Copeptin: a marker for ADPKD progression?

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Autosomal dominant polycystic kidney disease (ADPKD) accounts for ∼5–10% of patients with end-stage renal disease (ESRD) [1]. Mutations in the PKD1 and PKD2 gene, encoding polycystin-1 (PC-1) and -2 (PC-2), account for ∼85 and 15% of diseases, respectively. PC-1 interacts with PC-2 to build a multifunctional signalling complex that regulates intracellular Ca2+ signalling, and epithelial development and repair, which are essential mechanisms for maintaining a differentiated phenotype of renal epithelial cells [2, 3]. The exact pathology underlying renal cyst formation is still unknown, but it is generally accepted that adenosine3′-5′-cyclic monophosphate (cAMP) agonists accelerate cyst growth by stimulating mural epithelial cell proliferation and transepithelial Cl− secretion coupled to osmotic water flow [4].

Glomerular filtration rate (GFR) is recognized as a poor predictive marker of renal function decline in ADPKD [5] as glomerular hyperfiltration in functioning nephrons is able to compensate for the ongoing loss of renal tissue. In early ADPKD, the change in total kidney volume still appears to be the most sensitive marker of disease progression [6].

The antidiuretic hormone arginine vasopressin (AVP) essentially regulates the adenylyl cyclase activity and cAMP production by binding to the vasopressin-2 receptor (V2R) in the principal cells of the collecting duct, the predominant sites for cyst formation in ADPKD [7]. Experimental studies have described a detrimental role of V2R overexpression and hyperactivation in the pathophysiological process of ADPKD [8, 9]. Moreover, the pharmacological inhibition [8, 10, 11] or physiological suppression [12] of AVP activity in animal models of polycystic kidney disease results in an ameliorated cyst formation and maintenance of renal function.

However, sophisticated studies looking at the association between endogenous AVP release and severity of ADPKD have long been missed, which may be because AVP is difficult to measure due to its small size, binding to platelets and extremely high ex vivo instability [13, 14].

The recently developed copeptin assay is a readily available method for indirect AVP determination. Copeptin is the glycosylated, 39-amino acid long C-terminal part of the 164-amino acid AVP precursor peptide, which is released together with AVP from the neurohypophysis during precursor processing. More importantly, it provides a much higher ex vivo stability than the bioactive AVP [15, 16], and because of its larger size, copeptin can be measured by a highly sensitive sandwich immunoassay with two polyclonal antibodies, demonstrating a robust performance with an analytical detection limit of 0.4 pmol/L and an availability of results in a few hours instead of several days [15, 16].

As a marker of endogenous AVP secretion, prognostic and diagnostic properties of copeptin are well described in various clinical areas of cardiovascular and renal disease [17–19]. Moreover, recently a direct intrarenal pro-albuminuric effect of AVP has been hypothesized [20], although convincing data investigating additional effects on the Gs signalling pathway are still missing.

Against this background, Boertin et al., in this issue of Nephrology Dialysis Transplantation, report in a prospective investigation the association of copeptin levels with disease severity in 79 subjects with ADPKD followed up for >11 years. Study participants (43% male, age 36.8 ± 10.1 years, baseline GFR 96.8 ± 18.2 mL/min/1.73 m2) had a median copeptin concentration of 2.7 pmol/L that inversely correlated to changes in inulin clearance at 3.3-year follow-up and estimated GFR (eGFR) at 11.2 years. The inverse association between copeptin levels and renal function was statistically independent of patients’ age, gender, blood pressure and baseline GFR values. Subjects starting renal replacement therapy during long-term follow-up revealed a baseline copeptin concentration above the median.

These findings are in accordance with the results of a previous cross-sectional study from the same investigators [21] and provide some additional arguments that copeptin is associated with the renal outcome in patients with ADPKD. It remains to be determined if this effect is specific to ADPKD or rather is a more general association between reflecting the hormone response to chronic kidney disease [18, 19].

Several specific questions arise from this data. First and most importantly, the estimated GFR is probably not the most appropriate parameter to assess alterations in renal function in ADPKD [5], and the fact that the long-term outcome of kidney function was evaluated by eGFR measurement does essentially weaken the proposed inverse association between copeptin and kidney function in ADPKD.

Secondly, copeptin like AVP, are stress hormones influenced by a number of different conditions and blood drawing procedures. These processes require careful...
standardization. If not done appropriately, some of the associations of copeptin with other variables may reflect the impact of determinants of vasopressin secretion (like serum tonicity, volume status, stress or exercise) rather than the effects of vasopressin per se. This is especially true, if only one single baseline sample is taken under non-standardized conditions. Thus, these limitations of study design should engage the reader to interpret the results very carefully.

Thirdly, Boertin et al. did not investigate the possible impact of diet on plasma copeptin concentrations. For example, urinary sodium excretion and other osmolytes were not considered in the set of multivariate regression analyses. Therefore, it cannot be excluded that plasma copeptin release were not affected at least in some individuals by salt intake [22]. These limitations and the lack of data in non-cystic chronic kidney disease may hamper the conclusions on the possible causal relationship between copeptin (as a surrogate of AVP) and ADPKD progression.

Finally, it is clinically well acknowledged that ADPKD may dampen the urine concentration capacity [23], which may possibly independently lead to an increase in copeptin levels as a compensatory response to maintain body fluid. The integrity of the V2R-mediated cAMP signalling pathway, therefore, would be important to investigate in patients with ADPKD.

The present study has several clinical important implications. First, given the progressive character of ADPKD, interventions as early in life as possible to delay or prevent long-term consequences seem to be most appropriate. But prognostic markers helping to predict the renal outcome of a patient with this disease at an early stage of disease are rare, and either not specific enough [24], or very expensive and time-consuming in routine diagnostics [25, 26]. Here, plasma copeptin may provide a promising novel and simple to measure parameter to predict the patient’s risk for ESRD long before changes in the GFR may take place.

Secondly, the present study importantly strengthens the idea of a V2R-cAMP-related pathway affecting the development and progression of ADPKD. This hypothesis needs to be further investigated and confirmed, but is in keeping with some intriguing data from intervention studies with V2R antagonists in animal models of polycystic kidney disease [11, 27]. In fact, substantial experimental and clinical data have implicated the V2R-cAMP system in the pathogenesis of ADPKD [12, 28, 29]. However, evidence that treatment strategies specifically targeting the V2R are superior to current therapies more directed towards limiting morbidity and mortality from complications of ADPKD [30] is inconclusive. The TEMPO 3–4 study, a first large-scale randomized Phase III clinical trial investigating the efficacy of V2R antagonists in ADPKD (NCT00428948) [31], aims to evaluate whether Tolvaptan at a high dose is able to slow renal cystic progression in an ADPKD population at a relatively early stage of disease. According to the data from Boertin et al., it can be expected that patients with more severe ADPKD will probably show higher copeptin levels, suggesting that these subjects also need higher dosages of V2R antagonists to efficiently inhibit the hormonal activity of the higher AVP levels. Provided that high doses of V2R antagonists are associated with a tolerable risk and side effect profile (including polyuria, polydipsia and nocturia), the reactive increase in plasma copeptin levels due to competitive inhibition of the V2R may thus become a useful biomarker for long-term therapy effectiveness of this drug with regard to renoprotection.

In conclusion, the observational study by Boertin et al. makes a valuable contribution to the research field of prevention and control of polycystic kidney disease. The findings support the assumption that copeptin is associated with disease severity in ADPKD and may have useful implications for the design of future clinical trials. At present, dietary interventions consisting of an increased water intake or a decreased osmolyte intake appear as the only feasible tools to suppress endogenous AVP release. The V2R antagonists will hopefully provide a novel, future means to investigate the effects of AVP on the development and progression of ADPKD more specifically.

Conflict of interest statement. None declared.

(See related article by Boertien et al. Copeptin, a surrogate marker for vasopressin, is associated with kidney function decline in subjects with autosomal dominant polycystic kidney disease. Nephrol Dial Transplant 2012; 27: 4131–4137.)

References


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