Water for ADPKD? Probably, Yes

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"On systemic inquiry among the patients it was astonishing to find how frequently they reported having suffered from thirst, polydipsia and polyuria already at an early stage of the disease."
—Dalgaard, 1957

Since its early descriptions, an impaired urine-concentrating capacity has been a common feature of autosomal dominant polycystic kidney disease (ADPKD), even at early stages of the disease. Sixty-three of 71 patients who were studied by Dalgaard (1) were unable to concentrate the urine to a specific gravity ≥1022 during a concentration test. Eleven of 13 patients who had a mean GFR of 103 ml/min per 1.73 m^2 and were studied by Martinez-Maldonado *et al.* (2) were unable to concentrate the urine above 700 mOsm/kg after 24 h of dehydration and administration of vasopressin. Many other studies have confirmed these observations. Gabow *et al.* (3) found a lower mean urine osmolality after overnight dehydration and vasopressin administration in 87 patients who had ADPKD and a mean creatinine clearance of 102 ml/min per 1.73 m^2, as compared with 106 nonaffected relatives, as well as an inverse correlation between maximal urine osmolality and renal volume. More recently, Kaarainen *et al.* (4) and Seeman *et al.* (5) showed that 60% of children with ADPKD were unable to concentrate the urine maximally after dDAVP administration. Consistent with the concentrating defect, plasma vasopressin levels are increased in human ADPKD (6,7) and in animal models, where it has been ascertained (V.H. Gattone, Indiana University School of Medicine, personal communication, 2005).

The cause of the vasopressin-resistant concentrating defect is not known. Decreased generation of cAMP or expression of collecting duct concentration–associated genes seems unlikely because they are consistently increased *in vivo* (but not *in vitro*) in animal models of PKD (8–10). The concentrating defect often is attributed to disruption of the medullary architecture by cysts, because its presence and severity correlate with the extent of the cystic disease (3). Nevertheless, it precedes the development of cystic dilation of the collecting ducts in models of PKD that are induced by diphenylamine or diphenylthiazole (11,12), and overexpression of concentration-associated genes precedes the development of cysts in the cpk mouse (8). In some but not all studies, aquaporin 2 is found throughout the principal cells in cystic collecting ducts, whereas it is restricted mainly to their apical portion in normal collecting ducts (8,13). This would be consistent with a defective translocation of aquaporin 2 to the apical membrane (14).

Until recently, the concentrating defect and increased vasopressin levels have been deemed to have little clinical significance. The inhibition of cyst growth by V2 receptor antagonists in animal models of cystic disease has raised the possibility that vasopressin may be important in the progression of ADPKD (8–10,15). Alterations in intracellular calcium homeostasis, caused by mutations in *PKD1* or *PKD2*, may enhance renal cAMP accumulation and switch the proliferative phenotype of the principal cells from one that is inhibited to one that is stimulated by cAMP, thereby making them susceptible to the growth-promoting effects of vasopressin (16,17). Nagao *et al.* (18) in this issue of *JASN* demonstrate that suppression of vasopressin by drinking water is sufficient to ameliorate the course of PKD in PCK rats. Their results support the importance of vasopressin in the pathogenesis of PKD and confirm that the beneficial effect of V2 receptor antagonists in previous studies is due to the inhibition of the vasopressin effect on collecting ducts and not to a different mechanism that is not yet understood.

Vasopressin also may contribute to the development of hypertension and the progression of the renal insufficiency in ADPKD. A role in the development of hypertension could explain the inverse correlation between urine-concentrating capacity and 24-h BP in children with ADPKD (5) and the direct correlation between urine volume and mean arterial BP in the Modification of Diet in Renal Disease Study (MDRD) study (19). V1a receptor activation may increase BP by a direct effect on vascular smooth muscle and by reducing renal medullary blood flow and pressure natriuresis (20). V2 receptor activation enhances epithelial sodium channel–dependent sodium transport in the collecting duct, although the underlying mechanism remains uncertain (21). Conversely, V2 receptor activation may exert an antihypertensive effect by inducing nitric oxide synthesis in collecting ducts and increasing medullary blood flow (22). The relevance of these vasopressin effects to hypertension in ADPKD is uncertain.

Plasma vasopressin levels are increased in patients with and animal models of chronic renal insufficiency. Bankir *et al.* (23) advanced the hypothesis that V2 receptor activation contributes to the progression of chronic kidney disease. V2 receptor activation increases the concentration of osmotically active urea in

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the thick ascending limb of Henle by promoting intrarenal urea recycling, which results in reduction in NaCl concentration at the macula densa, suppression of tubuloglomerular feedback, glomerular hyperfiltration, proteinuria, and, if sustained, renal hypertrophy and tubulointerstitial disease. Conversely, the progression of chronic kidney disease after five-sixths nephrectomy or induction of diabetes by the administration of streptozotocin is attenuated in animals with central diabetes insipidus or by water loading or by the administration of a selective V2 receptor antagonist (24–26).

A retrospective analysis of the MDRD study (139 participants with and 442 without ADPKD; GFR at entry 25 to 55 ml/min per 1.73 m^2) was performed to examine the relationship between fluid intake (reflected by 24-h urine volume and urine osmolality) and renal disease progression. Higher urine volumes and lower urine osmolalities were associated with faster GFR decline regardless of whether the patient had ADPKD. The authors considered two possible explanations. The first was that excessive fluid intake and high urine volume cause faster renal disease progression and possibly cyst growth in ADPKD. The second was that high urine volume with low urine osmolality is the result and not the cause of faster renal disease progression (19). The results by Nagao *et al.* (18) do not support the first explanation; on the contrary, they suggest that increased fluid intake may be beneficial to some patients with ADPKD, at least in early stages of the disease.

If increased fluid intake, either by itself or together with the administration of V2 receptor antagonists, is proved to slow the rate of growth of polycystic kidneys, then its long-term safety will need to be considered. Caffeinated beverages should be discouraged because caffeine inhibits phosphodiesterase; enhances cAMP accumulation; and potentiates the effects of vasopressin on chloride secretion, cell proliferation, and cyst growth, at least *in vitro* (27). Calorically sweetened beverages and fruit drinks are major contributors to the epidemic of obesity in the United States and should be avoided (28). Because drinking tap water has been associated in some studies with a slightly increased risk for bladder cancer in men, whereas nontap water has not, high-quality or bottled water may be preferable (29).

A number of studies of other possible treatments for PKD have been published during 2005 to 2006. Long-acting octreotide may inhibit cAMP production, and a pilot study of patients with ADPKD has shown promising results (30). PD184352, an inhibitor of mitogen-activated protein kinase/extracellular signal–regulated kinase (31), and rapamycin, an inhibitor of mammalian target of rapamycin (32–34), have been effective in animal models of cystic disease. The pace of development of new potential therapies for ADPKD raises the hope that its inexorable clinical course soon may be modified.

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Please see the related article, "Increased Water Intake Decreases Progression of Polycystic Kidney Disease in the PCK Rat," on pages 2220–2227.