hours) in after chest pain onset, which in turn delays the accurate diagnosis of acute myocardial infarction, even after using highly sensitive troponin assays (hs-cTn), which increased the diagnostic sensitivity of acute myocardial infarction compared to normal tests, the troponin gap is still present [23]. In addition, electrocardiography is of low accuracy, as approximately 25–30% of patients with acute myocardial infarction did not show serious electrocardiography alternations during acute cardiac ischemia [17]. Accordingly, researches were directed towards finding novel biomarkers of acute myocardial infarction which must fulfill two important criteria accuracy and speed. The fast and early activation of vasopressin system in response to stress draw scientists’ attention towards copeptin. The first study to report that copeptin could help in early diagnosis of acute myocardial infarction was in 2009 [24]. Where Reichlin et al. found that when the serum concentrations of TnT were undetectable in the circulation, serum concentrations of copeptin were significantly high in patients with acute myocardial infarction, this is owing to the rapid and early release of copeptin in blood, directly after the onset of chest pain, compared to troponins [25]. The study also reported that combination between copeptin with concentration lower than 14 pmol/L and TnT concentration lower than or equal 0.01 µg/L excludes acute myocardial infarction at presentation with sensitivity of 98.8% [24]. A recent study reported that using both copeptin and TnI improve diagnosis of acute myocardial infarction in patients with onset chest pain in emergency department. The study targeted 271 patients complaining chest pain. Serum copeptin, creatine kinase-MB (CK-MB), and TnI concentrations were measured within six hours of onset. For acute myocardial infarction, the diagnostic performance of the biomarkers was assessed separately and in combination using ROC curve analysis [26]. It was found that copeptin was better than TnI in diagnosing chest pain patients within two hours of onset.

Additionally, combination of copeptin and TnI showed better diagnostic performance compared to CK-MB and TnI combination in patients with acute myocardial infarction and ST elevation myocardial infarction (STEMI) [26]. Another study also reported the ability of copeptin to improve prognosis and diagnosis of acute myocardial infarction especially when combined with troponins [27, 28].

3.2 Evidence of copeptin in modulating the risk of heart failure

As shown in previous study, the brain-type natriuretic peptide (BNP) and its precursor N-terminal brain-type natriuretic peptide (NT-pro-BNP) is confirmed to be the gold standard biomarkers of heart failure.
Concentrations of those two parameters within the circulation in response to cardiac stretching and they provide diagnostic and prognostic information especially in chronic heart failure, whereas it was found that heart failure is not significantly detected in approximately 55% of patients [29]. For this reason, emerging research were directed to find out novel serum biomarker to help in better diagnosis and prognosis of heart failure. Arginine vasopressin and copeptin levels show higher elevation in case of heart failure patients, even in cases with low plasma osmolality [30]. This might be due to the fact that release of arginine vasopressin is due to both osmotic and non-osmotic factors like intra-arterial pressures, intra-cardiac pressures, pain, angiotensin-2, and adrenergic (α-2) central nervous system stimuli. In case of edematous, states the non-osmotic stimuli are predominant over the osmotic stimuli, which explains the high concentrations of arginine vasopressin and copeptin levels in case of patients with chronic heart failure despite of lower osmolality [30].

Regarding the disease prognosis, several studies reported that copeptin was superior to BNP and NT-proBNP in predicting mortality and monitoring the disease risk for long- and short-term clinical outcomes [31]. In a study targeting 155 patients of heart failure acute symptoms who were monitored for 90 days concerning the composite end point of cardiovascular death or acute heart failure-related re-hospitalization, BNP, NT-pro-BNP, and copeptin concentrations were measured at admission. Copeptin was superior to BNP and NT-pro-BNP in predicting the disease development within 90 days period of follow up [32]. The superiority of copeptin over BNP and NT-pro-BNP in prognosis might be due to that BNP and NT-pro-BNP is closely correlated with age and renal function, meanwhile copeptin is not. Likewise, the fact that serum BNP concentrations are extremely variable over time in chronic heart failure might be another reason.

According to the published reports, it is better to combine copeptin together with symptoms and natriuretic peptides for more prognostic and diagnostic accuracy in heart diseases [17]. Another study where serum levels of copeptin and NT-pro-BNP were determined in 314 cases of acute dyspnea. The diagnostic value and prognostic significance of both were then analyzed in acute exacerbation of chronic obstructive pulmonary disease and acute heart failure patients. Other results revealed that copeptin was superior to NT-pro-BNP in predicting mortality in both acute heart failure and acute exacerbation of chronic obstructive pulmonary disease, whereas, serum NT-pro-BNP concentrations predicted mortality in acute heart failure cases only. Nevertheless, NT-pro-BNP showed higher diagnostic values compared to copeptin in diagnosis of acute heart failure in acute dyspnea patients [33]. Another study suggested that copeptin has high prognostic values in long term clinical outcomes in patients with heart failure. The primary outcome of the study was a combination between all-cause death and re-admission of heart failure. During approximately five-year of follow up higher serum copeptin concentrations were associated with both all-cause death and re-admission heart failure cases. After confounders’ adjustment copeptin remained an independent predictor for all-cause death and heart failure [34]. Several other studies are mentioned also assures the ability of copeptin could be identified as a useful marker in improving the prognosis and diagnosis of heart failure together with the natriuretic peptides [28].
4. Functions Of Copeptin In Other Diseases

4.1 Evidence of copeptin in modulating the risk of pulmonary diseases

According to the previous results of epidemiological investigations, the respiratory diseases are among the main causes of death and disability worldwide. Indeed, five of the thirty most common globally death causes are strongly correlated to respiratory diseases, which are chronic obstructive pulmonary disease, third reason of death all over the world, tracheal, lower respiratory tract infection, lung and bronchial cancer, asthma and tuberculosis [35].

Given that it has been firmly established that copeptin is associated with several diseases, current focus is shifting towards composing and implementing the underlying relationship between copeptin with the risk of pulmonary diseases. As reported, the serum concentrations of copeptin were observed to be elevated in several respiratory disturbances, which also reflects the increase of arginine vasopressin concentrations [36]. Patients with lower respiratory tract infection demonstrated the higher serum copeptin concentrations, especially in patients with the community acquired pneumonia, where copeptin showed a predictive role for deterioration, all-cause mortality, and clinical instability [37]. In addition, in chronic obstructive pulmonary disease, higher serum copeptin concentrations were useful in prognosis of exacerbation and all-cause mortality [38]. Notably, the increased serum copeptin concentrations were observed to have better predictive value for short-term mortality over NT-pro-BNP in case of acute pulmonary injury, cardiopulmonary edema, and acute respiratory distress syndrome [39]. As for diagnosis in daily clinical practice, copeptin was also demonstrated to embrace an important function in diagnosis and risk stratification in case of pulmonary hypertension and pulmonary embolism patients [40].

More recently, multiple studies found that the circulating copeptin concentrations were higher in patients with the severe corona virus disease-19 (COVID-19) compared to those in the moderate and mild patients, at admission and during the follow up period [41]. In addition, several recent studies indicated the probability to use copeptin to distinguish between the patients with community-acquired pneumonia and COVID-19 [42]. On the other hand, in case of obstructive sleep apnea, which is considered the most common sleep disorder, copeptin demonstrated an important function as a diagnosis biomarker of obstructive sleep apnea, since hypoxemia is a strong stimulant to facilitate the secretion of arginine vasopressin [43]. As for prognostic role in case of obstructive sleep apnea, it is a debatable matter as some studies revealed correlations between copeptin concentrations and severity of obstructive sleep apnea [44]. More studies also give an indication about the function of copeptin in both diagnosis and prognosis in several respiratory diseases [45, 46].

4.2 Evidence of copeptin in modulating the risk of renal diseases
As reported, the recent reports from the WHO state that the renal diseases are the top 10th leading cause of death all over the world. The mortality due to the renal diseases have risen from 813,000 deaths in 2000 to 1.3 million deaths in 2019, posing serious to the human health [47].

As mentioned in the previous studies, the main function of arginine vasopressin in the body is regulation of the extracellular fluid volume through regulating renal handling of water. Where arginine vasopressin performs its function by acting on renal collecting ducts through V2 receptors to increase water permeability, as the cyclic adenosine monophosphate (cAMP)-dependent mechanism, which results in decreasing urine formation [48]. In renal diseases, it was found that V2 receptors are responsible for both renal damage progression in diabetes and stimulating intracellular pathways related to polycystic renal development [49]. One of the most common renal diseases in the world is chronic kidney disease, according to several studies copeptin presented an important roles in both diagnosis and prognosis of chronic kidney disease. In a recent study, where copeptin was investigated in 149 patients with clinically stable chronic kidney disease, the increased serum copeptin concentrations were confirmed to be associated with the biopsy verified media calcification. Furthermore, after several analyses it was found that copeptin is correlated to the extent of vascular calcification with no association with age, gender, or diabetes mellitus [50]. Regarding predictive functions of copeptin in renal diseases, several studies showed that copeptin presented an important function in either predicting the development of the disease [51], or prognosis of disease severity [52]. On the other hand, it was observed that copeptin could predict the results and efficacy of Tolvaptan treatment in auto-somal dominant polycystic kidney disease, which is considered the most common hereditary kidney disease [53]. In a study took place on 100 patients of hyponatremia, which is the most common body fluid and electrolyte balance disorder [54], whereas the copeptin showed limited diagnostic ability for hyponatremia, its role in predicting the efficacy and the safety of treating hyponatremia patients with hypertonic saline [55].

**4.3 Evidence of copeptin in modulating the risk of neurological diseases**

Globally, according to the results of epidemiological investigation by WHO, the neurological diseases are considered as the second reason of mortality. In details, the activation of hypothalamus-pituitary axis was observed in some neurological diseases such as intracellular hemorrhage and ischemic stroke [56]. The hypothalamus-pituitary axis activation results in release of both corticotropin releasing hormone and arginine vasopressin leading to stimulation of adrenocorticotropic hormone release as a response to stress. This in turn may support the idea of using arginine vasopressin and copeptin as biomarkers in neurological diseases [57]. Several studies have examined patients with different neurological diseases such as Traumatic brain injury, ischemic stroke, transient ischemic attack, and, subarachnoid hemorrhage. Recent studies showed defines the functions of arginine vasopressin and copeptin as biomarkers in both diagnosis and prognosis of those diseases. In a study of 36 patients with Generalized convulsive seizures, it was observed that copeptin could help in diagnosis of Generalized convulsive seizures, where serum copeptin concentrations were increased after most Generalized convulsive seizures. Nevertheless, the authors suggested that copeptin specificity need to be tested [58].
Another study investigating serum neuro-filament light chain, prolactin and, copeptin concentrations in children with febrile seizures and epileptic seizures, although the serum copeptin and prolactin concentrations were increased in both febrile seizures and epileptic seizures in contrast with serum neuro-filament light chain, the authors could not approve them as prognostic biomarkers as neither of them was correlated with recurrent seizures [59]. In a group of 125 mixed trauma patients, copeptin was found to be a precise prognostic and diagnostic biomarker over lactate, where it showed more accuracy in hospital admission prediction, blood transfusion, and identification of patients with injury severity score (ISS) > 15 than lactate [60]. More recently, in a meta-analysis including 17 studies enrolling approximately 2,654 participants focusing on Traumatic brain injury, authors strongly suggested that copeptin could be a useful prognostic and diagnostic biomarker for Traumatic brain injury [61]. In addition, copeptin was observed to exhibit a prognostic function in subarachnoid hemorrhage [61, 62]. However, it is still necessary to conduct more studies to further explore the accurate relationship between copeptin with the risk of pulmonary diseases.

4.4 Evidence of copeptin in modulating the risk of psychological disorders

Importantly, the number of deaths and diseases caused by stress is so worrying. According to the Centers for Disease Control and Prevention (CDC), in the United States more than 50% might suffer from mental illness in a certain stage in their life. Even one in five adults might be diagnosed by mental illness in a given year. In addition, the emotional stress was found to be the main factor to six death causing diseases in the United States which are: respiratory disorders, cancer, accidental injuries, cirrhosis of the liver, coronary heart disease, and suicide [63]. Psychological disorders may be due to psychological stress or psychological diseases like major depressive disorder in other words depression, anorexia nervosa, and bipolar disorder.

In the CoEXAM study, where the effect of psychological stress on levels of copeptin was investigated in 25 healthy students prior and following a written examination. The serum copeptin concentrations before the exam showed higher values than after the exam. The same results were observed for cortisol, where serum cortisol levels were elevated before the exam in comparison to their levels after the exam [64]. In another study, a group of 100 healthy women and men were subjected to the Trier Social Stress Test (TSST) as a psychological stress, a positive correlation between copeptin percent changes and salivary and serum cortisol percent change was observed in males only, however in females there was no any significant association observed. In addition, the authors suggested the ability of copeptin to act as a biomarker for both arginine vasopressin and the activation of hypothalamus-pituitary axis [57]. Results obtained from a study made to compare serum copeptin concentrations in 25 normo-hydrated stable women with anorexia nervosa and 25 age-matched women as control group were unexpected. Where there was no noticeable change in serum copeptin concentrations between the two groups, which gives indication that anti-diuretic hormone may not be critical for the pathophysiological implication of psychological stress in cases of anorexia nervosa [65]. The probability of using copeptin as a biomarker of response to anti-depressant treatment in major depressive disorder was indicated in a pilot study [66].
Where serum copeptin, adrenocorticotropic hormone, and cortisol were measured in patients with major depressive disorder prior and after hypothalamus-pituitary axis manipulation. Copeptin levels showed significant differences before and after treatment, however cortisol and adrenocorticotropic hormone did not show any significant differences before and after treatment [66]. Bipolar disorder patients were found to be characterized by lower serum copeptin concentrations when compared to those in the healthy individuals [67]. Also, it was observed that abnormal serum copeptin concentrations are associated with abnormal metabolic parameters only in bipolar disorder cases.

4.5 Evidence of copeptin in modulating the risk of metabolic diseases

Metabolic diseases occur due to metabolism interruption in our bodies. In another word, the metabolic diseases are mainly characterized by abnormal glucose and lipids values in the body. These diseases may be acquired or congenital. Under chronic psychological stress, the hypothalamus-pituitary axis is activated by release of arginine vasopressin, resulting in cortisol secretion through V1a receptors activation, leading to glycogeno-lysis as a result of interrupting insulin activity and glucagon stimulation. In addition, epinephrine is released as a result of V1b receptors which leads to glycogeno-lysis and hyperglycemia [68]. Diabetes with its two types is considered to be the main common metabolic disorder. A study comparing copeptin values between prediabetes, diabetes mellitus without nephropathy, diabetic nephropathy and healthy individuals, the highest circulating copeptin concentrations were observed in prediabetes individuals, followed by diabetic nephropathy individuals, and diabetic individuals without nephropathy, control individuals showed the lowest circulating copeptin concentrations. In addition, participants with positive family history of diabetes mellitus showed higher serum copeptin concentrations compared to those of negative diabetes mellitus family history [69].

4.6 Evidence of copeptin in modulating the risk of hepatic diseases

According to recent researches, hepatic diseases account for approximately two million deaths per year globally, of which one million stands for cirrhosis complications, where cirrhosis is considered to be the 11th most common death disease worldwide [70].

Among multiple hepatic diseases, cirrhosis is mostly characterized by disturbance in body water hemostasis, which results in some complications from which increase in release of arginine vasopressin to regulate body water hemostasis [71]. In a cohort of 321 patients with both compensated and decompensated cirrhosis, the circulating copeptin concentrations were shown to be increasing progressively with the severity of cirrhosis thus the serum copeptin concentrations were higher in patients with decompensated cirrhosis compared to those with compensated cirrhosis. In additionally, the serum copeptin concentrations were higher in patients who developed disease complications. Regarding mortality, copeptin showed the ability of being an independent predictive biomarker for three months mortality [72]. Those results are in accordance with another study in which 40 cirrhosis individuals, divided into 4 groups, were investigated for the serum copeptin concentrations together with control
group. Additionally, the serum copeptin concentrations were higher in patients with cirrhosis accompanied with gastrointestinal hemorrhage, hepatorenal syndrome, and hepatic failure compared to compensated cirrhosis cases, thus giving evidence that copeptin could be a novel marker for liver cirrhosis prognosis. Also, it was observed that there is an association between serum copeptin and cirrhosis complications, thereby copeptin could be used in disease progression and follow up [73]. In a large cohort investigation, where 779 patients were admitted for acute decompensation, among them 139 patients were diagnosed for acute-on-chronic liver failure, at admission copeptin concentrations were higher in patients with both acute-on-chronic hepatic failure and acute decompensation compared to patients with acute decompensation only. Additionally, after 28 and 90 days of follow up copeptin demonstrated higher concentrations in patients who died or transplanted in comparison with those who survived or were in no need for transplantation, revealing that copeptin could be considered as an independent predictor biomarker in cirrhosis mortality [74].

A recent study investigating serum copeptin concentrations in chronic liver disease's complications, such as hepatic encephalopathy, portosystemic shunts, ascites, and all mortality causes, showed that copeptin concentrations were elevated in patients with hepatic cirrhosis accompanied by ascites and portosystemic shunts formation resulted from portal hypertension. In addition, patients with hepatocellular carcinoma and hepatic encephalopathy patients presented higher copeptin concentrations [75]. Also, the study results found that copeptin was strongly correlated with the parameter of hepatic function, such as albumin-bilirubin score, rather than renal function estimated glomerular filtration rate (eGFR) score, resultantly giving probability of using copeptin as a surrogate biomarker for complications of chronic liver disease's complications. Furthermore, it was observed that copeptin exhibited an important function in predicting both short-term mortality (approximately one year), and long-term mortality (approximately four years) in chronic liver disease's complications [75]. A most recent study stated that serum copeptin could predict the response of patients with hepatic cirrhosis associated with ascites to Tolvaptan treatment. The study cohort was 113 hepatic cirrhosis patients with ascites, where serum copeptin together with several treatment related factors were investigated for their ability to predict response of patients to Tolvaptan treatment. Circulating copeptin concentrations together with zinc-α₂-glycoprotein, and basal blood urea nitrogen were higher in non-responders compared to responders to Tolvaptan [76].

5. Conclusions And Future Perspectives

The fact that copeptin and arginine vasopressin are released in equimolar amounts, and due to the advantages of copeptin over arginine vasopressin, copeptin was approved as a surrogate serum biomarker of arginine vasopressin and vasopressinergic activation. Recent studies showed the role of copeptin as a prognostic and diagnostic marker for several diseases. In some cases, due to its low specificity, a combination of copeptin with another biomarker provided a more accurate diagnosis and prognosis for a variety of diseases. Copeptin was able to diagnose a variety of diseases earlier than other approved biomarkers, especially in cardiovascular diseases which could help in the early management of
certain diseases, accordingly decreasing death rates, and improving health care services. It is worthy to have more studies with large cohorts providing more clear information about the predictive values of copeptin in daily clinical practice.

**Abbreviations**

SON, supraoptic; PVN, paraventricular; RIA radio-immuno-assay; CK-MB, creatine kinase-MB; WHO, World Health Organization; TnT, troponin T; TnC, troponin C; TnI, troponin I; STEMI, ST elevation myocardial infarction; BNP, brain-type natriuretic peptide; NT-pro-BNP, precursor N-terminal brain-type natriuretic peptide; COVID-19, corona virus disease-19; eGFR, estimated glomerular filtration rate

**Declarations**

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Not applicable.

**Author contributions**

P.L.W., Y.C., and X.S. contributed to the study design; L.L.W. and B.W. wrote the manuscript. All authors reviewed drafts and approved the final version of the manuscript.

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**Ethical approval**

This article does not contain any studies with human participants performed by any of the authors.

**Declaration of Competing Interest**

The authors have no other competing interests or conflicts of interest to declare.

**References**


47. M. Sazgar, Kidney Disease and Epilepsy, J Stroke Cerebrovasc Dis 30(9) (2021) 105651.
49. A.A. Gonzalez, N. Salinas-Parra, F. Cifuentes-Araneda, C. Reyes-Martinez, Vasopressin actions in the kidney renin angiotensin system and its role in hypertension and renal disease, Vitam Horm 113 (2020) 217-238.


75. R. Shigefuku, M. Iwasa, A. Eguchi, Y. Tamai, K. Yoshikawa, R. Sugimoto, Y. Takei, Serum copeptin level is a biomarker associated with ascites retention and the formation of a portosystemic shunt in chronic liver disease, J Gastroenterol Hepatol 36(4) (2021) 1006-1014.


**Figures**
Figure 1

The structure of arginine vasopressin, which is shown as C46H65N15O12S2
The precursor of arginine vasopressin is subjected to several enzymatic cleavages resulting in production of arginine vasopressin, Neurophysin-2, and copeptin. Abbreviation: AVP, arginine vasopressin.
Pro-arginine-vasopressin is produced in the hypothalamus followed by two different release mechanisms towards the anterior and posterior pituitary glands.

**Figure 3**