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REVIEW

Is serum copeptin a modifiable biomarker in autosomal dominant polycystic kidney disease?

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Abstract

The availability of disease-modifying drugs for the management of autosomal dominant polycystic kidney disease (ADPKD) has accelerated the need to accurately predict renal prognosis and/or treatment response in this condition. Arginine vasopressin (AVP) is a critical determinant of postnatal kidney cyst growth in ADPKD. Copeptin (the C-terminal glycoprotein of the precursor AVP peptide) is an accurate surrogate marker of AVP release that is stable and easily measured by immunoassay. Cohort studies show that serum copeptin is correlated with disease severity in ADPKD, and predicts future renal events [decline in renal function and increase in total kidney volume (TKV)]. However, serum copeptin is strongly correlated with creatinine, and its additional value as a prognostic biomarker over estimated glomerular filtration rate and TKV is not certain. It has also been suggested that copeptin could be a predictive biomarker to select ADPKD patients who are most likely to benefit from AVP-modifying therapies, but prospective data to validate this assumption are required. In this regard, long-term randomised clinical trials evaluating the effect of prescribed water intake on renal cyst growth may contribute to addressing this hypothesis. In conclusion, although serum copeptin is aligned with the basic pathogenesis of ADPKD, further rigorous studies are needed to define if it will contribute to enabling the delivery of personalised care in ADPKD.

Key words: Polycystic kidney disease; Copeptin; Biomarker

Core tip: Serum copeptin is correlated with disease severity in autosomal dominant polycystic kidney disease (ADPKD), and predicts future renal events (decline in renal function and increase in total kidney volume). The aim of this review is to critically evaluate the role of copeptin as a prognostic biomarker of renal outcomes in ADPKD, and if it has potential as a predictive marker of treatment response.

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INTRODUCTION

The life-time risk for end stage kidney disease (ESKD) in autosomal dominant polycystic kidney disease (ADPKD) is characterised by high intra- and interfamilial variability[1]. Epidemiological data indicates that only 50% of patients with ADPKD will develop ESKD by the age of 60[2]. This variability in risk for ESKD is likely due to the interaction of genic factors[3] with environmental variables[4] that alter the expressivity of the clinical phenotype[5,6]. Routine tests performed during the initial clinical evaluation of affected patients, such as estimated glomerular filtration rate (eGFR), lack sensitivity as prognostic markers in early disease[7], and other clinical information (such as family history of early-onset of ESKD) do not have precision[8]. The uncertainty in predicting renal prognosis causes tremendous anxiety to patients and their families[9]. Furthermore, the introduction of disease-modifying drugs to treat ADPKD has catalysed an urgent need to identify and validate a panel of reliable and easily measurable clinical, genetic molecular and imaging biomarkers in predicting the risk for ESKD[10].

The arginine vasopressin (AVP)-cAMP signalling pathway has a central role in the initiation of lifetime growth of kidney cysts in ADPKD[11]. Serum copeptin is a surrogate marker of AVP release[12], and the availability of a sensitive commercially available immunoassay, has led to several cohort studies to evaluate its role as prognostic biomarker in ADPKD. The role of copeptin as a clinical diagnostic test is also under evaluation in several other diseases including in the differential diagnosis of polyuria-polydipsia (where it is being considered as a replacement for the direct measurement of serum AVP)[13,14], and in the diagnostic evaluation of other disorders (such as acute myocardial infarction[15] and sepsis[16]) where its potential utility is less certain. In this regard, to date, copeptin is not funded for reimbursement for routine measurement in patients in ADPKD in any country, providing an indirect indicator that its value as a prognostic biomarker in this setting has also not been proven and that further data is needed. The aim of this review is to critically evaluate the role of copeptin as a prognostic biomarker of renal outcomes in ADPKD, and if it has potential as a predictive marker of treatment response.

ROLE OF AVP-CAMP SIGNALLING IN THE PATHOGENESIS OF RENAL CYST GROWTH IN ADPKD

The role of AVP in the pathogenesis of ADPKD has been reviewed elsewhere[11], but briefly, it is considered to be the most important factor that determines the postnatal rate of renal cyst growth. The most compelling preclinical evidence to support this hypothesis is that the congenital deficiency of AVP almost completely abrogated the formation of renal cysts in the pck rat[17]. Furthermore, in mouse models of PKD, small-molecule vasopressin-receptor antagonists were highly effective in reducing kidney cyst growth[18]. In humans, the evidence is supported by the TEMPO 3:4 and REPRISE trials which collectively showed that tolvaptan (a highly specific vasopressin-receptor antagonist) reduced the rate of increase in total kidney volume (TKV) in early-stage ADPKD and also the decline in renal function in late-stage disease[19,20]. Given its critical importance, it seems logical to consider markers of AVP release as potential biomarkers in ADPKD.

SYNTHESIS, FUNCTION AND DEGRADATION OF COPEPTIN

Synthesis of copeptin

As shown in Figure 1, copeptin is the C-terminal end of the AVP precursor molecule (pre-proAVP), a 164-amino acid peptide consisting of four segments: (1) The signal peptide at the N-terminus (amino acids 1-19); (2) AVP (amino acids 20-28); (3) neurophysin (amino acids 32-124); and (4) copeptin (amino acids 126-164), a 39-aminoacid glycopeptide that makes up the C-terminal part of pro-AVP. As summarised in Table 1, the precursor peptide (pre-proAVP) is produced in two anatomically distinct regions of the hypothalamus.

Function of copeptin

While the physiological function of AVP is well defined by its effects on tissue-specific receptors (V_{1a} receptor, mediates vasoconstriction and platelet aggregation; V_{1b} receptor: ACTH secretion; and V_2 receptor: water balance), the exact role of copeptin in normal physiology is unclear as it has no known receptors. In this regard, copeptin has been hypothesised to function as a chaperone for pre-proAVP release from the magnoceullar

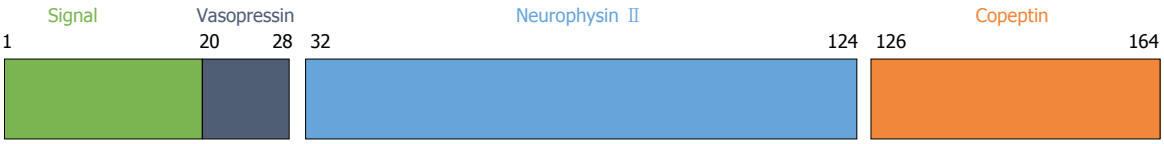

Figure 1 The precursor peptide of arginine vasopressin, also known as pro- arginine vasopressin. The numbers of indicative of the amino acid positions of the peptide. Copeptin is the C-terminal peptide of pro-AVP and is released with AVP during precursor processing. Figure adapted from Reference[22]. AVP: Arginine vasopressin.

Table 1 Distinct production sites of precursor arginine vasopressin in hypothalamus

Site of synthesis in hypothalamus	Magnocellular neurons (Supra-optic and paraventricular)	Parvocellular neurons
Process of AVP	Occurs during axonal transport in the infundibulum with copeptin and neurophysin acting as chaperones for correct AVP folding	Occurs in the parvocellular neurons where it released with other releasing hormones, such corticotrophin releasing hormone
Storage	Posterior pituitary	Hypothalamus
Stimuli for release	Osmotic and haemodynamic stimuli from the posterior pituitary gland	Released in response to humoural stress together with CRH, which both act on the adrenal gland to release cortisol

AVP: Arginine vasopressin.

Table 2 Summary of vasopressin limitations compared to copeptin advantages as a biomarker using the thermo scientific B.R.A.H.M.S KRYPTOR assay (adapted from Thermo Fisher scientific)

Features	Limitations of measuring AVP	Advantages of CT-proAVP (Copeptin)
Ex vivo stability	Unstable (even at -20 ℃)	Stable at > 3 d at room temperature
Sample volume required	400 L	50 L
Time to results	3 working days	approximately 1 h
Sensitivity	Low (small molecule size, measured only by competitive immunoassay)	High (larger size, can be measured using a sensitive sandwich immunoassay)
Measuring range	1.15-73.8 pmol/L	0.7-500 pmol/L and up to 2000 pmol/L with automated dilution
Handling	Manual	Automatic

AVP: Arginine vasopressin.

neuron, but its role in peripheral tissues (if any) remains unknown. Thus, the literature has considered that copeptin is simply an inert biomarker with no direct role in the pathogenesis kidney cyst formation, but clearly further studies (such as gene knockout experiments in mice) are needed to evaluate this premise.

Degradation of copeptin

Another gap in knowledge is that little is known about the pharmacokinetics and degradation of copeptin. Available data suggests that it is rapidly cleared from the circulation either through the degradation by tissue-bound proteases, renal excretion and/or hepatic metabolism. New data on this topic are likely to emerge in the future and in this regard, a recent study reported that while the release of copeptin in response to elevation in the serum osmolality in healthy individuals was similar to AVP, its decay in the serum was two-fold longer than AVP[21]. Understanding the clearance of copeptin also has major implications for interpreting values in the setting of renal impairment, as reduced glomerular filtration is associated with elevated serum copeptin and thereby, confounds its value as a unique prognostic biomarker in ADPKD (as discussed below).

ADVANTAGES AND DISADVANTAGES OF COPEPTIN MEASUREMENT IN THE LABORATORY

It is well known that the laboratory testing of AVP is time-consuming and not practical (primarily because it is rapidly removed from the circulation with a half-life of less than 30 min requiring a large volume of serum) and is unstable in serum[22,23]. On the other hand, copeptin is released in equimolar amounts with AVP[24], is stable for up to 14 d in serum at room temperature; can be rapidly measured (0.5-2.5 h); and requires only 50 L of serum, making it potentially suitable for a high-throughput clinical pathology laboratory[12]. These analytical comparisons in methodology are summarised in Table 2.

The disadvantage of the copeptin assay is that in many countries, including in Australia, the most widely used and validated assay is a sandwich immunoluminometric method by ThermoFisher Scientific which requires purchase of specific instrument[22]. As there is insufficient evidence for the use of copeptin in routine clinical practice, it is not currently provided by most clinical pathology laboratories and therefore, not readily

accessible. Other manufacturers other than Thermo-Fisher Scientific produce in-house ELISA kits[25] to measure copeptin, and this might make it easier to access the assay, but this is suitable for the clinical setting and large numbers of samples need assayed using a standardised technique. In sum, insufficient clinical evidence has not allowed further development of copeptin for clinical use in ADPKD, and the assay remains primarily restricted to the research setting.

MULTIPLE LIFESTYLE FACTORS INFLUENCE THE BASAL LEVELS OF SERUM COPEPTIN

Several lifestyle factors modify the basal level of copeptin in an individual. The most well studied variable is fluid intake. In healthy individuals, a chronic increase in total fluid intake by approximately 1 L/d above baseline reduced serum copeptin from 5.18 to 3.90 pmol/L[26]. Similarly, in patients with Stage 3 CKD (n = 28), the median copeptin level was 17 pmol/L and declined to 4.2 pmol/L with fluid intake over a 6-week period[27], confirming that: (1) Patients with CKD have higher levels of copeptin; and (2) increasing fluid intake can attenuate long-term copeptin levels. The type of fluid consumed may also influence the change in copeptin, as preclinical data in rats shows that rehydration with 20% hypertonic fructose increased plasma osmolality, AVP release and oxidative renal injury in rats with mild dehydration, whereas this effect was not seen with plain water[28].

Multiple other factors may influence the basal levels of copeptin. A cross-sectional analysis of the Groningen population-based cohort study (n = 6801) showed that in addition to low fluid intake, other dietary factors (high sodium, high protein and low potassium), alcohol intake and smoking were all associated with higher serum copeptin levels[29]. However, it is noteworthy that, in contrast to the Groningen study, alcohol suppresses the release of vasopressin from the pituitary gland[30,31]. Similarly, smoking is well known to stimulate the release of AVP in the blood plasma. In rabbits, an injection of 0.5 mg/kg of nicotine increased AVP concentrations by nearly 40 times[32]. The relative importance of each of these factors in influencing copeptin levels, and how they should be considered prior to collecting blood for copeptin in individuals, has not been standardized and further studies are required.

BASELINE SERUM COPEPTIN IS NOT DIAGNOSTIC OF ADPKD AND IS STRONGLY CORRELATED WITH RENAL FUNCTION

Several investigators have raised the hypothesis that serum AVP, and therefore copeptin, could be mildly elevated in ADPKD patients compared to the general healthy population[33]. For example, in a small study of 30 patients, the difference in mean serum copeptin was 8.92 pmol/L [inter-quartile range (IQR): 0.66-21.86] in ADPKD patients (eGFR 100 ± 23 mL/min/1.73 m^2) compared to 6.08 pmol (IQR 0.92-10.79) in healthy individuals (eGFR 104 ± 12 mL/min/1.73 m^2) (P = 0.22). This mild elevation is most likely due to subclinical volume depletion due to increased urinary losses as a result of impaired urinary concentrating ability and nephrogenic diabetes insipidus, as following water deprivation for 14 h, the difference in mean serum copeptin between ADPKD compared to healthy patients become statistically significant (ADPKD: 17.01 pmol/L; IQR 7.94-17.78 *vs* healthy: 7.75 pmol, IQR 3.81-8.80; P = 0.04)[33]. However, based on published studies, there is little evidence to support that these findings are specific or diagnostic of ADPKD. In particular, a recent study showed that: (1) Mean levels of copeptin in ADPKD patients were comparable to patients with other types of CKD, such as IgA nephropathy (ADPKD: 26.6 pmol *vs* IgA nephropathy: 20.7 pmol/L; P = 0.84)[34,35], and (2) the levels were more strongly correlated with the serum creatinine rather than the specific cause of CKD[35].

IS SERUM COPEPTIN A PROGNOSTIC BIOMARKER OF RENAL OUTCOMES IN ADPKD?

With this background, the remainder of this article will evaluate the specific utility of copeptin as biomarker in ADPKD. The National Institutes of Health Biomarker Consortium defines a "biomarker" as a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions[36]. More specifically, the two sub-groups that are relevant to the discussion of copeptin and ADPKD are a "prognostic biomarker" (defined as biomarker that identifies the likelihood of a clinical event, recurrence or progression), and a "predictive biomarker" (defined as a biomarker that identifies those who are likely to respond to a treatment than those that are negative for biomarker). Furthermore, Park and Ahn[37] outlined that the ideal biomarker in ADPKD should fulfil three characteristics: (1) It should correlate with the clinical severity of ADPKD; (2) it should detect patients at high-risk of progression; and (3) short-term changes should predict a clinical endpoint. In addition, validation is the process of assessing the biomarker and its measurement performance characteristics, and determining the range of conditions under which it provides reproducible and accurate data. The assessment of whether serum copeptin fulfils the criteria and validation in ADPKD is limited by the paucity of data, as only 26 articles were identified by a PubMed search using the terms "copeptin" and "ADPKD" (with at least

6 being review articles). Furthermore, many of these studies consist of small sample sizes. Despite this, the available data was analysed to answer two questions.

Are serum and urinary copeptin levels correlated with markers of disease severity?

Several cross-sectional studies show that serum copeptin is positively correlated with TKV and negatively correlated with eGFR. Furthermore, longitudinal studies show that higher copeptin levels had significantly higher TKV and urine osmolality, evidently shown by a study where TKV increased by 71% as copeptin levels increased by 23%[38,39]. Furthermore, a recent study also showed that serum copeptin predicted changes in fibromuscular dilatation in patients with ADPKD, an indicator of cardiovascular disease. To date, only one cohort has evaluated the role of urinary copeptin to creatinine ratio, which reported moderate correlations with ht-TKV (r = 0.383, P = 0.008) and eGFR (r = -0.304, P = 0.036) in 50 Japanese patients with ADPKD[40].

Are there any confounding factors that influence the interpretation of serum and urinary copeptin in ADPKD?

Several studies show that copeptin has a strong relationship with eGFR. Corradi *et al*[35] recently demonstrated that glomerular filtration affects copeptin to a greater extent rather than its correlation to AVP. The authors of a previous study indicated that after the removal of a kidney, the copeptin levels relatively remained stable, however, only GFR had declined by 40%[33,34]. A greater number of nephrons in the body would indicate a relatively higher AVP activity, and hence, a proportional increase in copeptin. The latter, however, opposes this theory, suggesting that perhaps copeptin is only a filtration marker rather than a disease severity marker for ADPKD. Furthermore, it is not known whether eGFR also confounds the level of urinary copeptin[40].

IS SERUM COPEPTIN A PREDICTIVE BIOMARKER OF TREATMENT RESPONSE TO VASOPRESSIN RECEPTOR ANTAGONISTS OR PRESCRIBED FLUID INTAKE IN ADPKD?

Several authors have suggested that higher baseline levels of copeptin could be used as method to select patients for AVP blocking therapies, such as tolvaptan or prescribed fluid intake[12]. While this is an attractive hypothesis, it has yet to be formally tested and validated. In this regard, it would certainly be possible to perform a post-hoc analysis of the large randomized controlled trials involving tolvaptan to answer this question. Similarly, an ongoing randomized controlled trial of prescribed fluid intake will evaluate the long-term changes in serum copeptin and its effect on the progression of TKV[41].

CONCLUSION

There is strong interest in the role of copeptin as a molecular biomarker in ADPKD. While aligned with the pathogenesis of ADPKD, copeptin seems attractive for this purpose, but many questions remain. The most important question is whether measuring serum copeptin add extra value over the standard clinical management tools (such as the PRO-PKD score, eGFR, TKV) to predict renal prognosis[42]? If so, does this predict whether patients with elevated copeptin are more likely to respond to therapies that suppress AVP (either or both pharmacological or life-style factors, such as fluid intake)? If these fundamental questions can be answered, other issues can be addressed, such as: What level of copeptin will be effective in attenuating renal cyst growth? How often should copeptin be measured? Should it be evaluated in all patients who present for the first time? What are the confounding factors that might influence interpretation of the data? Does copeptin itself have a direct pathological role in ADPKD? What is the value of measuring urinary copeptin, and how does serum copeptin compare with other markers of the AVP axis, such as urinary cAMP excretion?

Clearly, well designed prospective studies and health economic data will assist in answering these questions and evaluating the role of copeptin in the management of patients with ADPKD. Until this evidence is available, it will be difficult to influence policy-makers and regulatory bodies to utilize this test in the routine clinical care of patients with ADPKD.

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