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Copeptin: A Novel Marker for Diagnosis and Prognosis of Various Diseases Associated With Diabetes

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Abstract. Copeptin is an arginine vasopressin (AVP) precursor whose C-terminal has evolved into 39 amino acids. This AVP precursor is converted into equimolar amounts of copeptin, neurophysin II, and AVP. A strong connection between the release of AVP and copeptin was observed. Measurement of AVP concentration remains complicated since AVP is an unstable peptide and, additionally, it is bound by platelets. Copeptin remains stable in serum or plasma for several days in a warm environment and testing for copeptin yields findings in 1 h. Consequently, the quantity of copeptin might serve as a perfect replacement for reflecting the level of AVP.

Copeptin has become identified as a beneficial measure in various diseases. The physiology and structure of copeptin, as well as its potential, to act as a predictive and diagnostic indicator of different diseases associated with diabetes, are the goals of the current review.

Keywords: Arginine vasopressin, copeptin, diabetes insipidus, diabetes mellitus, metabolic syndrome.

INTRODUCTION

A group of metabolic illnesses known as diabetes includes polyuria, polydipsia, and weight loss. Diabetes mellitus [DM] is a metabolic disorder marked by impaired glucose homeostasis that causes blood sugar to rise owing to insufficient insulin production, insulin action defects, or both [1]. Two etiopathogenetic types account for the majority of diabetes cases. The first is type 1 diabetes, which is brought on by a complete lack of insulin secretion. The second is type 2 diabetes mellitus, which has both insulin action resistance and inadequate compensatory insulin production as its causes. Even before obvious fasting hyperglycemia manifests in type 2 diabetes, pathologic and functional alterations in several tissues may already be present in the early stages of aberrant glucose metabolism [17].

Another type of diabetes is diabetes insipidus characterized by inadequate arginine vasopressin (AVP) synthesis or efficacy, resulting in hypotonic polyuria that is accompanied by compensatory polydipsia. The role of AVP has been reported among the causes of type 2 diabetes [15].

Copeptin and AVP are both descended from the same progenitor molecule. Copeptin and AVP have a very significant correlation; it reacts to osmotic, hemodynamic, and general stressful stimuli just as quickly as AVP. The physiological functions of homeostasis of fluid balance, regulation of vascular tone, and control of endocrine stress are roles of AVP, whereas the purpose of copeptin is yet uncertain [4].

The 39-amino acid copeptin is created from the C-terminal of the precursor arginine vasopressin (AVP). AVP, neurophysin II, and copeptin are all produced in equimolar levels from the AVP precursor. Additionally, a strong connection between the release of AVP and copeptin was observed [19]. Measurement of AVP concentration remains complicated since AVP is an unstable peptide and, additionally, it is bound by platelets. Compared with AVP, copeptin is more stable because it remains stable in serum or plasma for several days and has greater testability since copeptin findings are accessible in 1 h [32] and at room temperature [4] (Figure 1). Consequently, the quantity of copeptin might serve as a perfect replacement to reflect the level of AVP [7].

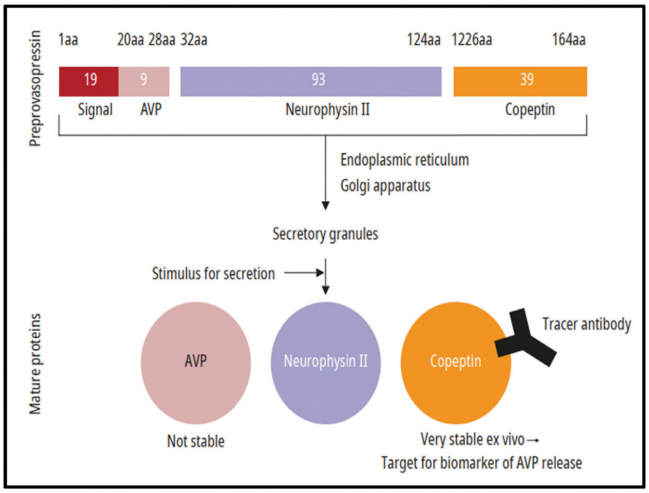

Figure 1. Schematic presentation of the peptide precursor of arginine vasopressin (AVP). The prohormone is packaged into neurosecretory granules of magnocellular neurons. During axonal transport of the granules from the hypothalamus to the posterior pituitary, the final products are vasopressin, neurophysin II, and copeptin. By enzymatic cleavage of the prohormone copeptin, which is coreleased with AVP, is more stable following blood withdrawal. Numbers denote the number of amino acids (aa) present in each part [21].

The first section of this review will be devoted to the structure, physiology, and role of copeptin. Second, the main focus will be on how copeptin may be used as a diagnostic and prognostic marker for various disorders associated with diabetes.

PHYSIOLOGY OF COPEPTIN

Vasopressin is generated from the same precursor peptide (pre-pro-vasopressin) as arginine copeptin and vasopressin (AVP). Physiological factors induce both peptide changes that are comparable to conditions, such as osmotic stimulation, hypovolemia, or stress [23]. Conditions, median Copeptin plasma levels in healthy volunteers at baseline were found to be 4.2 pmol/L, with a wide range of 1–13.8 pmol/L and slightly higher values in men than women. Copeptin levels do not vary with time of day or with age. Consumption of meals and the menstrual cycle do not appear to have any impact on copeptin release [30].

Copeptin is rapidly removed from the circulation by bioactive peptides rather than accumulating there, and this fast clearance no longer takes place *ex vivo*. Copeptin appears to be either broken down by tissue-bound proteases or quickly excreted by the liver or kidneys. However, no specific copeptin receptor or copeptin removal mechanisms are currently understood [8].

While the precise physiological role of copeptin *per se* is largely unclear, the physiological functions of AVP include controlling vascular tone, fluid balance, and the endocrine stress response [24]. However, it was asserted that the chaperone-like molecule copeptin is crucial for the structural development of pro-AVP and may play a role in the proper folding of the precursor molecule pre-pro-AVP by acting on the glycosylation pattern [19].

Copeptin's clinical significance as an AVP marker is based on the fact that both AVP and copeptin are released simultaneously after being transported from the hypothalamus to the posterior pituitary.

According to data obtained from Google Scholar and the PubMed database, the measurement of copeptin in sera might serve as an important marker for assessing the risk of complications as well as outcomes in several diseases in general medicine, where vasopressinergic disturbances may play a role in the pathogenesis [4].

COPEPTIN AS A MARKER FOR A DIABETES INSIPIDUS DIFFERENTIAL DIAGNOSIS

Polyuria polydipsia syndrome is a term used to describe several illnesses, and hypotonic polyuria is eventually either a result of inadequate AVP production effectiveness or is frequently accompanied by compensatory polydipsia. That syndrome falls into one of three categories: First, because of inadequate AVP production in response to osmotic stimulation, central diabetes insipidus (CDI) develops. Second, renal insensitivity to typical AVP secretion is the cause of nephrogenic diabetes insipidus (NDI). Third, primary polydipsia persists despite intact AVP secretion and a favorable renal response (PP) involving excessive fluid intake *per se* that can produce polyuria [15].

The water deprivation test, which has since been supplanted by the hypertonic saline test plus copeptin measurement or arginine-stimulated copeptin measures, was the commonly acknowledged test for decades as a possible differential diagnosis for polyuria and polydipsia. To differentiate between nephrogenic and central diabetes insipidus, copeptin levels may be simply assessed. Copeptin dependably differentiates several entities of polyuria polydipsia syndrome; baseline levels >20 pmol/L without preceding fluid deprivation classify patients with nephrogenic diabetes insipidus, whereas levels measured upon osmotic stimulation with hypertonic saline or upon nonosmotic stimulation with arginine differentiate primary polydipsia from central diabetes insipidus [8]. (Figure 2 Copeptin as a marker in metabolic disorders.)

Copeptin as a Marker in Metabolic Syndrome

Insulin resistance, central obesity, hypertension, hyperglycemia, and dyslipidemia are all metabolic disorders that are considered to be part of the multifactorial condition known as metabolic syndrome (MetS). MetS is highly associated with the development of nonalcoholic fatty

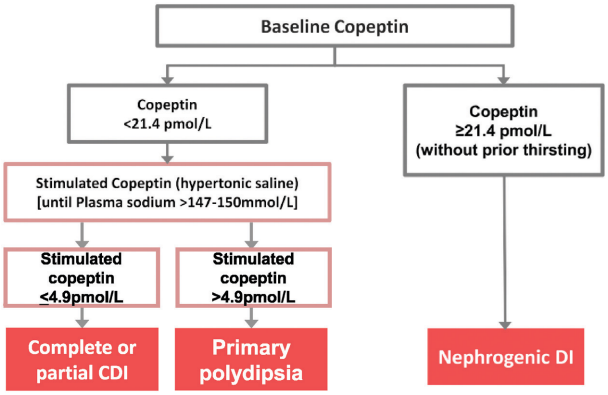

Figure 2. A proposed new algorithm for differential diagnosis polydipsia of polyuria syndrome [8].

liver disease, type 2 diabetes (T2DM), and cardiovascular disease (CVD) [25].

Animal and human studies have shown that copeptin acts as a valid surrogate measure for circulating levels of AVP and that AVP has a function in lipid metabolism and glucose homeostasis [2]. Several studies in humans have shown that high copeptin levels were related to T2DM [27], insulin resistance (IR), and other components of MetS [13], mainly in the adult or elderly population [6]. Plasma copeptin is an independent predictor of metabolic syndrome, including abdominal obesity, increased fasting plasma glucose and insulin concentrations, the homeostasis model assessment of insulin resistance (HOMA-IR), prevalent and incident type 2 diabetes (T2DM), and decreased HDL-cholesterol [10].

Moreover, copeptin levels were shown to be greater in patients with MetS compared to controls, and copeptin was connected to MetS features such as BMI, waist, hypertension, lipids, and diabetes. These results show that elevated copeptin levels in MetS may be used to track the course of the disease, and copeptin readings may indicate the earliest stage of MetS development [11].

In addition, the association of high copeptin levels with MetS was described, and copeptin levels remained independently associated with obesity, insulin resistance, and chronic low-grade inflammation (Popovic et al., 2020).

Furthermore, there is a notable difference in plasma copeptin levels between women and men. A significant correlation was found between the degree of obesity and copeptin but not the other parameters of the MetS. Copeptin was significantly related to obesity in obese children as pubertal boys but not prepubertal boys had higher copeptin levels than girls [26]. On the contrary, it was found that high-plasma copeptin was associated with reduced insulin sensitivity and an increased risk for T2DM in men [2].

Animal studies investigating the association between serum copeptin level and metabolic syndrome (MetS) parameters in both male and female albinos showed comparable results [16].

Copeptin as a Marker in Diabetes Mellitus

A multisystem metabolic condition called diabetes mellitus (DM) is characterized by impaired glucose homeostasis. The development of diabetes is affected by several pathogenic processes. These range from autoimmune destruction of the pancreatic cells and resulting insulin deficiency to defects that result in resistance to insulin action [1]. Two etiopathogenetic types account for the majority of diabetes cases. The first is type 1 diabetes mellitus, which is brought on by a complete lack of secreted insulin. The second is type 2 diabetes mellitus; its cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response [17].

The role of AVP has been found to have a part in the pathogenesis of diabetes [9], and higher plasma copeptin levels are linked to a higher risk of developing diabetes [31]. It was found that vasopressin levels are increased in diabetics, and selective vasopressin V2-receptor antagonist treatment abolished the albuminuria elevation in diabetics [8].

Awad et al. [3] showed that there was a significant elevation of plasma copeptin levels in adolescents with T1DM, which is significantly higher in the presence of microvascular complications, principally diabetic kidney disease. Moreover, it was reported that there is a significant increase in serum copeptin levels accompanied by a positive correlation with the albumin/creatinine ratio in children with T1DM [14].

Regarding insulin resistance, it was reported that serum copeptin was significantly higher in comparison to controls, with a substantial HOMA-IR connection among obese kids and kids with insulin resistance [30].

Additionally, it was shown that there is a significant association between serum copeptin levels and a positive family history of diabetes, indicating that copeptin may have a role in predicting the onset of diabetes if measured sooner. The same study discovered a positive correlation of copeptin with urinary albumin excretion (UAE), which is an early marker of renal damage, as well as a urinary albumin-to-creatinine ratio (UACR), which is the gold standard for diagnosing nephropathy, with the copeptin not only in patients with DM but also levels at various stages from the onset of diabetes to the onset of its complications (controls, prediabetes, DM, and DM with nephropathy) [22].

In a study that analyzed the plasma concentrations of adropin, copeptin, neprilysin, and chitotriosidase in type 2 diabetic patients with or without retinopathy (DR), it was found that copeptin is the best marker to assist in the diagnosis of DR among others [20].

Copeptin as a Marker in Nonalcoholic Steatohepatitis

Barchetta et al. [5] showed a clear correlation between high copeptin levels and the incidence of nonalcoholic fatty

liver disease (NAFLD) and steatohepatitis (NASH). It was found that copeptin levels predict the presence of biopsy-proven NAFLD in obese individuals, regardless of body adiposity and the existence of other metabolic disorders. Elevated copeptin was hypothesized to be independently linked to NAFLD in a population of mixed racial and ethnic backgrounds [12].

Copeptin may be used to diagnose liver cirrhosis and explain systemic infections that contribute to the progression of the condition [29]. Moreover, Kerbert et al. [18] reported that higher copeptin concentrations upon hospital admission are associated with acute-on-chronic liver failure (ACLF) in individuals hospitalized with acute decompensation (AD) and those with classic AD of cirrhosis. Copeptin has been independently linked to the short-term survival and growth of ACLF. Copeptin is a sensitive biomarker that can identify individuals with end-stage liver disease who are at risk for short-term mortality (7 days) as well [28].

CONCLUSION

Copeptin regularly reflects blood AVP concentrations and is released at equimolar levels to AVP. Since copeptin is stable *ex vivo*, is simple to test, and yields findings in an hour, copeptin measurement offers a number of benefits over AVP. Recently, copeptin has been suggested as a potential marker for the differential diagnosis of polyuria-polydipsia syndrome. Copeptin may be useful to serve as a marker for the development of metabolic disorders such as metabolic syndrome, diabetes, and liver conditions.

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