A NOVEL STRESS NEUROHORMONE COPEPTIN: ITS POTENTIAL ROLE IN DIAGNOSIS AND PROGNOSIS OF VARIOUS DISEASES

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ABSTRACT

The need for faster diagnosis, more accurate prognostic assessment and treatment decisions in various diseases has led to the investigations of new biomarkers. The hope is that this new biomarker will enable early decision making in clinical practice. Arginine vasopressin is one of the main hormone of the hypothalamic-pituitary-adrenal axis. Its main stimulus for secretion is hyperosmolarity, and exposure of the body to endogenous stress. Reliable measurement of arginine vasopressin concentration is difficult because it is subject to preanalytical and analytical errors. It is therefore not used in clinical practice. Copeptin, a 39-aminoacid glycopeptide, is a C-terminal part of the precursor pre-provasopressin. Activation of arginine vasopressin system stimulates copeptin secretion into the circulation from the posterior pituitary gland in equimolar amounts with arginine vasopressin. Therefore, copeptin directly reflects arginine vasopressin concentration and can be used as surrogate biomarker of arginine vasopressin secretion. Even mild to moderate stress situations contributes to release of copeptin. These reasons have led to a handful of research on copeptin in various diseases. This review summarizes the current achievements in the research of copeptin as a diagnostic and prognostic marker, risk stratification, therapeutic modalities, and also discusses its association in different disease processes.

KEYWORDS

Copeptin, arginine vasopressin, hypothalamic-pituitary axis, endogenous stress, biomarker.
INTRODUCTION

Copeptin, a 39-amino acid glycopeptide is a C-terminal part of pre-provasopressin (pre-proAVP),[1] initially described by Holwerda in 1972.[2] Pre-proAVP is a precursor protein which consists of a signal peptide, arginine vasopressin (AVP), neurophysin II and copeptin. These components are separated during axon transport from the cell body to the axon terminals in the posterior pituitary gland.[3] Copeptin is stored in the neurohypophyseal vesicles together with AVP and neurophysin II[4] and is found in equimolar amounts with AVP in the circulation of healthy and critically ill subjects.[5] Diagnosis and prognosis of diseases are very demanding and time-consuming, hence new biomarkers are in need to aid clinicians in making faster treatment decisions and more accurate prognostic assessment. Copeptin has been proposed as a prognostic marker in different illnesses where it may help in early detection and diagnosis.[6]

Copeptin in circulation

Normal values of copeptin in healthy volunteers range between 1.70-11.25 pmol/L[7] with minimal intra-individual variations.[8] Copeptin concentration are lower in women when compared to men, but there is no significant difference in copeptin rise between men and women with changes in osmolality or volume status.[9] Kinetics of copeptin in vivo are similar to those of AVP, while, ex vivo, it has an extraordinary stability of one to two weeks at room temperature.[10] This favorable discrepancy allows for the precise measurement of copeptin as a surrogate marker for the unstable AVP.

Function of AVP

AVP is a vasoactive neuropituitary hormone of the hypothalamic-pituitary-adrenal (HPA) axis with its primary function in water regulation and homeostasis of electrolytes. The main stimulus for AVP release is hyperosmolality, however hypotension, hypoxia, acidosis, infection, insulin-induced hypoglycemia, pain, nausea, vomiting, certain drugs and other non-specific causes of stress can also increase concentration of AVP in the circulation.[3] AVP binds to 3 different receptors, V1a, V1b and V2 receptor, based on their intracellular transduction mechanisms. The V1a and V1b receptors are associated with phosphoinositol turnover, while the V2 receptor activates adenylate cyclase.[11] The V1a receptor is widely expressed and mediates AVPs prothrombotic and vasoconstrictor effects. Thus, AVP agonists are used in treating bleeding and hypotensive disorders.[12] Through V1a receptor AVP also mediates liver glycogenolysis. The V1b receptor is expressed in the pituitary gland and
pancreas. Through this receptor AVP stimulates the release of adrenocorticotropic hormone (ACTH) which activates the HPA axis and mediates a response to stress. The V2 receptor is expressed in the renal collecting ducts and through these receptors the antidiuretic effect of AVP is mediated. Pharmacological blockade of V2 receptor has been used to treat hyponatremia and heart failure.\[13\]

**Copeptin correlation with AVP and cortisol**

AVP, also known as antidiuretic hormone, is one of the key hormones of HPA axis. AVP and copeptin are secreted from the neurohypophysis upon hemodynamic or osmotic stimuli.\[14\] A strong correlation between copeptin and AVP, in vivo, is a prerequisite before labeling copeptin as a surrogate marker of the AVP system.\[3\] Physiological fluctuations are generally in line with those of AVP with an upsurge during fasting and a rapid fall after water intake. A study comprising of healthy volunteers, plasma copeptin levels were reported to increase after water deprivation with further increase after additional hypertonic saline infusion. In contrast, after hypotonic saline infusion, copeptin levels demonstrated a significant and rapid decline in a similar manner to AVP.\[15\] The correlation between AVP and copeptin were demonstrated in critically ill patients: in a case of severe septic shock, both AVP and copeptin levels were reported to increase initially during the first 36 hrs with a subsequent continuous decline followed by a secondary peak in their levels in response to extubation related stress.\[3\] Furthermore, reliable measurement of AVP is hindered by several factors: Over 90% of AVP is tightly bound to platelets, and its estimation is influenced by the number of platelets, incomplete removal of platelets or pre-analytical processing steps. AVP is highly unstable in isolated plasma even when stored at \(-20\) °C.\[3\] Activation of AVP system stimulates copeptin secretion into the circulation from the posterior pituitary gland in equimolar amounts with AVP. Therefore, copeptin directly reflects AVP concentration and can be used as surrogate biomarker of AVP secretion. Even mild to moderate stress situations contribute to the release of copeptin.\[16\] Corticotropin-releasing hormone (CRH) and AVP appears to have a synergistic effect, resulting in ACTH and cortisol release. High cortisol levels reflect a higher degree of stress, but are dependent on the integrity of the HPA-axis. Copeptin appears to be superior to cortisol in determination of the stress level, as cortisol is further downstream in the stress response, has a strong circadian rhythm and is also challenging to measure as a free hormone.\[17\] In contrast to AVP and cortisol, copeptin is stable both in serum and plasma at room temperature and can be easily measured ex vivo as a ‘shadow’ fragment of AVP in the circulation, in manual or fully automated chemiluminescence assays, and results available
within one hour, which is crucial for any useful biomarker in the emergency department setting. These reasons have led to several different lines of research in various disease states. The purpose of this review is to summarize role of copeptin as a biological marker in the diagnosis, prognosis, risk stratification and its therapeutic modality in various diseases and also summarizes recent progress made in this field.

**Acute Myocardial Infarction**

Acute myocardial infarction (AMI) is the major cause of death and disability worldwide, with an ongoing increase in incidence. Rapid assessment of these patients is critical to direct further diagnostic and therapeutic strategies. Electrocardiography (ECG) and cardiac troponin form the current diagnostic cornerstones and complement clinical assessment in current AMI guidelines, but major limitation of cardiac troponin assays is a sensitivity deficit at presentation due to a delayed increase of circulating levels and normal or unspecific ECG findings. Therefore, markers with a pathophysiologic background independent of cell necrosis improves rapid diagnosis of AMI. The release pattern of copeptin in AMI patients (an immediate rise after onset of chest pain and decrease toward physiologic levels within 5 days) and its potential use in rule-out of AMI has been described recently. Combination of a marker of cardiac necrosis, such as cardiac troponin, with a pathophysiologically different biomarker reflecting acute endogenous stress, copeptin might allow for a rapid and accurate rule out of AMI at initial presentation without serial blood sampling. Endogenous stress occurring with the onset of AMI results in a rapid release of vasopressin and copeptin. With increasing time after onset of symptoms, there is decreasing levels of copeptin, in contrast to increasing levels of cardiac troponin. The fall in copeptin levels reflects a mechanism of adaptation by the endogenous stress system exposed to a continuous stress such as AMI or the consequence of resolution. An alternative trigger of AVP/copeptin secretion from the posterior pituitary could be a baroreceptor stimulation by the threat of hypotension as a result of AMI or direct damage to the cardiac baroreceptors. As copeptin is elevated in many clinical states in which endocrinologic stress signals are present, it will have low specificity for an individual disease such as myocardial infarction, however; because myocardial infarction presents with activation of the hypothalamic stress axis, copeptin biomarkers demonstrate good sensitivity for the disease state. Thus, copeptin seems to be a good biomarker added to cardiac troponin for exclusion of AMI in the setting of triage in the emergency department.
**Post-Acute Myocardial Infarction**

Myocardial remodeling after an AMI is characterized by infarct expansion and a compensatory dilatation of the non-infarct territory may be associated with myocardial failure,\(^{[27]}\) and plays a key role in the development of congestive heart failure in post-AMI patients with large infarcts. Copeptin is associated with ventricular remodeling in AMI where they are inversely correlated with left ventricular ejection fraction at discharge and on follow-up. This may indicate that activation of the AVP system as quantified by increased copeptin levels may not only be regarded as a consequence, but as a contributor to heart failure after an AMI.\(^{[28]}\) Therefore, regardless of baseline heart failure signs and symptoms, copeptin serves as an excellent and independent predictor of death in post-AMI patients.

**Stress Cardiomyopathy (Tako-Tsubo Cardiomyopathy)**

Tako-tsubo cardiomyopathy (TTC) has been considered as a form of reversible and benign cardiomyopathy mostly in post-menopausal women induced by a variety of stressful events (emotional, postsurgical, etc.). Copeptin levels might remain persistently elevated in a portion of TTC patients which is suggestive of ongoing stress after the initial trauma and associated with prolonged disease course and enhanced risk of arrhythmogenesis indicating prognostic value of copeptin in these patients. In patients with TTC, the ratio of serum copeptin/N-terminal prohormone brain natriuretic peptide (NT-proBNP) has recently been suggested as a relatively more independent and accurate index of absolute endogenous stress.\(^{[29]}\) However, copeptin in patients suffering from TTC are insufficient indicating further studies on this issue.

**Arrhythmogenesis**

Enhanced activity of AVP system (as quantified by substantial copeptin levels) will result in poor left ventricular function (and hence increased arrhythmogenesis), and also exert direct arrhythmogenic effects on myocardium largely through creation of an arrhythmogenic substrate (induction of hypertrophy, collagen synthesis). However, copeptin is a promising marker of arrhythmogenesis in patients without heart failure due to its relation with endogenous stress levels. Enhanced endogenous stress is associated with sympathetic hyperactivity\(^{[30]}\) that may induce malign arrhythmias in arrhythmia-prone patients.\(^{[31]}\) Further studies are still warranted to investigate the clinical implications of copeptin in arrhythmogenesis.
Heart Failure

The prognostic role of neurohumoral markers in heart failure is of great interest and clinical importance. Heart failure is commonly associated with hyponatremia, and is also characterized by increased concentrations of basal AVP and copeptin. AVP through its V1 and V2 receptor-mediated effects, contributes to the progression of left ventricular dysfunction by worsening systolic and diastolic wall stress and by stimulating both ventricular hypertrophy and myocardial remodeling. AVP secretion caused by osmolarity stimulus is overridden by the non-osmolarity stimulus, which leads to reduced cardiac output, resulting in insufficient filling of arteries leading to carotid sinus and aortic arch baroreceptor activation. It is also known that angiotensin II increases concentration of AVP. Increased release of AVP is associated with increased preload, increased filling pressures and increased afterload. High copeptin concentration which reflects rise of AVP in the blood therefore predicts poor prognosis in patients with chronic heart failure. The typical range of copeptin for patients with chronic or acute heart failure is between 10-50 pmol/L. Copeptin reflects different pathological pathways that lead to a deterioration of heart failure than brain natriuretic peptide (BNP) or NT-proBNP, hence copeptin in combination with BNP or NT-proBNP, improves in predicting outcome of diseases. Thus, copeptin is exciting for heart failure research today, as it provides prognostic information and also the role of vasopressin blockade as a potential new therapeutic target.

Acute Dyspnea

The identification of dyspneic patients at the highest risk for adverse outcomes is difficult because acute dyspnea often occurs due to several reasons such as cardiac, pulmonary or inflammatory causes. In these patients copeptin secretion is probably connected with three possible mechanisms. Firstly, AVP released in heart failure is mainly driven by inadequate filling of arteries which activates the carotid sinus and aortic arch baroreceptors. Secondly, in severe COPD, AVP has vasoconstrictive effect which is induced by hypoxia. Elevated concentration of AVP can compensate for the inadequate regulation of V1 receptors after exposure to ongoing hypoxemia. Finally, copeptin is significantly elevated in bacterial infection and febrile conditions. A study done by Potocki et al. pointed out that copeptin concentration is significantly higher in patients with acute decompensated heart failure (ADHF) compared to patients with other diagnoses responsible for acute dyspnea. Also, in that study, copeptin was significantly higher in patients who did not survive compared to patients who survived at 30 days, regardless of the presence of ADHF. Therefore, copeptin
could be a promising prognostic biomarker for short term mortality in patients with acute dyspnea.

**Chronic Obstructive Pulmonary Disease**

In chronic obstructive pulmonary disease (COPD) insufficient tissue oxygenation makes cardiovascular adaptation easier through elevated AVP concentration which has a vasoconstrictive effect by creating negative inotropic effect on the right ventricle. This links increased AVP and copeptin with poor clinical outcome in COPD.\(^{[36]}\) Compared with C-reactive protein (CRP) and procalcitonin (PCT), copeptin is superior in predicting the course of COPD exacerbation. Elevated copeptin concentration predicts the final outcome in patients with acute exacerbation of COPD and serves as a risk factor for long term clinical failure, regardless of age, comorbidity, hypoxemia or functional pulmonary disorder.\(^{[37]}\)

**Ventilatory Assisted Pneumonia**

Ventilatory assisted pneumonia (VAP) impose stress by promoting cardiovascular instability and an elevated demand for vasopressin and glucocorticoid secretion. As both peptides are initially secreted in an equimolar ratio, this could be an indication that AVP is rapidly consumed in extreme physiological conditions, thus resulting in a relative AVP insufficiency. Hence, AVP therapy could be useful particularly in those patients who have discrepant copeptin/AVP ratio. Thus, copeptin is an independent predictor of mortality in VAP and helps to assess the disease severity to optimize clinical decision-making and therapy.\(^{[39]}\)

**Community Acquired Pneumonia**

Community acquired pneumonia (CAP) is associated with a high risk of developing respiratory failure or severe sepsis with organ dysfunction or shock, resulting in high mortality rates in hospitalised patients. Initial risk stratification is required to guide management and treatment decisions by a disease severity based approach.\(^{[40]}\) Biomarkers have been found to improve risk stratification and management decisions in CAP.\(^{[41]}\) In high risk CAP, elevated levels of copeptin reflects the degree of progressive septic disease or decompensating/newly developing cardiac or renal disease, demanding more intensive monitoring and management.\(^{[42]}\) Several clinical scores have been evaluated for mortality prediction in CAP (CRB-65 and PSI scores) which are not optimal to identify patients at risk for deteriorating or non responding disease.\(^{[43]}\) Copeptin reflects cardiovascular impairment and outperforms inflammatory markers like CRP and PCT regarding their prognostic value in
CAP. Thus, copeptin improves the predictive properties of existing clinical scores and predicts early deterioration and persistent clinical instability in hospitalised CAP patients.

**Intracerebral Hemorrhage**

In intracerebral hemorrhage (ICH) formation of edema in the brain indicates an unfavorable outcome. AVP has an important role in the formation of brain edema thus blockade of AVP receptors reduces brain edema. Measurement of copeptin can indicate existing or developing brain edema which can help in identifying patients with increased risk of edema formation. After ICH copeptin concentration in plasma is significantly increased, reflecting the severity of hemorrhagic damage and predicting long-term clinical outcome. Copeptin also helps to identify patients with risk of early neurological deterioration and correlates with hematoma volume, which is directly associated with clinical severity and outcome after ICH. Thus, copeptin as a prognostic biomarker is used in combination with other biomarkers in the management of ICH.

**Stroke**

Stroke is the primary cause of long term disability and activation of the HPA axis is among the first measurable physiological response to cerebral ischaemia. The prognostic accuracy of copeptin in stroke patients is superior to that of other commonly measured laboratory parameters, such as blood glucose, CRP and white blood cell count, as well as clinical measures (e.g: blood pressure, temperature). Copeptin also improves the prognostic accuracy of the National Institutes of Health Stroke Scale (NIHSS) score. The combination of the clinical score with copeptin, reveals a significantly higher area under the curve (AUC) of 0.79 to predict functional outcome, if compared to the clinical score or the marker alone. Thus, copeptin allows improved risk stratification and allocation of targeted therapies for stroke patients.

**Head Injury**

In head injury, copeptin concentration elevated in peripheral blood is associated with mortality and poor neurologic outcome. A study done by Yu et al. reported that copeptin increases with severity of brain injury and therefore, its measurements after brain injury provides an opportunity to distinguish patients with a one-year good or poor outcome.
Autosomal Polycystic Kidney Disease

Evidences suggest that AVP plays an important role in the initiation and progression of chronic kidney disease, kidney transplantation and specific role in disorders, such as autosomal adult polycystic kidney disease (ADPKD). ADPKD is the most common hereditary kidney disease characterized by progressive cyst formation in both kidneys. AVP modifies vascular tone in renal microvessels acting via the V2 receptors reducing the efficiency of sodium and urea excretion thus increasing glomerular filtration rate and imposing increased energetic demands on the kidney. In addition, AVP also promotes mitogenesis and proliferation of mesangial cells via the V1 receptors, which mediate AVP-induced cell contraction. AVP has a direct influence on cysts, by stimulating the formation of cAMP, a potent stimulator of cyst growth, particularly of cysts that originate from the distal nephron segments that express V2 receptors. These results confirm preclinical and experimental findings that blocking the endogenous activity of AVP on V2 receptor might counteract the cystic phenotype. Higher copeptin concentration is associated with poor renal function, lower effective renal blood flow, enlarged kidneys and albuminuria. Since copeptin reflects AVP concentration, measurement of copeptin provides a valuable information about the severity of ADPKD and serves to identify patients who benefit from an intervention aimed at countering AVP.

End Stage Renal Disease

Dialysis patients are at a very high risk of death (about 20% per year). Thus, the identification of new risk factors with the potential of applying intervention strategies to improve outcome in the future is of utmost importance. It is assumed that AVP in end stage renal disease (ESRD) patients with little or no residual urine output can probably not efficiently act via V2 receptors. Thus, down regulation of V2 receptor mRNA and a deficient AVP-stimulated adenyl cyclase result in resistance of V2 receptors in earlier stages of chronic kidney disease. These findings suggest that, in ESRD, AVP might primarily act via the V1a and V1b receptors. Thus, an increase in cardiovascular risk and all-cause mortality in ESRD patients might be partly linked to the predominant activation of V1a and V1b receptor function. Copeptin levels are highly increased (median, 81 pmol/L) in chronic kidney disease due to decline in renal function hence less sensitive to the actions of copeptin, or that increased copeptin may result from reduced renal elimination. In addition, copeptin is correlated with ultrafiltration volume, suggesting that volume depletion during dialysis might be responsible for an increase in AVP concentrations. Furthermore, resistance
of V2 receptors is present already at earlier stages of chronic kidney disease,\(^5\) probably involving activation of feedback mechanisms with a regulatory increase of plasma AVP levels. In addition, left ventricular dysfunction,\(^2\) endothelial stress, and type 2 diabetes mellitus might also be contributive factors.\(^5\) Thus, high copeptin levels reflects AVP action in ESRD.\(^5\) Thus, copeptin has a putative role of AVP blockade as an intervention strategy.

**Diabetes Mellitus**

Diabetes mellitus is one of the major risk factors for coronary heart disease and congestive heart failure, but the causes of this interaction are not completely understood. One possible link is the hormones implicated in cardiac diseases which may play a role in the development of diabetes mellitus. Markers that are not part of the diagnostic criteria for diabetes mellitus such as copeptin may signal diabetes susceptibility earlier in the prediabetes state. Thus, the novel risk markers as screening tools for future diabetes risk could be particularly useful in individuals with normal fasting blood glucose, who are likely to be less closely monitored than individuals with impaired fasting glucose.\(^5\) Several studies in humans and animals have suggested role for the AVP system in glucose homeostasis, insulin resistance, and diabetes mellitus.\(^6\) AVP action has been linked to liver glycogenolysis through V1a receptor, insulin & glucagon secretion through V1b receptor\(^6\) and ACTH release through V1b receptor.\(^6\) This crosslink between the AVP and HPA-axis could be of relevance for diabetes development.\(^6\) Impaired signaling through V1a receptor leads to elevated levels of AVP, which in turn stimulates V1b receptor and contributes to insulin resistance and the development of diabetes mellitus.\(^6\) Understanding these pathophysiologic processes provides opportunities for designing pharmacologic interventions to target mediators of these processes.\(^6\) Thus, copeptin provides incremental information for the prediction of diabetes mellitus and considered a new tool for comparing the efficiencies of new therapeutic modalities in diabetes mellitus.

**Diabetes Insipidus**

AVP is released into the circulation following hypoglycemic stimulus. In patients with normal pituitary function, insulin-induced hypoglycemia leads to a threefold increase in AVP concentration. Since copeptin strongly correlates with AVP, copeptin can separate healthy people from patients with diabetes insipidus. Copeptin concentration measured 45 minutes after injection of insulin has the best sensitivity and specificity for detection of diabetes insipidus (DI).\(^6\) DI is a clinical syndrome characterized by polyuria due to a defect in the
urinary concentrating mechanism and associated compensatory polydipsia.\textsuperscript{[68]} The syndrome comprises three main types central, nephrogenic, gestational and a related syndrome, primary polydipsia.\textsuperscript{[69]} DI should be differentiated from primary polydipsia as the latter differs from DI as it is not associated with variants of AVP secretion or activity – but rather from excessive fluid intake over extended periods of time. Copeptin shows identical changes during disordered water states and may help in the differential diagnosis of primary polydipsia and DI. Thus, an accurate differentiation of the underlying pathology is necessary for effective treatment of DI.\textsuperscript{[17]}

A copeptin index is derived by the following equation

\textbf{Delta Copeptin} \[8 \text{ - } 16 \text{ h}] \times 1000 \text{ [pmol/L:mmol/L]S-Na+ [16 h]}

Patients with a copeptin index of <20 are classified as having central DI whereas patients with values >20 have primary polydipsia.\textsuperscript{[70]} If the patient has central diabetes insipidus, the AVP concentration will not increase – even though there has been a significant decrease in body weight or increase in plasma osmolarity. However, if the patient has nephrogenic DI, AVP will appropriately increase in parallel to dehydration status progression and the increase in plasma osmolarity.\textsuperscript{[17]} The first blood sample is able to aid in the distinction between central and nephrogenic DI by comparing the plasma levels of copeptin. Concentrations of Copeptin that are <2.6 pmol/L indicate central DI whereas concentrations >20 pmol/L indicate nephrogenic DI. Patients with intermediate values between 2.6 and 20 pmol/L undergo a further 8 hrs of fluid deprivation. Higher copeptin concentration is associated with poor renal function, lower effective renal blood flow, larger kidneys and albuminuria.\textsuperscript{[3]} Thus, copeptin has been used as a novel approach for the diagnosis of DI.

\textbf{Metabolic Syndrome}

Copeptin is associated with several components of metabolic syndrome including obesity, dyslipidemia, elevated concentration of triglycerides and low HDL-cholesterol. The association of copeptin with higher triglyceride concentration may be secondary to increased hepatic triglyceride synthesis due to glucocorticoids, glucagon and epinephrine released under stress (all of which are regulated by AVP).\textsuperscript{[71]} The association between copeptin at baseline and the incidence of diabetes mellitus is independent of the incidence of abdominal obesity and vice versa, so it is possible that AVP independently triggers two different pathways leading to diabetes mellitus and abdominal obesity.\textsuperscript{[72]} Thus, there is a possibility
that a primary elevation of AVP by increasing abdominal fat deposition leads to the development of diabetes mellitus.

**Hyponatremia and Syndrome of Inappropriate Antidiuretic Hormone Secretion**

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) refers to disorders related to water and sodium balance characterized by the impairment of urinary dilution and hypotonic hyponatremia in the absence of renal disease or other identifiable non-osmotic stimuli known to activate the release of AVP. Hyponatremia, defined as serum sodium levels \(<135 \text{ mmol/L}\), is the most frequent electrolyte disorder occurring in 15%–30% of hospitalized patients. Distinguishing patients with SIADH from patients with hyponatremia in clinical practice is a diagnostic challenge. Mean values of copeptin are higher in patients with hyponatremia compared to patients with SIADH. A study done by Fenske et al. found that isolated measurements of copeptin has only limited value for identification of patients with polydipsia, a combination of copeptin and urinary sodium gives superior performance to the reference standard in discriminating volume depleted from normovolemic hyponatremic disorders. The ratio of copeptin in serum and sodium in urine is diagnostically very useful. This ratio can be used in differentiating normovolemic hyponatremia (ratio \(\leq 30 \text{ pmol/mmol}\)) as SIADH, from hypovolemic hyponatremia (ratio \(>30 \text{ pmol/mmol}\)), i.e. in differentiation of inappropriate from appropriate secretion of AVP. Thus, the correct identification of pseudohyponatremia is essential to avoid unnecessary and dangerous treatments aiming at restoring normal sodium values as overly rapid correction can lead to severe permanent neurological deficits and death.

**Vasodilatory Shock**

Copeptin concentration in plasma is elevated in patients with severe vasodilatory shock and reflects the severity of the disease, a higher incidence of complications and a greater risk of death. AVP infused in patients with severe vasodilatation to supplement a lack of endogenous AVP resulted in decreased concentration and reducing the use of potentially high and toxic doses of catecholamines. During therapy with exogenous AVP, copeptin concentration is decreased, suggesting the suppression of endogenous AVP system. High copeptin levels before treatment and the extent of decrease during treatment with exogenous AVP is associated with severity of disease and mortality. Thus, high copeptin in the presence of vasodilatory shock may indicate insufficient endogenous AVP production and warrants exogenous substitution.
Sepsis
Elevated AVP plasma levels is found in patients in the early phase of sepsis, in an attempt to restore blood pressure, which later tends to decrease due to inflammatory mediators. In the late phase, despite progressive hypotension, the plasma AVP levels are low, contributing to septic shock and death. AVP secretion can be induced by inflammatory mediators such as interleukin 1, tumor necrosis factor α which occur in patients with severe sepsis. Increased cytokine levels, particularly interleukin-1β, trigger the inducible isoform of nitric oxide synthase (iNOS) gene expression in the hypothalamus resulting in production of large nitric oxide (NO) levels, which may act dually on mitochondrial bioenergetics affecting oxygen consumption and enhancing the generation of superoxide anions by decreasing the electron flow through cytochrome c oxidase. These change results in “metabolic hypoxia” and hydrogen peroxide formation, which further stimulates iNOS expression and, consequently, an increase in NO levels. Metabolic hypoxia may also induce the expression and stability of the α subunit of hypoxia-induced factor (HIF)-1α. Dimerization of HIF-1α with the constitutive HIF-1β subunit generates the functional transcription factor HIF-1, which regulates the expression of various genes involved in cellular energy metabolism and in the apoptosis pathway. These alterations promote transient pore formation, which facilitates the release of cytochrome c and other pro-apoptotic molecules from the intermembrane mitochondrial space. The other proposed mechanisms for possible sepsis associated dysfunction of AVP system include autonomic dysfunction of afferent pathways and inadequate production of AVP with consequent depletion of storage in the neurohypophysis. These cellular bioenergetics changes occurring in AVP-producing magnocellular supraoptic nucleus neurons affects AVP synthesis and impairment of hormone secretion seen during the late phase of sepsis. Unlike the AVP whose values don’t differ in patients with sepsis who survived and those who didn’t survive, copeptin is higher in non-survivors compared to survivors. This suggests that copeptin could represent a prognostic biomarker in sepsis.

Fetal Growth Restriction
Fetal Growth Restriction (FGR) is defined as an estimated fetal weight obtained by ultrasound of less than the 10th percentile for gestational age, which is an important clinical problem resulting in morbidity and mortality in fetal life and neonatal period. The early identification of patients with an increased risk for FGR is one of the most important goals in obstetrics. The increased maternal serum copeptin levels in pregnancies associated with
FGR and constitutionally small fetuses may be due to the stress thrown on the pregnant women who know that their fetuses were small for gestational age and may be at risk. This stress results in increased secretion of copeptin & CRH from the hypothalamus.\[^{87}\] These findings suggests that maternal serum copeptin may be used as a test to differentiate between the normal sized healthy and unhealthy growth restricted small fetus in late pregnancy, and to aid in the identification of a group of patients requiring increased fetal surveillance.

**Perinatal Stress**

Labour is considered as an extreme degree of physical and emotional stress resulting in an endocrinal response which might be involved in the mechanism of maternal and fetal adaptation to such a stressful condition.\[^{88}\] Maternal serum copeptin level just after vaginal delivery was significantly higher than following cesarean section in spite of added surgical and anesthethic stress in the latter group suggests that the process of vaginal delivery is the one of the most stressful event that occurs during life and is associated with a large release of copeptin that exceeds the levels in shock, sepsis and trauma.\[^{89}\] Neonates born by vaginal delivery had elevated copeptin cord serum levels compared to those born by elective repeat cesarean delivery which is due to the stress of labor that stimulates for the release of copeptin in the fetus mainly due to temporary utero-placental ischemia resulting in fetal stress. Copeptin level in umbilical cord serum were elevated who were delivered by intrapartum cesarean section for intrauterine fetal distress and those who were not, due to perinatal stress such as birth acidosis and asphyxia.\[^{90}\] Thus, copeptin is a highly sensitive marker of fetal perinatal stress.

**Preeclampsia**

Patients suffering from preeclampsia had significantly higher levels of copeptin as compared with the normal pregnant women. This is explained by the fact that AVP is known to directly stimulate cortisol release in humans by activating the V1a receptors on the adrenal cortex cells that result in salt and water retention causing preeclampsia. AVP also activates the receptors on the chromaffin cells in the adrenal medulla to increase the vasoconstrictive epinephrine levels, which subsequently contribute to hypertension in preeclampsia.\[^{91}\] Thus, increased maternal levels of copeptin is involved in the pathogenesis of preeclampsia and may be useful in the assessment of the severity of the disease.
Perinatal Asphyxia

Neonatal infections account for over one million neonatal deaths worldwide every year\(^{[92]}\) occurring in approximately 0.6% of term and up to 1.5% of preterm infants and contributes significantly to neonatal mortality.\(^{[93]}\) Therefore, early treatment of neonates with suspected infection is crucial to prevent life threatening complications.\(^{[94]}\) Perinatal asphyxia is an extreme of a stress situation where in vasopressin system in the neonate is strongly activated.

The strength of this correlation was comparable between very preterm, late preterm and term infants, suggesting that the vasopressin response is already present at an early gestational age. Perinatal acidosis results from diminished fetal blood and oxygen supply due to maternal, placental or cord complications leading to lactic acidosis. Copeptin cord blood concentration are strongly and inversely correlated with umbilical artery pH, umbilical artery base excess, and lactate, where the concentrations is above 400 pmol/l with a high sensitivity and specificity for asphyxia.\(^{[95]}\) Thus, copeptin concentrations in cord blood are strongly correlated to perinatal stress with the highest values found in neonates with perinatal asphyxia. Further studies are in need to determine whether copeptin is related to asphyxia severity and whether copeptin may improve outcome prognostication after asphyxia.

CONCLUSION

Copeptin, as a biomarker released into the circulation under endogenous stress, could be a potential biomarker in diagnosis of various diseases and prediction of functional outcomes. Since it is not specific to a certain disease, copeptin could be used as an adjunct with more specific biomarkers where it may increase diagnostic accuracy and aid clinicians in making better diagnostic judgements and also comparing the efficiencies of new therapeutic modalities. In summary, together with adrenergic system and HPA axis, AVP system is also substantially implicated in the stress response against disrupted homeostatic balance. Thus, copeptin has emerged as a promising biomarker of non-specific stress response that may aid in the diagnosis, prognosis, risk stratification and therapeutic modalities of a variety of clinical conditions. However, further trials specifically aiming to make head-to-head comparisons among various stress markers are still warranted to find out the most reliable and independent marker or index of stress response.

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