Riding the waves: evidence for a beneficial effect of increased water intake in autosomal dominant polycystic kidney disease patients?

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Autosomal dominant polycystic kidney disease (ADPKD) can lead to end-stage kidney disease and accounts for ~10% of people receiving renal replacement therapy. Until recently, no treatment had been proven to effectively postpone kidney failure. Interestingly, experimental studies that have been published over the past decades have suggested a detrimental role for the antidiuretic hormone arginine vasopressin (AVP) in ADPKD. V2 receptor activation by AVP was discovered to result in an increase of 3',5'-cyclic adenosine monophosphate (cAMP) [1]. In turn, cAMP stimulates cell proliferation and fluid secretion, leading to cyst formation and cyst growth [2–4]. ADPKD patients appeared to have high serum levels of AVP, and AVP levels were, in cross-sectional studies, associated with disease severity [5] and, in longitudinal studies, with disease progression [6, 7].

These observations formed the rationale to study interventions that block this cAMP-mediated pathway using V2 receptor antagonists. In various animal models for cystic kidney disease, these interventions were successful to reduce cyst growth [8–10]. Subsequently, the selective AVP V2 receptor antagonist tolvaptan was tested for its efficacy in ADPKD patients in the TEMPO 3:4 trial. For the first time, a medical treatment proved to be beneficial with respect to kidney outcomes. In 1445 ADPKD patients, relatively early in the disease, treatment with tolvaptan slowed the rate of growth in total kidney volume by ~50% and the rate of estimated glomerular filtration rate (eGFR) loss by ~30% compared with placebo. In 2013, however, the US Food and Drug Administration (FDA) decided against approval of tolvaptan for the indication ADPKD, but to ask for additional evidence. The decision of the European Medicines Agency is expected late in 2014.

With tolvaptan at present not being available for clinical care, other options that lower AVP activity should be considered. An alternative might be to lower AVP concentration by increasing water intake [14]. In a rat model for polycystic kidney disease, a 3.5-fold increased water intake reduced urinary osmolality, renal expression of the AVP V2 receptor and reduced kidney weight compared with normal water intake [15] (Figure 1).

Given the theoretical background and the promising animal data, Higashihara et al. investigated the effects of increased water intake on disease progression in ADPKD, a clinically important and very timely topic. In their study, published in this issue of NDT, 34 ADPKD patients with a relatively preserved kidney function were divided based upon their preference into a high and a free water intake group.
Patients in the high water intake group were instructed to drink 50 mL/kg water per day, and patients in the free water intake group did not receive instructions regarding the volume of water to drink. Total kidney volume was measured by magnetic resonance imaging at baseline and at 1 year, at the end of the study. eGFR and 24-h urine volume were measured every 4 months. Already prior to the study, 24-h urine volume (and thus water intake) was significantly higher in the high water intake group (2.0 versus 1.5 L per 24 h). This difference increased slightly during the study period (2.6 versus 1.4 L per 24 h). As a result, the patients in the high water intake group had decreased plasma osmolality and plasma AVP concentration when compared with subjects in the free water intake group, although there was considerable overlap between both groups.

In contrast to the hypothesis, however, no difference in change in kidney volume or kidney function was found during the study, and if any, there was a trend towards more rapid renal disease progression in the high water intake group. Furthermore, a trend towards a negative association between urine volume and slope of kidney function was found. For 30 of 34 patients who participated in the study, data were available of the pre-study change in kidney function and kidney volume (an observation period of almost 3 years). These variables were not different between both groups pre-study. After the study started, however, slopes of changes in eGFR and total kidney volume became steeper in the high water intake group (P = 0.01 and 0.05, respectively), whereas they remained unchanged in the free water intake group, which is the third argument that an increase in water intake may be associated with more rapid renal disease progression in this study.

Three reasons come to mind why this study does not confirm the hypothesis that an increased water intake is beneficial in ADPKD. First, it could be caused by the study design. Major strengths of the study by Higashihara et al. are that the abundance of data is shown in all detail, allowing the reader to draw their own conclusions, and that pre-study slopes for change in eGFR and total kidney volume are available. Limitations of this study are the small number of patients, the lack of randomization and the short study duration. This may lead to false-negative conclusions. Because of ethical concerns, patients were allocated to the study groups based on their own preference. Imbalances in baseline characteristics may strongly influence study results. For instance, subjects in the high water intake group also had a higher sodium and protein intake, which could theoretically lead to higher AVP levels and consequently to a more rapid disease progression. Fortunately, the authors measured AVP as well as its surrogate copeptin. They actually found lower levels in the high water intake group, suggesting that these differences in diet did not play a major biasing role. It could also be that the higher baseline 24-h urine volume in some patients was not the reflection of a conscious increase in water intake, but the reflection of impaired urine concentrating capacity, as is often found in subjects with more severe renal cystic interstitial lesions and that predisposes to worse outcome. Finally, V2 receptor antagonists have been shown to induce an acute, reversible decrease in kidney function [16]. Lowering AVP with high water intake may have a similar effect. Because of the relatively short time frame of the study, potential beneficial long-term effects on eGFR of increased water intake could have been obscured by this acute renal haemodynamic effect.

Second, the hypothesis may be correct, but water intake should be higher than was achieved in this study to suppress AVP concentration sufficiently. Although in this study, the groups, on average, were different with respect to 24-h urine volume, there was still considerable overlap in 24-h urine volumes, plasma osmolality and plasma AVP concentration. Moreover, the advised fluid intake (on average 3.15 L/24 h) was not achieved, given the measured 24-h urine volume (2.66 L/24 h). This questions feasibility of such a dietary intervention. Increasing water intake may indeed be challenging for patients during prolonged periods of time. In a pilot study in ADPKD, in 3 of 8 patients, urinary osmolality could not adequately be suppressed during 1 week of oral water loading [17]. In a study investigating potential beneficial effects of water loading on chronic kidney transplant failure, a loss of adherence to the higher fluid intake (4 L/24 h) regimen was seen over time in the 33 participating patients [18].

Third, maybe the hypothesis is wrong. Although vasopressin V2 receptor blockade is beneficial in ADPKD, an increase in water intake may not. Two potential explanations come to mind. Although not likely, it could theoretically be possible that the compensatory-elevated AVP levels in V2 receptor antagonist-treated patients have not yet identified beneficial effects on the other, non-antagonized AVP receptors (the V1a or V1b receptors) [19]. In addition, already in early ADPKD, AVP levels are high, probably to compensate for the impaired urinary concentrating capacity that is observed in this disease [20]. Maybe, even a sustained, considerable increase in water intake is not able to suppress AVP as low as necessary to induce beneficial effects for a longer period, whereas vasopressin V2 receptor blockade can inhibit AVP’s detrimental effects more effectively. In agreement with this, it has been shown that an increased water intake of 3 L induced, on short-term basis, a decrease in urinary cAMP, which is supposed to be a reflection on AVP activity, whereas chronic water loading did not [21].

All in all, the study by Higashihara et al. deals with an important topic. Their results are not in favour of increasing water intake in ADPKD. However, because of the aforementioned methodological considerations, beneficial effects of water loading in ADPKD cannot be ruled out either. Further
investigations are therefore needed, preferably in a randomized trial with larger number of patients and with longer follow-up. Until such investigations become available, the present data form the waves that we can ride.

**CONFLICT OF INTEREST STATEMENT**

The results presented in this paper have not been published previously in whole or part.

(See related article by Higashihara et al. Does increased water intake prevent disease progression in autosomal dominant polycystic kidney disease? Nephrol Dial Transplant 2014; 29: 1710–1719.)

**REFERENCES**


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