The Vasopressin System in the Risk of Diabetes and Cardiorenal Disease, and Hydration as a Potential Lifestyle Intervention

Sofia Enhörninga,b Olle Melandera,c

aDepartment of Clinical Sciences, Lund University, Malmö, Sweden; bDepartment of Endocrinology, Skåne University Hospital, Malmö, Sweden; cDepartment of Internal Medicine, Skåne University Hospital, Lund University, Malmö, Sweden

Abstract

Background: Type 2 diabetes, chronic kidney disease (CKD) and its cardiovascular complications are increasing as health problems worldwide. These diseases are interrelated with overlapping occurrence and once diabetes is established, the risk of cardiorenal disease is dramatically elevated. Thus, a search for unifying modifiable risk factors is key for effective prevention. Summary: Elevated fasting plasma concentration of vasopressin, measured with the marker copeptin, predicts new onset type 2 diabetes as well as renal function decline. Furthermore, we recently showed that increased plasma copeptin concentration independently predicts the development of both CKD and other specified kidney diseases. In consequence, high copeptin is an independent risk factor for cardiovascular disease and premature mortality in both diabetes patients and in the general population. Vasopressin is released when plasma osmolality is high, and the easiest way to lower plasma vasopressin and copeptin concentration is to increase water intake. In a human water intervention experiment with 1 week of 3 L/day increased water intake, the one third of the participants with the greatest copeptin reduction (water responders) were those with a phenotype of low water intake (high habitual plasma copeptin and urine osmolality, and low urine volume). The water-responders had a copeptin reduction of 41% after 1 week of increased water intake compared to a control week; in contrast, a 3% reduction occurred in the other two thirds of the study participants. Among water responders, increased water intake also induced a reduction in fasting glucagon concentration. Key Messages: Elevated copeptin, a measure of vasopressin, is a risk marker of metabolic and cardiorenal diseases and may assist in the detection of individuals at higher risk for these diseases. Furthermore, individuals with high copeptin and other signs of low water intake may experience beneficial glucometabolic effects of increased water intake. Future randomized control trials investigating effects of hydration on glucometabolic and renal outcomes should focus on individuals with signs of low water intake including high plasma copeptin concentration.

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**Type 2 Diabetes, Cardiovascular and Renal Disease**

Type 2 diabetes is a growing problem worldwide. The cause of the epidemic increase is most likely a result from rapid changes in personal habits, including caloric overconsumption and decreasing physical activity; these trigger disease development in genetically predisposed individuals [1]. The dramatic increase in prevalence of type 2 diabetes leads to multiple complications and high healthcare costs. The late complications of diabetes include damage and failure of several organs. The microvascular damage of diabetes leads to retinopathy, neuropathy and nephropathy. However, most of the morbidity and mortality associated with diabetes is caused by macrovascular complications, including myocardial infarction and stroke [2, 3]. The causes of the interaction between diabetes and cardiovascular disease (CVD) are incompletely understood, and studies have not consistently been able to show that improvement of glucose control in diabetes leads to decreased risk of CVD mortality [4, 5]. Thus, it is relevant to find pharmacologically modifiable risk factors other than glucose level that are linked to CVD in diabetes patients, giving clinicians a possibility to slow or prevent disease development. Chronic kidney disease (CKD) and need for dialysis is also increasing as a health problem worldwide, and identification of the pathophysiological pathways contributing to CKD progression is crucial in order to find new preventive strategies.

**Vasopressin and Copeptin**

In recent years, it has been suggested that vasopressin may be a key player in the development of diabetes, renal disease and CVD.

Vasopressin, also called antidiuretic hormone, is a hormone secreted from the posterior pituitary to restore plasma osmolality. It is a short-lived hormone in plasma, with a mean half-life of 24 min [6]. Except from controlling plasma osmolality, vasopressin exerts a variety of different physiological effects in the body mediated through 3 receptors – the V1a receptor, the V1b receptor and the V2 receptor. The V1a receptor is widely expressed in the body and mediates, for example, vasoconstriction and platelet aggregation in blood vessels [7, 8], and glycogenolysis and gluconeogenesis in the liver [9, 10]. The V1b receptor is a component of the hypothalamic-pituitary-adrenocortical (HPA) axis. The receptor is expressed in the anterior pituitary gland and mediates release of adreno-corticotrophin hormone (ACTH). This release, together with corticotrophin-releasing hormone (CRH) effects, is important for the maintenance of ACTH and corticosterone levels in the endocrine stress response [11, 12]. Vasopressin is also reported to be locally released within the adrenal gland, where it hypothetically mediates cortisol release and acts as a paracrine factor to stimulate adrenal steroidogenesis [13]. Furthermore, the V1b receptor is expressed in the pancreas where it mediates glucagon and insulin secretion [14, 15]. The antidiuretic action of vasopressin mainly depends on V2 receptor-mediated effects in the renal collecting duct [16].

The vasopressin precursor protein, prepro-vasopressin (Fig. 1), is synthesized in magnocellular and parvocellular neurons of the hypothalamus and transported via axons to the posterior lobe of the pituitary gland, or released into the pituitary portal system to the anterior pituitary gland where it mediates ACTH release. During transport, prepro-vasopressin is cleaved into the product peptides vasopressin, neurophysin II and the C-terminal copeptin [17]. Neurophysin II is a carrier protein that serves to stabilize vasopressin during transport and storage, and to help in the correct folding and targeting of the vasopressin precursor [17, 18]. Copeptin is also suggested to play a role in the correct folding and maturation of the vasopressin precursor [19], but the peptide has no other known physiological effects. All 3 peptides are released from the posterior pituitary gland when neurons in the hypothalamus are depolarized by osmoreceptor or baroreceptor stimuli [17, 20]. The osmoreceptors, which are neurons in the lamina terminalis, are excluded from the blood brain barrier and thus are affected by changes in the concentration of systemic fluid solutes [21], thereby stimulating both thirst and vasopressin secretion during conditions of increased plasma osmolality. Sodium and its anions normally represent more than 95% of the osmotically active solutes in plasma; sodium is the most powerful solute to stimulate vasopressin release [22]. Vasopressin release is said to be suppressed to undetectable levels below a certain threshold level of osmolality (around 280 mosmol/L) [23, 24]. Above the threshold level, vasopressin is released proportionally to an increase in plasma osmolality (Fig. 2).

Because of its small size, it is not possible to detect vasopressin with sandwich immunoassays [25]. Thus, an assay was introduced in 2006 to quantify vasopressin release by the measurement of plasma copeptin (Fig. 1). Copeptin correlates well with vasopressin levels and can be measured reliably in plasma over a wide range of physiological changes in plasma osmolality [25–27] in indi-
Individuals with estimated glomerular filtration rate (eGFR) >28 mL/min/1.73 m². A correction for renal function may be required below this level of eGFR [28].

**Vasopressin and Diabetes**

It has been known since 1979 that individuals with diabetes have elevated vasopressin levels [29]. However, the exact causes of this elevation are not yet known. Recently it was discovered that diabetic rats, in contrast to control rats, have increased hypothalamic vasopressin synthesis due to upregulated chloride transporters and an excitatory response evoked by the neurotransmitter GABA. These findings thus reveal a potential mechanistic explanation for elevated vasopressin concentration in diabetes [30].

We and others previously showed that elevated fasting plasma concentration of vasopressin, measured as copeptin, strongly and independently predicts new onset type 2 diabetes [31–33] and is associated with all components of the metabolic syndrome (i.e., abdominal obesity, insulin resistance, hypertension, chronic inflammation and microalbuminuria) [34, 35]. Furthermore, a human Mendelian randomization study suggested causality between elevated vasopressin concentration and elevated plasma glucose concentration [36].

The mechanisms that underlie the vasopressin-associated development of metabolic diseases are not yet unravelled. Vasopressin mediates ACTH and cortisol release, enhances the effects of CRH, and elevates glucocorticoid concentration in plasma upon stressful stimuli [11–13]. Furthermore, the vasopressin-induced ACTH release has been shown to be resistant to glucocorticoid feedback in contrast to the CRH-induced ACTH release [37], suggesting that excessive vasopressin release overstimulates the HPA axis. Elevated glucocorticoid concentration in plasma could explain the Cushing’s syndrome-like phenotype seen in subjects with high copeptin including development of overweight and insulin resistance [38]. Other suggested links between the vasopressin system and metabolic disturbances include (a) Serum- and Glucocorticoid-inducible Kinase 1, which is upregulated as part of the pleiotropic effects of glucocorticoids [39]; and (b) V1b receptor-mediated GLP-1 release from intestinal L-cells, which increases plasma glucocorticoid concentration and hypothetically modulates osmolality by a glucocorticoid-mediated increase of intestinal sodium and water absorption [40]. Yet another potential link between vasopressin and metabolic disorders, which further adds to the complexity, is the influence of hydration status on modulation of cell volume, which has been shown to change cellular metabolism. For example, hypoosmotic liver cell swelling decreases glycogenolysis and glycolysis in vitro [41].

**Potential Improvement of Glucose Metabolism and Cardiometabolic Health with Increased Hydration**

Previous trials and observational studies have demonstrated that high water intake may promote better glucose control, weight loss and decreased cardiovascular risk [42–45]. It is known that individuals with low water intake have elevated vasopressin concentrations [46], and we recently showed in healthy adults that increased water intake over 6 weeks effectively lowered circulating copeptin concentration [47]. A beneficial role of increased water intake.
intake and decreased circulating vasopressin (measured as copeptin) for cardiometabolic health in humans was recently supported by animal studies where we showed not only that glucose tolerance in rats was impaired during sustained infusion of vasopressin but also that when rats had a high water intake, leading to low concentration of vasopressin, their insulin resistance and hepatic fat accumulation were reduced [48]. Conversely, a detrimental effect of 3 days of water restriction was demonstrated during an experimental study investigating glucose homeostasis in hypohydrated men with type 2 diabetes. In this study, impaired glucose regulation during an oral glucose tolerance test was paralleled by elevated plasma osmolality and cortisol concentrations, suggesting vasopressin-mediated ACTH and cortisol release [49]. In line with this finding, it is known that habitual low drinkers (≤1.2 L water/day) have elevated plasma cortisol concentration when compared to high drinkers (2–4 L water/day) [46].

A Water Intervention Experiment

To investigate the role of a decreased vasopressin load on glucose metabolism in humans we recently conducted a water intervention experiment [50]. Increased water intake was used to decrease plasma osmolality and thus vasopressin concentration in plasma. After a rapid oral water intake of 1 L in healthy adults (n = 37), copeptin decreased within minutes and remained low for several hours (Fig. 3). Furthermore, an excess intake of 3 L of water per day (above habitual water intake) during 1 week (water week) significantly lowered copeptin concentration. The one third of the participants with the greatest copeptin reduction after water week (water-responders) habitually exhibited a low water intake, high urine osmolality, low urine volume and high baseline copeptin. Furthermore, among water responders, a significantly lower fasting glucagon was observed after water week, compared to after a week of normal (habitual) water intake (control week).

These data suggest that individuals with elevated copeptin, and thus higher risk for metabolic diseases, may experience improved gluco-regulation following increased water intake.

Vasopressin in Renal Disease and the Role of Hydration on Kidney Health

A randomized controlled water intake trial, examining the effects of increased water intake on eGFR in subjects with CKD, was recently completed [51]. In line with the epidemiological findings of a kidney protective hydration
effect [52, 53], previous experimental studies in humans and animals suggest beneficial effects on kidney function from increased water intake [54], genetic lack of vasopressin [55, 56], and vasopressin receptor antagonism [57]; in contrast, impaired renal function has been observed during vasopressin exposure [55, 58]. Furthermore, we and others have shown that elevated copeptin, as a proxy for low water intake, is associated with microalbuminuria [32, 59] and independently predicts renal function decline, measured as decline in eGFR, in diabetes patients [60–62] and in the general population [63, 64].

We recently extended our previous finding that copeptin predicts eGFR decline by showing that elevated baseline copeptin was independently associated with increased risk of CKD development in 2 population-based Swedish cohorts [65]. The Malmö Preventive Project (MPP) and Malmö Diet and Cancer Cardiovascular Cohort (MDC-CC) were followed for 9 and 20 years, respectively, and incident cases of renal disease were identified by national registers covering 99% of all hospital discharges, hospital-based outpatient care, and all deaths among Swedish residents. Furthermore, in the MPP cohort and in a meta-analysis of the MPP and MDC-CC cohorts, association between elevated copeptin and increased risk of specified kidney diseases other than CKD was observed. Among this set of widely diverse diagnoses, the most frequently occurring specified kidney disease diagnoses were acute tubulointerstitial nephritis and hydronephrosis in both of the cohorts. In a subanalysis, we found that elevated copeptin mainly increased the risk of tubulointerstitial kidney disease, a finding that was hypothetically linked to the fact that the V2R are localized in the tubuli.

These convincing epidemiological and experimental data point at a causal link between high circulating vasopressin concentration and renal disease, even though large randomized controlled trials to test if lowering or blocking of vasopressin is renoprotective are needed to understand whether the link is causal or not. Similar to the vasopressin-associated development of diabetes and the metabolic syndrome, the mechanisms that underlie the vasopressin-associated development of renal disease are not known. However, studies in rats have shown that vasopressin induces an increase of renal plasma flow and glomerular filtration rate (hyperfiltration), which is thought to be at least partially involved [56, 66]. Interestingly, chronic exposure to elevated glucocorticoids in patients with Cushing’s syndrome causes a decreased glomerular filtration rate [67], suggesting that excessive vasopressin release followed by overstimulation of the HPA axis may not only be linked to the development of the metabolic syndrome, as described above, but also to renal function decline.

Conclusion

Elevated vasopressin is an independent risk factor for the development of diabetes and cardiorenal disease, and extensive epidemiological and experimental data suggest a causal link. In the future, the vasopressin marker copeptin may help detect individuals who are at higher risk for disease development and who might benefit from vasopressin-lowering therapy and lifestyle interventions such as increased hydration.

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