



What can copeptin tell us in patients with autosomal dominant polycystic disease?

Lise Bankir, Daniel G. Bichet

► To cite this version:

Lise Bankir, Daniel G. Bichet. What can copeptin tell us in patients with autosomal dominant polycystic disease?. *Kidney International*, 2019, 96, pp.19 - 22. <10.1016/j.kint.2019.02.037>. <hal-03484470>

HAL Id: hal-03484470

<https://hal.science/hal-03484470v1>

Submitted on 20 Dec 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC 4.0 - Attribution - Non-commercial use - International License

Invited Commentary for Kidney International

WHAT CAN COPEPTIN TELL US IN PATIENTS WITH ADPKD ?

Lise BANKIR ^{1, 2} and **Daniel G. BICHET** ^{3, 4}

1. INSERM, Unité 1138, Centre de Recherche des Cordeliers, Paris, France;
2. Sorbonne Université, Centre de Recherche des Cordeliers, Paris, France;
3. Université de Montréal, Montréal, QC, Canada;
4. Départements de Pharmacologie, Physiologie et de Médecine, Hôpital du Sacré-Coeur de Montréal, Montréal, QC, Canada.

Running Head : Copeptin and ADPKD progression

Word Count : 1806 words

Address for Correspondence

Lise BANKIR

INSERM U 1138, Centre de Recherche des Cordeliers

15 rue de l'Ecole de Médecine, 75006 PARIS, France

Tel : 33 1 47 35 34 15 or 33 6 82 94 80 10

E-mail : lise.bankir@inserm.fr

Abstract

Vasopressin is known to contribute to disease progression in ADPKD by its influence on cAMP that directly promotes cyst growth. In addition, vasopressin probably also contributes to progression by inducing a glomerular hyperfiltration, as shown in other forms of chronic kidney diseases. The measurement of plasma copeptin, a marker of vasopressin secretion, could help identify patients at greater risk of fast progression and those expected to benefit the most of vasopressin V2 receptor blockade. Further studies should evaluate the optimal level of suppression of vasopressin effects in ADPKD.

Key words

Vasopressin
Hyperfiltration
V2 receptor
Urine osmolality
cAMP

In autosomal dominant polycystic disease (ADPKD), the development of cysts within the kidney leads to a progressive decline in kidney function. The rate of progression of the disease is highly variable among subjects. It is thus important to determine what are the factors that contribute to accelerate the renal functional decline, and what are the subjects at risk of a faster decline. Adequate markers are also needed to evaluate the efficacy of various pharmacological and/or nutritional and behavioural interventions. Studies undertaken in the last ten years have shown that total kidney volume (TKV) is a good marker of ADPKD progression and that the increase in TKV precedes the decline in glomerular filtration rate (GFR) [1, 2].

1. Copeptin plasma concentration in ADPKD

The antidiuretic hormone vasopressin (AVP) is known to contribute to disease progression in ADPKD because, upon binding to V2 receptors (V2R) in collecting duct cells, its second messenger, cyclic AMP, directly promotes cyst growth and thus degradation of normal nephron function [3]. Several experimental studies and a wide 3-year clinical trial (TEMPO 3-4 trial, 1445 subjects, 18-50 y, with TKV \geq 750 ml and estimated creatinine clearance \geq 60 ml/min) have demonstrated the benefit of inhibiting the action of vasopressin by using the selective V2R antagonist, tolvaptan [4]. Thirst sensation and vasopressin secretion are known to be very variable among subjects. It is obvious that 24-h fluid intake, urine flow rate and urine osmolality are also very diverse in healthy subjects. The same diversity is probably found in subjects with ADPKD at an early stage of the disease and during its progression.

AVP measurement in plasma is difficult and time consuming, and is often not sensitive enough because of the very low concentration of AVP (in the picomolar range). The plasma concentration of copeptin (a bigger peptide that is part of the vasopressin precursor molecule) is considered to be a valid indicator of vasopressin secretion. No specific function and no copeptin receptors have been identified so far. In a recent study [5], Gansevoort et al evaluated, in 1280 subjects from the TEMPO 3-4 trial cohort, the relationship between plasma copeptin concentration at baseline and the rate of change of TKV and of the estimated GFR (eGFR) in order to determine if copeptin could serve as a marker of disease severity and disease progression. The subjects were divided into sex-adjusted quartiles of copeptin at baseline. Median copeptin concentrations were 2.8, 5.1, 8.3 and 16.1 pmol/L, and mean urine osmolality 448, 506, 546 and 505 mosm/kg H₂O, in the four quartiles,

respectively. The copeptin concentrations in the first two quartiles, with a relatively well preserved renal function (eGFR is $> 85 \text{ ml/min.1.73 m}^2$) are comparable to those reported previously in several studies of general populations (3-5 pmol/L). However, because patients with ADPKD exhibit a significant defect in urinary concentrating ability, vasopressin secretion might be expected to rise. Thus, this apparently normal copeptin/vasopressin values suggest an early defect in osmoregulation, with a blunted release of arginine vasopressin. In studies in which plasma AVP and plasma copeptin concentrations have been measured in healthy subjects in the same samples, copeptin is about three to five fold higher than AVP. Thus, AVP concentrations in half of the subjects in Gansevoort et al study [5] would probably be below or very close to the detection limit of available AVP immunoassays.

V2R antagonism is known to induce a rise in vasopressin/copeptin secretion. Indeed, median copeptin was tripled three weeks after initiation of tolvaptan treatment and went down below pre-treatment level after withdrawal of the treatment, at the end of follow up [5]. Interestingly, the correlation between two copeptin measurements at a 3-week interval in the placebo group was highly significant, thus showing a high intra-subject reproducibility of this AVP marker, and thus probably of plasma AVP itself. The tolvaptan-induced rise in plasma AVP does not seem to induce any significant V1a receptor-dependent adverse effects because neither blood pressure nor blood glucose elevations have been reported in tolvaptan-treated patients.

2. Progression of kidney disease in ADPKD : two additive mechanisms

In Gansevoort et al study, [5], a multivariate analysis at baseline, showed that plasma copeptin was positively associated with TKV and negatively with eGFR ($p < 0.001$ for both). In the placebo group, in which the spontaneous evolution of the disease can be observed, baseline copeptin was significantly associated with the annual TKV growth rate and the annual eGFR decline during follow-up, independently of sex and age. But the statistical significance was reduced (for TKV growth rate) or lost (for eGFR decline) when adjusted for baseline TKV and eGFR. In the tolvaptan-treated group, the benefit of the treatment for slowing the rate of TKV increase and eGFR decline over time was higher, when compared to placebo, in subjects with the highest copeptin at baseline (note however that more subjects in this higher quartile discontinued the study). Altogether, these results suggest that a measurement of copeptin in subjects with ADPKD could help select those at greater

risk of rapid progression and those expected to benefit the most of vasopressin V2R blockade.

It is important to note that, in ADPKD, vasopressin exerts adverse effects by two independent and additive mechanisms, as depicted in Figure 1. The first mechanism results from the influence of vasopressin on cyst growth mediated by its second messenger, cyclic AMP [3]. This deleterious influence is probably directly proportional to the concentration of AVP and the resulting rise in intracellular cAMP concentration. Thus, the influence of AVP on kidney growth and thus on TKV is likely very direct, and should worsen when the urine concentrating defect due to the disruption of renal medullary architecture induces a progressive rise in AVP secretion.

In contrast, the second mechanism by which AVP may exert a detrimental influence on kidney function and thus GFR (or eGFR) is much more indirect. It is common to all forms of chronic kidney disease (CKD) whatever the initial cause of the disease, and therefore it should also occur in ADPKD, although it has received little attention so far. In experimental studies, AVP or its selective V2R agonist dDAVP have been shown to induce a significant hyperfiltration, the intensity of which increases with increasing urine osmolality (U_{osm}) (see review in [6]). A similar rise in GFR is also associated with the V2R-mediated influence on urine osmolality in humans since GFR has been observed to fall upon initiation of tolvatpan treatment and to rise again upon cessation of this treatment [7, 8]. Hyperfiltration is known to induce a progressive deterioration of kidney function. The mechanism is probably indirect because AVP or V2R agonists have not been shown to induce a rise in GFR acutely. It is assumed to depend upon a reduction of the tubulo-glomerular feedback (TGF) control of the GFR secondary to the influence of AVP on the nephron and collecting duct [6] (Figure 1).

However, it is important to note that the relationship between urine osmolality and GFR is biphasic. It follows a "J-shape" curve. When urine is concentrated, a higher GFR is observed with increasing U_{osm} . But the reverse is observed when U_{osm} falls below a certain threshold (probably close to plasma osmolality) (see review in [6]). Actually, a further reduction in GFR when the kidney needs to produce dilute urine would be functionally detrimental because the generation of solute-free water heavily depends on the amount of solutes delivered to the distal nephron. A reduced GFR would thus compromise the diluting ability of the kidney. Because of this J-shape relationship, the kidney may undergo some hyperfiltration not only when the urine concentrating capacity is still preserved, but also when it is abolished by the

V2R antagonist to a level that induces the production of hypo-osmotic urine. Such a biphasic effect of the influence of AVP on GFR may perturbate the possible associations between baseline copeptin and the rate of eGFR decline because, in the TEMPO 3-4 trial, the average U_{osm} in the tolvaptan-treated group was distinctly about 100 mosm/kg H_2O below plasma osmolality during the entire 3-y follow-up [9].

3. Which subjects should best benefit of V2R antagonism? And how much should the intensity of V2R effects be reduced?

Among subjects treated with tolvaptan, those with the highest pre-treatment copeptin values showed a significantly better treatment effect on slowing both kidney growth and eGFR decline [5]. Therefore, a single copeptin measurement could be added to the evaluation of ADPKD subjects (based on recognized predictive classifications including the PROPKD score, TKV and eGFR measurements) and guide the introduction of the tolvaptan treatment in those with high copeptin level and a still relatively well preserved urine concentrating capacity.

The primary aim of the treatment by a V2R antagonist is of course to limit cyst growth by reducing AVP-dependent formation of cAMP, but it should not induce another burden by too much reducing U_{osm} . Because of the "J-shape" influence of vasopressin on GFR, it is important to lower U_{osm} by antagonizing V2R influence of AVP, but only to a level that will ensure the production of iso-osmotic urine. A decline below this threshold could induce some hyperfiltration associated with the urine diluting process, as explained above.

4. The need for additional studies

The two AVP-dependent mechanisms contributing to progression ADPKD are acting simultaneously and have additional effects. The respective influence of each of them is unknown, as are the consequences of the process of urine dilution on progression of the disease. New interventional studies may be useful to evaluate the optimal level of V2R suppression in ADPKD. What is the best compromise between partially opposite demands? An important issue that should also be considered is that a less aggressive treatment should result in a better adherence of the patients, and less side effects.

Copeptin appears to be a new pathophysiological biomarker of significant interest in kidney diseases in which vasopressin is known to play a detrimental role. It reflects the intensity of vasopressin secretion and thus, the risk of accelerated progression of the disease. Its measurement may help determine which patients should show the best benefit of V2R blockade.

Given the relatively low values of plasma copeptin concentration observed in Gansevoort et al study, it seems important to evaluate when is copeptin first found to be increased, relative to plasma osmolality, in subjects with ADPKD. This information could be relevant to initiate an early treatment in young subjects. It would require integrating periodic measurements of copeptin, as part of the routine examinations in these subjects.

Antagonizing V2R-mediated AVP effects by a vaptan should mostly benefit to patients with a relatively high copeptin level, especially because Gansevoort's study showed a greater benefit of tolvaptan treatment in those with high baseline copeptin concentration. New interventional studies should be designed to determine the level of copeptin at baseline above which to initiate a treatment with a vaptan and to determine the optimum level of suppression of vasopressin V2R-dependent effects.

Several additional relevant references have been provided as Supplemental Information.

Supplementary material can be found on Kidney International's website.

Figure legend

In ADPKD, two additive mechanisms contribute to the progression of the disease. One is due to the direct influence of AVP on cAMP production in collecting duct cells, because cAMP is known to stimulate cyst growth. The other is more indirect and is common to all forms of chronic kidney disease. It depends on the fact that AVP, and the resulting increase in urine osmolality induce an increase in GFR, probably as a result of AVP influence on sodium, urea and water handling in the collecting duct. TGF = tubulo-glomerular feedback; CKD = chronic kidney disease.

References

1. Alam A, Dahl NK, Lipschutz JH, Rossetti S, Smith P, Sapir D, Weinstein J, McFarlane P, Bichet DG. Total Kidney Volume in Autosomal Dominant Polycystic Kidney Disease: A Biomarker of Disease Progression and Therapeutic Efficacy. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2015;66(4):564-76.
2. Grantham JJ, Torres VE. The importance of total kidney volume in evaluating progression of polycystic kidney disease. *Nature reviews Nephrology*. 2016;12(11):667-677.
3. van Gastel MDA, Torres VE. Polycystic Kidney Disease and the Vasopressin Pathway. *Annals of nutrition & metabolism*. 2017;70 Suppl 1:43-50.
4. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *The New England journal of medicine*. 2012;367(25):2407-18.
5. Gansevoort RT, van Gastel M, Chapman A, Blais J, Czerwiec F, Higashihara E, Lee J, Ouyang J, Perrone R, Stade K, Torres V, Devuyst O. Copeptin to predict disease progression and tolvaptan efficacy in ADPKD. Results of the TEMPO 3:4 Trial. *Kidney Int*. 2019.
6. Bankir L, Bouby N, Ritz E. Vasopressin: a novel target for the prevention and retardation of kidney disease? *Nature reviews Nephrology*. 2013;9(4):223-39.
7. Irazabal MV, Torres VE, Hogan MC, Glockner J, King BF, Ofstie TG, Krasa HB, Ouyang J, Czerwiec FS. Short-term effects of tolvaptan on renal function and volume in patients with autosomal dominant polycystic kidney disease. *Kidney international*. 2011;80(3):295-301.
8. Boertien WE, Meijer E, de Jong PE, Bakker SJ, Czerwiec FS, Struck J, Oberdhan D, Shoaf SE, Krasa HB, Gansevoort RT. Short-term renal hemodynamic effects of tolvaptan in subjects with autosomal dominant polycystic kidney disease at various stages of chronic kidney disease. *Kidney international*. 2013;84(6):1278-86.
9. Devuyst O, Chapman AB, Gansevoort RT, Higashihara E, Perrone RD, Torres VE, Blais JD, Zhou W, Ouyang J, Czerwiec FS. Urine Osmolality, Response to Tolvaptan, and Outcome in Autosomal Dominant Polycystic Kidney Disease: Results from the TEMPO 3:4 Trial. *Journal of the American Society of Nephrology : JASN*. 2017;28(5):1592-1602.

