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The Effect of Renal Function and Hemodialysis Treatment on Plasma Vasopressin and Copeptin Levels

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Introduction: Copeptin is increasingly used in epidemiological studies as a substitute for vasopressin. The effect of renal function *per se* on copeptin and vasopressin concentrations as well as their ratio have, however, not been well described.

Methods: Copeptin and vasopressin levels were measured in 127 patients with various stages of chronic kidney disease, including 42 hemodialysis patients and 16 healthy participants in this observational study. Linear (segmental) regression analyses were performed to assess the association between renal function and copeptin, vasopressin and the C/V ratio. In addition, clearance of copeptin and vasopressin by hemodialysis was calculated.

Results: Both copeptin and vasopressin levels were higher when renal function was lower, and both showed associations with plasma osmolality. The C/V ratio was stable across renal function in subjects with an eGFR >28 ml/min per 1.73 m^2. In contrast, the C/V ratio increased with worsening renal function in patients with eGFR ≤ 28 ml/min per 1.73 m^2. During hemodialysis, the initial decrease in vasopressin levels was greater compared with copeptin and, consequently, the C/V ratio increased. This was, at least in part, explained by a greater dialytic clearance of vasopressin compared with copeptin.

Discussion: Our data indicate that copeptin is a reliable substitute for vasopressin in subjects with an eGFR >28 ml/min per 1.73 m^2, whereas at an eGFR ≤ 28 ml/min per 1.73 m^2, that is, CKD stages 4 and 5, a correction for renal function is required in epidemiological studies that use copeptin as a marker for vasopressin. Intradialytic copeptin levels do not adequately reflect vasopressin levels because vasopressin clearance by hemodialysis is higher than that of copeptin.

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Arginine vasopressin is essential for maintaining fluid homeostasis in the human body. Vasopressin is released from the posterior pituitary gland in response to hyperosmolality, hypotension, and hypovolemia.[1] This hormone regulates water balance via V2 receptor–mediated renal water reabsorption and increases blood pressure via V1 receptor–mediated vasoconstriction. In addition to these important physiological effects, evidence is emerging that vasopressin also has deleterious effects and may play a role in the progression of renal disease.[2] Experimental data showed that desmopressin, a selective V2 receptor agonist, induced transient proteinuria[3,4] and worsened progression of CKD.[3]

Copeptin, a fragment of the vasopressin precursor preprovasopressin, is used as a substitute for estimating vasopressin levels because it is easier to measure and allegedly more stable *ex vivo*.[5–8] When preprovasopressin is split in the pituitary gland, copeptin and vasopressin are secreted in equimolar amounts into the circulation.[5,8,9] Several studies have investigated the reliability of copeptin as a marker for vasopressin and have demonstrated a strong correlation between plasma vasopressin and copeptin levels in healthy individuals[5,7,10,11] as well as in critically ill patients.[5,12,13] In addition, it has been shown that the plasma concentration of both peptides responds similarly to

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changes in fluid status and plasma osmolality.[6,14,15] Given the recent interest in the effects of vasopressin on kidney health, measurement of copeptin in epidemiological studies gains popularity.[16,17]

Vasopressin as well as copeptin are small-sized molecules (1 and 5 kDa, respectively),[5,18] and both are therefore theoretically subjected to renal clearance. As yet, it is not clear whether renal function affects both analytes to the same extent and therefore whether copeptin can be used as marker for vasopressin in patients with impaired renal function. Several studies found an inverse association between copeptin and renal function.[10,19–23] However, concurrent measurement of vasopressin is pivotal to understand whether increased copeptin levels accurately reflect vasopressin levels in patients with chronic kidney disease (CKD).[24] In case copeptin and vasopressin are cleared similarly, the copeptin-to-vasopressin ratio (C/V ratio) is expected to be stable across the full range of kidney function.

In hemodialysis patients, differential extracorporal clearance could also result in divergent plasma copeptin and vasopressin levels, because copeptin is larger than vasopressin and may therefore be cleared less by the artificial kidney. However, copeptin removal by hemodialysis has not yet been studied.

Because copeptin is used as a surrogate for vasopressin in patients with decreased renal function while it is unknown whether renal function affects copeptin and vasopressin concentrations in a similar fashion, we investigated in the present study the association of copeptin and vasopressin in subjects over a broad range of renal function as well as the kinetics of these analytes during hemodialysis.

METHODS

Participants and Study Protocol

For this study, samples were used of subjects that participated in 4 studies performed at the Nephrology Department of the University Medical Center Groningen between March 1, 2010 and March 1, 2016.[24] The cohort was established from patients with either autosomal dominant polycystic kidney disease or IgA nephropathy with normal and impaired renal function from whom plasma vasopressin and copeptin levels were available and in hemodialysis patients participating in a study on vasopressin. In these studies, blood samples were drawn according to a strict protocol to allow reliable measurement of plasma copeptin and vasopressin levels after completion. Blood was collected in chilled ethylenediamine tetraacetic acid tubes, immediately centrifuged in a cooled centrifuge at 4 °C, and the plasma supernatant was stored frozen at −80 °C in plastic 2 ml aliquots until measurement that took place within 1 year of storage. Samples were available of healthy subjects ($n = 15$), CKD patients with either autosomal dominant polycystic kidney disease ($n = 54$) or IgA nephropathy ($n = 16$), and hemodialysis patients ($n = 42$). All participants gave written informed consent. The studies were performed in accordance with the principles of the Declaration of Helsinki and approved by the Medical Ethical Committee of the University Medical Center Groningen.

Outcome and Measurements

The primary outcome in the present study is the C/V ratio across different stages of renal function and its association with estimated glomerular filtration rate (eGFR). Vasopressin was measured by radioimmunoassay (DRG International Inc., Springfield, NJ) with a lower limit of detection of 0.25 pmol/l and a functional assay sensitivity of 0.5 pmol/l with 2.0 ml of plasma. The interassay and intraassay coefficients of variation were both <7% in the low and high concentration range (i.e., around 4 and 20 pmol/l, respectively). Copeptin was measured by an automated sandwich immunofluorescent assay (CT-proAVP; Thermo Fisher Scientific, B.R.A.H.M.S GmbH, Hennigsdorf, Germany) with a lower limit of detection of 0.9 pmol/l and a functional assay sensitivity of 2 pmol/l. The interassay and intraassay coefficients of variation for copeptin concentrations >15 pmol/l were <5% and 4% respectively.

In healthy subjects and in patients with CKD, GFR was estimated from plasma creatinine concentration, age, and sex with the Chronic Kidney Disease Epidemiology Collaboration equation that expresses GFR indexed for 1.73 m^2 body surface area.[25] In hemodialysis patients, residual renal function was assumed to be present when diuresis was ≥200 ml/day and GFR was estimated as 0.5 × (24-hour urea clearance + 24-hour creatinine clearance) and similarly expressed per 1.73 m^2 body surface area.[26] A 24-hour urine sample was used to estimate residual renal function, this urine sample is collected every 4 months after the longest interdialytic interval preceding the first dialysis session of the week (i.e., Monday or Tuesday).

Plasma and urine creatinine was measured with the Roche enzymatic creatinine assay. Plasma and urine urea were measured with the colorimetric method on a Roche Modular analyzer. Plasma sodium was measured with the indirect method of ion-selective electrode (Roche Modular, Mannheim, Germany) and plasma osmolality was measured by freezing-point depression (Osmo Station Osmometer, Kyoto, Japan).

In hemodialysis patients, blood samples for measurement of plasma copeptin and vasopressin were collected from the arterial line at the initiation of