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Copeptin as a novel biomarker of cardiometabolic syndrome

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Abstract

Arginine vasopressin (AVP), which is also called antidiuretic hormone (ADH), is a neurohormone synthetized from a pre-pro-hormone precursor in the supraoptic and paraventricular nuclei of the hypothalamus in response to increased plasma osmolality and decreased blood volume. AVP exerts several effects by binding to three different receptors: V1aR, V1bR, and V2R. In recent years, it has been suggested that increased plasma concentration of AVP may play a causal role in the development of type 2 diabetes, the metabolic syndrome, renal dysfunction and cardiovascular disease by influencing glucose homeostasis and lipid metabolism through several possible mechanisms involving V1aR and

V1bR. V1aR located in the liver is involved in hepatic glycogenolysis and gluconeogenesis. V1bR, found in the pituitary gland and pancreas, mediates secretion of adrenocorticotrophic hormone (ACTH), insulin, and glucagon. However, AVP's clinical use as a biomarker is limited due to its short half-life in plasma (16–20 minutes), small size, and poor stability, which make direct measurement difficult. Copeptin, the biologically inactive, stable, C-terminal part of pro-vasopressin, is co-secreted with AVP in equimolar amounts and thus is considered an adequate and clinically useful surrogate marker of AVP. The aim of this review is to assess the current state of knowledge about the potential role of copeptin as a novel biomarker of cardiometabolic syndrome on the basis of recent scientific literature published up to December 2020 and searches of the PubMed, Google Scholar, and Web of Science databases.

Key words: copeptin; AVP; metabolic syndrome; type 2 diabetes; cardiometabolic risk

Introduction

Arginine vasopressin (AVP), which is also called antidiuretic hormone (ADH), is a neurohormone synthesized from a pre-pro-hormone precursor in the supraoptic and paraventricular nuclei of the hypothalamus in response to increased plasma osmolality and decreased blood volume. It is then transported via axons to the neurohypophysis and released in response to osmo- or baroreceptor stimuli. During the transport pre-pro-vasopressin is cleaved to vasopressin, neurophysin II, and the C-terminal copeptin [1-4]. AVP exerts several effects by binding to 3 different receptors: V1aR, V1bR, and V2R (Fig. 1) [4]. One of AVP's most important physiological functions is maintaining stable plasma osmolality by promoting renal water conservation through vasopressin type 2 receptors located in the renal collecting ducts [3, 4].

Recently, it has been pointed out that the AVP system significantly influences glucose homeostasis and lipid metabolism through several possible mechanisms [1, 5–9]. Firstly, AVP promotes hepatic glycogenolysis, gluconeogenesis, and triglyceride production through the activation of V1aR [1, 3, 4, 7, 9–11]. Secondly, V1bR, which is mainly expressed in the adenohypophysis, mediates the release of adreno-corticotrophin hormone (ACTH) and in turn stimulates cortisol secretion in response to stress factors. Under those circumstances the synergistic effect of both AVP and corticotrophin-releasing hormone (CRH) is over 30 times greater than that of CRH alone [12, 13]. Interestingly, AVP-stimulated increased pituitary-adrenal axis activity is resistant to cortisol negative feedback loop, leading to hypercortisolaemia and development of a mild Cushing-like phenotype [14, 15]. Moreover, the V1bR is also expressed in the Langerhans islets of the pancreas, where it mediates either insulin or glucagon secretion, depending on the extracellular glucose level [9–11].

In recent years, it has been suggested that increased plasma concentration of AVP may play a causal role in the development of type 2 diabetes, metabolic syndrome, and chronic kidney and cardiovascular diseases [1, 3, 5, 7, 13–15]. However, AVP's clinical use as a biomarker is limited due to its short half-life in plasma (16–20 minutes), small size, and poor stability, which make direct measurement difficult [3, 4, 6]. Copeptin, the biologically inactive, stable, C-terminal part of pro-vasopressin, is co-secreted with AVP in equimolar amounts and is thus considered an adequate and clinically useful surrogate marker of AVP [2, 7, 15–17]. In healthy individuals the copeptin plasma concentration ranges from 1 to 13.8 pmol/L, with an average of 4.2 pmol/L and with a significant difference between women and men – with lower values in females [2, 4, 6, 16].

The aim of this review is to outline the potential role of copeptin as a novel biomarker of cardiometabolic syndrome.

Copeptin and metabolic syndrome

Lately, it has been emphasized that the AVP system is involved in regulating metabolic homeostasis in humans. High circulating plasma copeptin levels have been associated with several components of metabolic syndrome, such as abdominal obesity, insulin resistance, glucose intolerance, hyperinsulinaemia, hypertension, and dyslipidaemia [14, 15, 18–21]. Several studies have been carried out on a Swedish cohort from the Malmo Diet and Cancer Study (MDC). The first showed a positive association – independent of other well known risk factors – between plasma copeptin and components of metabolic syndrome such as hypertension, abdominal obesity, obesity, c-reactive protein, and the metabolic syndrome itself. Moreover, high plasma copeptin was associated with high fat intake and low physical activity [22]. However, in a subsequent study on the same population, during a long-term follow-up of 15.8 years, copeptin independently predicted only abdominal obesity but not the cluster of the metabolic syndrome [23].

In a recent observational, population-based study an association between elevated plasma copeptin and various features of metabolic syndrome, including haemoglobin (HbA_{1c}), glucose, triglycerides, high-density lipoprotein (HDL) cholesterol, body mass index (BMI), and waist circumference, were found [24]. Similarly, in another study, subjects with metabolic syndrome had plasma copeptin concentration above 5 pmol/L [3, 9]. Vintila et al. showed that increased concentrations of copeptin were associated with metabolic syndrome and its components such as obesity, dyslipidaemia, and insulin resistance in a Romanian population [25]. A Swiss multicentre, population-based study investigated the association of copeptin with insulin resistance and metabolic syndrome. The authors concluded that insulin resistance was positively correlated with copeptin concentrations, but only in the eldest group of participants (age 54–69 years) [26]. However, there are limited data concerning the influence of weight loss on copeptin levels. Interestingly, a study by Aktimur et al. showed that copeptin

concentrations decrease after weight loss induced by bariatric surgery [27]. Of note, several animal and human studies revealed that the AVP system has a significant effect not only on glycaemia and glucose tolerance but also on hepatic steatosis [28–30].

In a population-based study, carried out on South Africans with mixed ethnicities, Enhorning et al. demonstrated a significant correlation between elevated copeptin and higher occurrence of non-alcoholic fatty liver disease (NAFLD). Furthermore, copeptin was positively correlated with elevated HbA_{1c}, insulin, HOmeostatic Model Assesment – Insulin Resistance (HOMA-IR), BMI, and waist circumference, and was negatively correlated with HDL. No significant differences between ethnicities were found [30]. Similar results were presented by Barchetta et al. The association between elevated plasma copeptin concentrations and higher prevalence of metabolic syndrome, visceral obesity, and NAFLD, confirmed by the liver biopsy, was revealed in this study [29].

Copeptin and diabetes mellitus

The association between hyper-secretion of AVP and copeptin and the risk of developing type 2 diabetes has been recently investigated in several studies [11, 13, 25, 31]. Previously, it has been suggested that increased levels of AVP in diabetes mellitus result from a hyperglycaemia-mediated increase in plasma osmolality and polyuria leading to a relative reduction in extracellular fluid volume [32]. However, recently, most authors indicate a causal pathogenic role for AVP in diabetes rather than an increase induced by the disease itself, because in healthy subjects AVP infusion has been reported to cause hyperglycaemia, and elevated copeptin concentrations are observed many years before the onset of diabetes [5, 33].

Based on data emerging from animal studies, suggesting a pathogenic role of AVP in glucose metabolism, Enhorning et al. carried out a population-based study to assess the

association between plasma levels of copeptin and prevalent diabetes, insulin resistance, and incident diabetes during 12.6 years of follow-up [5]. The results showed that plasma copeptin levels were higher among individuals with diabetes compared to non-diabetic subjects. Moreover, elevated plasma copeptin predicted future development of type 2 diabetes mellitus, independently of glucotoxicity or insulin resistance at baseline. Subjects who developed diabetes mellitus after 12.6 years of follow-up had a median copeptin level 40% higher than control subjects [3, 5]. Additionally, plasma copeptin concentrations positively correlated with hyperinsulinaemia. Another study, based on the same population, showed a positive correlation between increased copeptin levels at baseline and the development of incident type 2 diabetes, abdominal obesity, and microalbuminuria during a long-term follow-up of 15.8 years [23]. Popovic et al. observed that median copeptin concentrations increased depending on the diabetic status of the subjects, from 6.0 pmol/L (people without diabetes), through 7.3 pmol/L (prediabetes), to 8.5 pmol/L (type 2 diabetes). A similar correlation was found between copeptin levels and patients with BMI above or below 35 kg/m^2 [34]. Roussel et al., in a large community-based cohort study, reported an association between high plasma copeptin concentrations at baseline and reduced insulin sensitivity and increased risk of IFG or type 2 diabetes during a 9-year follow-up [35]. Interestingly, there are a few studies that point out the gender-related difference of the correlation between copeptin and risk of type 2 diabetes, with the association stronger in men [33] or in women [8].

Copeptin and diabetic complications

In recent years, several studies have provided strong evidence that increased levels of copeptin are linked to diabetic macro- and microvascular complications [36–39].

Copeptin and diabetic microangiopathy

Several studies provide evidence that AVP contributes to the development and progression of diabetic nephropathy and renal failure [23, 32, 37]. Plasma copeptin concentrations have been inversely associated with renal function estimated with the estimated glomerular filtration rate (eGFR) in subjects with diabetes [32, 37, 40], and they seemed stronger than the association between well known risk factors such as smoking, HbA_{1c}, and cholesterol [41]. Furthermore, a positive correlation between plasma copeptin and other markers of renal dysfunction such as blood urea nitrogen (BUN), creatinine, urinary albumin excretion (UAE), and urine albumin-to-creatinine ratio (UACR) were found [32, 41]. One explanation of the association between copeptin and eGFR, based on results obtained from animal studies, suggests that the underlying mechanism may be that AVP leads to hyperfiltration and then to albuminuria and glomerulosclerosis [41]. These results indicate that plasma copeptin might be a new prognostic marker for renal function decline in type 2 diabetes patients [40–42].

A few studies have recently focused on the relationship between copeptin and diabetic retinopathy. The results show that plasma copeptin levels are significantly higher in type 2 diabetes patients with diabetic retinopathy when compared with those without diabetic retinopathy [38, 43]. Thus, plasma copeptin could potentially serve as an independent marker of diabetic retinopathy [44].

Copeptin and diabetic macroangiopathy

An increasing body of data suggests that high circulating levels of copeptin are associated with increased risk of heart and cardiovascular disease as well as premature mortality, especially in patients with diabetes [2, 13, 14, 19, 30]. There is increasing evidence

that copeptin is a biomarker of atherosclerosis in diabetic people [36, 40]. The pathophysiological mechanism underlying this phenomenon is yet not fully understood. However, it is well known that high concentrations of AVP stimulate V1aR preferentially, inducing vasoconstriction and platelet aggregation, thus potentially contributing to the cardiovascular complications of diabetes [45]. Moreover, V2R activation in endothelium increases the circulating levels of coagulation factor VIII, von Willebrand factor, and tissue plasminogen activator [36]. In the British Regional Heart Study copeptin serum levels correlated significantly with markers of endothelial dysfunction and inflammation independently of insulin resistance [46].

Enhorning et al. designed a study aimed to assess the role of copeptin as a prognostic marker for diabetic heart disease and death. A strong relationship, independent of conventional risk factors such as age, sex, LDL, HDL, systolic blood pressure, or smoking, was found between copeptin and the primary end-point composed of coronary artery disease, heart failure, and death in diabetic individuals [39]. Interestingly, the association was stronger among incident diabetic individuals than among prevalent ones. The results suggest that the AVP system, with its prothrombic and vasoconstrictive properties, may potentiate diabetic endothelial dysfunction, resulting in an increased risk of cardiac complications of diabetes [36, 39].

Velho et al., in a study on two independent cohorts of people with type 2 diabetes, confirmed an association between baseline plasma copeptin levels and the incidence of myocardial infarction, coronary revascularisation, congestive heart failure, and cardiovascular death during a five-year follow-up [40]. Smaradottir et al. analysed copeptin levels in patients with type 2 diabetes and myocardial infarction at admission, discharge and three months later and discovered that copeptin serum concentrations at admission were significantly higher than

at subsequent time points. Moreover, copeptin turned out to be a significant predictor for cardiovascular events at all time points [47].

Copeptin and PCOS

Recently, attention has been drawn to the association between copeptin and insulin resistance in polycystic ovary syndrome (PCOS) patients. A case-control study on 158 women with PCOS showed a correlation between copeptin and the risk of increased HOMA-IR ≥ 2.5 [12]. Increased serum copeptin levels have been reported in PCOS patients, especially the obese ones [48–50]. Moreover, a positive correlation between serum copeptin concentrations and cardiometabolic parameters such as BMI, WHR, hirsutism score, total testosterone, and HOMA-IR has been reported [48–50], making copeptin potentially useful for detecting future cardiovascular risk in PCOS patients.

The influence of water intake on metabolic profile

The secretion of AVP strongly depends on the level of hydration [28]. People with low water intake have a considerably higher circulating plasma AVP, lower 24-hour urine volume, and higher urine osmolality than individuals with higher water intake [51, 52]. Notably, low water intake and high urine osmolality are linked to an unfavourable metabolic profile at a population level, indicating that AVP lowering interventions could be beneficial to metabolic health [14, 24]. Several recent clinical trials and observational studies suggest that increased water intake is associated with favourable metabolic profile, better glucose control, weight loss, and decreased cardiovascular risk [53–57]. The water-induced change in copeptin concentrations was examined by Enhorning et al. [1]. The author reported that 1 week of increased hydration led to a 15% reduction of copeptin on average. Of note, subjects with

habitual low-water intake and high copeptin presented an even greater reduction in copeptin of up 40% [1].

In another study, a significant reduction of both fasting copeptin and glucose concentrations was observed in low-drinking individuals after subjecting them to a 6-week period of increased water intake (1.5 L/day) [24, 55]. This effect can be explained by the fact that water responders express a water-induced reduction of the diabetogenic hormone glucagon [55]. Those findings indicate that water supplementation in persons with habitual low water intake may improve metabolic profile and reduce diabetes risk.

Conclusions

Several recent studies indicate that plasma copeptin, the C-terminal part of the preprovasopressin, might be used as a potential novel risk factor for cardiometabolic syndrome. Interventions designed to lower AVP plasma concentrations may be beneficial for the prevention and treatment of various metabolic-related diseases.

Founding

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Conflict of interest

The authors declare that they have no conflict of interest.

Contributions

All authors contributed significantly to this paper.

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Figure 1. The physiological functions of vasopressin receptors