Vasopressin, from Regulator to Disease Predictor for Diabetes and Cardiometabolic Risk

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Key Words

Vasopressin · Hydration · Diabetes mellitus · Copeptin · Cardiovascular disease

Abstract

Background: Type 2 diabetes and its cardiovascular disease complications are the major public health threats of our century. Although physical activity and dietary changes are the cornerstones in prevention of diabetes, their broad implementation is not elementary and other complementary lifestyle regimens are needed. **Summary:** Vasopressin (VP) is the main regulator of body water homeostasis, and at insufficient water intake, normal plasma osmolality can be maintained by increased pituitary VP secretion through VP-2 receptor mediated renal water reabsorption. During the last 6 years several independent studies have shown that high circulating VP, measured by the stable VP marker copeptin, predicts development of type 2 diabetes as well as the metabolic syndrome, cardiovascular disease and premature mortality. Interestingly, VP stimulates adrenocorticotrophic hormone, and as a consequence cortisol secretion, through pituitary VP-1B receptors, which could explain why the 25% of the middle-aged population with high circulating VP have a mild Cushing's syndrome-like phenotype. In rats, high VP results in deterioration of glucose tolerance whereas low VP,

obtained by high water intake, ameliorates the VP associated dysmetabolic state, suggesting that the relationship between high VP and risk of diabetes and cardiometabolic disease in humans may be causal and reversible by increasing water intake. **Key Messages:** With the emerging evidence that high VP, which is present in 25% of the population, is an independent risk factor for diabetes and cardiometabolic disease, VP reduction through water supplementation appears as an attractive candidate intervention to prevent diabetes and its cardiovascular complications.

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The Importance of Prevention of Type 2 DM in Order to Reduce the Burden of Cardiovascular Disease

The number of patients with type 2 diabetes in Europe and the world increases constantly and represents a major threat to global cardiovascular health, as a potent risk factor for cardiovascular morbidity and mortality [1, 2]. Importantly, the excess cardiovascular risk seems to start at non-diabetic levels of glycemia long before clinical diagnosis of type 2 diabetes [3]. Apart from disturbed glucose metabolism, both patients with overt type 2 diabetes and healthy people with elevated risk of diabetes development

are typically characterized by insulin resistance and clusters of other cardiovascular risk factors (e.g., obesity, in particular abdominal obesity with excess hepatic fat or liver steatosis, insulin resistance, hypertension, dyslipidemia, microalbuminuria and chronic inflammation). This diabetes and pre-diabetes related clustering of risk factors, sometimes referred to as ‘the metabolic syndrome’, puts affected individuals at extreme cardiovascular risk [4–6].

Intriguingly, many trials aimed at reducing blood glucose in patients with manifest type 2 diabetes, in order to reduce the marked excess risk of cardiovascular disease and death that these patients suffer from, have failed to do so [7–9]. One likely explanation is that treatment is initiated too late; this assumes that, when type 2 diabetes is established and diagnosed, the atherosclerotic burden is so advanced that it is difficult to reverse by blood glucose lowering therapies. This emphasizes the need for diabetes prevention in order to avoid its macrovascular complications. Although dietary changes and physical activity are the cornerstones in the prevention of obesity and diabetes, it is not elementary to broadly implement these preventive interventions, and they have not been able to satisfactorily reduce obesity and diabetes rates. Thus, new complementary preventive easy-to-implement lifestyle interventions need to be discovered.

The Vasopressin System

Vasopressin (VP), also named antidiuretic hormone, is released from the posterior pituitary gland with the main physiological role of maintaining constant plasma osmolality during altered hydration states. When water intake is low, increased pituitary VP secretion prevents hyper-osmolality by enhancing renal water reabsorption and leading to urine concentration through VP stimulation of the VP-2 receptor in the renal collecting ducts. At high levels of water intake, VP secretion is suppressed, leading to low circulating VP concentration and low urine osmolality [10]. Severe hypotension is another stimulus for VP secretion, as observed in patients with septic shock involving VP stimulation of the VP-1A receptor (V1AR), which promotes vasoconstriction [11]. The VP drive is also enhanced in certain diseases state such as myocardial infarction, chronic kidney disease and heart failure [12–14]. However, during normal conditions, the main determinant of circulating VP level is the loss or gain of body water (i.e., hydration status).

Fig. 1. Arginine VP (AVP) stimulates ACTH-cortisol secretion through stimulation of the pituitary V1BR. Unlike the CRH- ACTH-cortisol axis, AVP stimulated ACTH/cortisol secretion lacks negative feedback control.

Measuring VP in plasma is cumbersome, partly due to its short half-life in plasma and ex vivo instability [15, 16], which led to the development of an assay targeting a stable C-terminal fragment of the VP precursor hormone copeptin. Copeptin is released in equimolar amounts with, and thus correlates well with, VP [13]. Due to its stability in vivo and ex vivo, it has been proposed to be a better marker of VP secretion than measurement of the mature hormone itself [16].

High Levels of VP: Can Diabetes and Cardiometabolic Disease Be Circumvented by Drinking More Water?

Adrenal hyper-secretion of cortisol, as a result of autonomous cortisol producing adrenal adenomas or adrenocorticotrophic hormone (ACTH) producing pituitary adenomas, causes Cushing’s syndrome [17]. The phenotype of Cushing’s syndrome is an extreme form of the metabolic syndrome including abdominal obesity, hypertension and dyslipidemia; most of these patients develop diabetes and die from cardiovascular disease. In normal subjects, elevation of cortisol is counterbalanced by a reduction of corticotrophin releasing hormone (CRH) and ACTH, which normalizes cortisol secretion in a steady state, via a negative feedback loop (fig. 1, blue arrows). Interestingly, ACTH secretion can also be stimulated by VP, through stimulation of the pituitary VP-1B receptor

Table 1. New-onset diabetes in relation to quartiles of baseline plasma copeptin concentration

Dependent variable	OR (95% CI)			p (test for linear trend)
	Q2 _{copeptin} vs. Q1 _{copeptin}	Q3 _{copeptin} vs. Q1 _{copeptin}	Q4 _{copeptin} vs. Q1 _{copeptin}	
Incident diabetes among non-DM*				
Crude	1.28 (0.76–2.15)	1.94 (1.19–3.14)	2.64 (1.66–4.19)	<0.001
Adjusted [‡]	1.37 (0.78–2.39)	1.79 (1.06–3.05)	2.09 (1.23–3.56)	0.004
Incident diabetes among non-IFG [†]				
Crude	1.85 (0.81–4.20)	2.12 (0.95–4.73)	4.56 (2.18–9.52)	<0.001
Adjusted [‡]	1.80 (0.78–4.16)	1.92 (0.84–4.38)	3.48 (1.58–7.65)	0.001

IFG = Impaired fasting glucose; FBG = fasting blood glucose.

* Subjects who developed diabetes during follow-up (n = 174) among all subjects without diabetes at baseline (n = 4,377).

[†] Subjects who developed diabetes during follow-up (n = 79) among all subjects without impaired fasting glucose at baseline (n = 3,702).

[‡] Adjusted for age, sex, high-density lipoprotein, triglycerides, blood pressure, antihypertensive treatment, body mass index, waist, waist/hip ratio, cystatin C, C-reactive protein and prevalent cardiovascular disease, smoking, family history of diabetes, low-density lipoprotein, FBG and fasting insulin.

(V1BR); this mechanism results in hyper-secretion of cortisol [18–20]. Importantly, VP-induced hyper-secretion of ACTH and cortisol does not have a negative feedback loop, and a high concentration of VP can thus result in a vicious circle, a Cushing's syndrome-like phenotype, metabolic syndrome and high risk of diabetes development (fig. 1, red arrows). In addition to these pituitary effects, VP is implicated in glucose homeostasis through regulation of insulin and glucagon via stimulation of pancreatic V1BR; VP also promotes hepatic glycogenolysis and gluconeogenesis via stimulation of the V1AR [21–23].

We showed in 2010 that fasting plasma concentration of VP, measured by copeptin, strongly predicted new-onset diabetes independently of all other major diabetes risk factors [24] (table 1), a finding that was replicated in subsequent large prospective population-based studies [25, 26]. In the population with normal fasting glucose, subjects in the top quartile of copeptin (i.e., 25% of the population, corresponding to plasma concentration of copeptin of >6.1 pmol/l in women and >10.7 pmol/l in men) had a 3.5-fold multivariate adjusted increased risk of diabetes mellitus (DM) development, compared to subjects in the lowest quartile of plasma copeptin [24] (table 1). It is remarkable that (a) a high plasma copeptin concentration is predictive of new-onset DM development independent of all diabetes risk factors, including the level of blood glucose at baseline and (b) the effect size associated with high copeptin in relation to diabetes risk is large and

comparable to the diabetes risk associated with obesity [24, 27]. Interestingly, the phenotypic similarity between subjects who have high circulating copeptin concentrations and Cushing's syndrome patients is not limited to the fact that both conditions are accompanied by a high risk of developing DM. We and other research groups found that subjects with high VP concentration are more likely to suffer from all components of the metabolic syndrome including abdominal obesity, insulin resistance, hypertension, chronic inflammation and microalbuminuria [24, 28–30]. Thus, the 25% of the population with the highest copeptin concentrations, reflecting a high VP drive, have a phenotype which resembles a mild form of Cushing's syndrome, putting them at high risk of not only type 2 diabetes but the entire metabolic syndrome. Furthermore, we and other researchers have shown that high copeptin is an independent risk factor for cardiovascular disease and premature mortality and that this risk seems to be especially pronounced in patients with DM [31–33]. Although these studies cannot prove causality, they collectively suggest that elevation of VP concentration is linked to risk of developing DM and the metabolic syndrome, followed by increased risk of cardiovascular disease and premature death [24–26, 28–33].

Assuming that the statistically independent relationship between high VP in healthy subjects and risk of future development of DM, metabolic syndrome and cardiovascular morbidity and mortality is indeed causal, inhibition of VP secretion emerges as a novel attractive

strategy to prevent diabetes and its associated cardiovascular sequels. In subjects without severe hypotension, chronic kidney disease, heart failure or acute myocardial infarction, the most likely cause of high circulating VP is insufficient water intake, as this stimulates VP secretion and renal water reabsorption in order to maintain constant plasma osmolality; conversely, increased water intake inhibits VP secretion [10, 34]. In light of this, increasing water intake appears as the prime candidate intervention to reduce the risk of DM, metabolic syndrome and cardiovascular morbidity and mortality linked to having a high level of circulating VP. In addition, increasing water intake is safe and appears easy-to-implement given its broad availability.

Evidence from both observational studies and intervention trials suggests that high water intake may protect humans from obesity, diabetes and cardiovascular disease [35–38]. Interestingly, epidemiological studies of water intake show that as much as 50% of the European population has a lower daily water intake than that recommended by the European Food Safety Authority [39]. Furthermore, a causal relationship between level of water intake, VP and cardiometabolic disease risk was recently supported by studies in animals. Our research team found that glucose tolerance was reduced when rats were chronically exposed to high VP; but when rats were put on high water intake, leading to low levels of VP, insulin resistance and hepatic fat accumulation (i.e., 2 hallmarks of the metabolic syndrome) were markedly ameliorated [40].

In summary and conclusion, during the last 6 years, a large number of studies have established high circulating level of VP as a novel risk factor for the development of diabetes, metabolic syndrome and cardiovascular morbidity and mortality. The most likely cause of this relationship is insufficient water intake leading to enhanced VP secretion which, in turn, leads to hyper-secretion of ACTH and cortisol and results in a Cushing syndrome-like phenotype. A causal relationship between high VP and high cardiometabolic risk, as well as a favorable effect, achieved by VP reduction with improved hydration status, is supported by studies in rodents. Because 25% of the middle-aged population of Malmö, Sweden have a high plasma VP level, which is linked to marked elevation in the risk of 2 great public health problems of our century (i.e., diabetes and cardiometabolic disease), hydration-induced reduction of VP appears to be a broadly applicable, safe, cost-effective and easy-to-implement primary preventive intervention that should be evaluated in future large randomized controlled clinical trials. Missing the opportunity to gain a new life style regimen in the fight against diabetes and cardiometabolic disease would be unethical.

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