A Case for Water in the Treatment of Polycystic Kidney Disease

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Autosomal dominant polycystic disease (ADPKD) is an inherited disorder characterized by the development within renal tubules of innumerable cysts that progressively expand to cause renal insufficiency. Tubule cell proliferation and transepithelial fluid secretion combine to enlarge renal cysts, and 3′-5′-cyclic adenosine monophosphate (cAMP) stimulates that growth. The antidiuretic hormone, arginine vasopressin (AVP), operates continuously in ADPKD patients to stimulate the formation of cAMP, thereby contributing to cyst and kidney enlargement and renal dysfunction. Studies in animal models of ADPKD provide convincing evidence that blocking the action of AVP dramatically ameliorates the disease process. In the current analysis, the authors reason that increasing the amount of solute-free water drunk evenly throughout the day in patients with ADPKD and normal renal function will decrease plasma AVP concentrations and mitigate the action of cAMP on the renal cysts. Potential pitfalls of increasing fluid intake in ADPKD patients are considered, and suggestions for how physicians may prudently implement this therapy are offered.

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Convergent findings in the last decade have established that 3′-5′-cyclic adenosine monophosphate (cAMP) stimulates mural epithelial cell proliferation and secretion of fluid into cysts of patients with autosomal dominant polycystic kidney disease (ADPKD), contributing to massive renal enlargement and dysfunction (1). AVP promotes cAMP production in the distal nephron and collecting ducts (CDs) by acting on AVP-V2 receptors (V2R). Preclinical evidence has shown in four different genetic models of polycystic kidney disease (PKD) that blocking the effect of AVP, thereby decreasing cAMP levels, slows cyst and renal enlargement and improves renal function (2–4).

A novel treatment for ADPKD that targets AVP/cAMP is currently being evaluated in an international clinical trial (TEMPO NCT00428948). An inhibitor of V2R (tolvaptan) is administered to patients with the intent to diminish intracellular cAMP levels in cyst epithelial cells. V2R inhibition also diminishes the reabsorption of solute-free water in CDs, thereby causing partial nephrogenic diabetes insipidus and thirst. Daily urine volumes 5 d after starting different split doses of tolvaptan (15/15, 30/0, 30/15, 30/30 mg) in a preliminary phase 2 study were 4 to 6 L (5). This polyuria requires ingestion of enough water to maintain normal fluid balance, and TEMPO trial participants are instructed to drink enough to prevent or minimize thirst.

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Another way to decrease the effect of AVP on the kidney is to suppress its secretion by increasing fluid ingestion above what normal thirst would command. This strategy is hardly new, as a high fluid intake to dilute the urine likely is the oldest existing treatment in nephrology. Up to 3000 cc of water per day, drunk relatively evenly throughout waking hours and before going to bed, is frequently recommended to prevent urine supersaturation for lithogenic salts and to mitigate stone formation. Unlike V2R inhibition, thirst does not ordinarily drive patients to drink this much water, and it is hard for them to comply with the water prescription (6,7).

It is not surprising that discerning physicians and highly informed and motivated patients with ADPKD have inquired about simply increasing the ingestion of plain water as a convenient and physiologic way to reduce the long-term impact of AVP, thereby avoiding the thirst of V2R blockade (8). In view of the widely accepted long-term administration of water in nephrolithiasis, it seems that increased water intake would be a safe physiologic means to ameliorate ADPKD. However, the potential adverse renal consequences of prolonged water diuresis have not been critically analyzed.

Here we examine the rationale for decreasing the effect of AVP in ADPKD, review the role of AVP in renal water excretion in healthy subjects, evaluate the consequences of drinking increased amounts of water in ADPKD, and offer a recommendation for how much water patients may safely drink to persistently lower the plasma concentration of AVP.

Why Decrease the Effect of AVP in ADPKD?

Renal cysts are rather simple biologic structures. Originating in tubules, primarily from the distal nephron and CDs, they

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evolve as out-pouchings of epithelial monolayers surrounding a cavity filled with urine-like liquid. These eventrations eventually separate from the original tubule and expand as liquid is transported into the cavity and mural cells proliferate fast enough to accommodate fluid secretion.

The recognition of AVP and cAMP as central components in the pathogenesis of renal cyst growth began with studies of Madin-Darby canine kidney (MDCK) cells (9). cAMP, the product of V2R stimulation of adenylyl cyclase, provoked net transepithelial chloride-dependent fluid secretion and increased the proliferation of MDCK monolayers. AVP or cAMP stimulated the progressive expansion of three-dimensional MDCK microcysts within collagen gels. These observations raised the possibility that the AVP signaling pathway might have a role in ADPKD. Mural epithelial cells grown from human renal cysts proliferate and secrete fluid when stimulated with AVP or cAMP, whereas cells from normal kidneys do not proliferate (10–12). The proliferative response to cAMP is a cardinal phenotypic feature of cyst epithelial cells that differentiates them from normal cells.

The centrality of AVP/cAMP in the pathogenesis of PKD provided a rationale for, and was reinforced by, preclinical trials of V2R antagonists. OPC-31260 strikingly inhibited renal enlargement and improved renal function in *cpk* mice, a recessive model of explosive cystic disease, and in three models orthologous to human autosomal recessive PKD (ARPKD, PCK rat), ADPKD (*Pkd2*$^{-tm1Som}$) and juvenile nephronophthisis (*pcy* mouse) (2–4). Tolvaptan, an antagonist with high potency and selectivity for the human V2R, was also effective in the orthologous models (13). High water intake by itself exerted a protective effect in PCK rats, likely by suppressing AVP secretion (14). Moreover, genetic elimination of AVP in PCK rats yielded animals born with normal kidneys that remained relative free of cysts unless an exogenous V2R agonist was administered (15). These results, along with the observation that V2R inhibitors lowered renal cAMP levels in the cystic kidneys, suggest that AVP/cAMP sparks a 'final common pathway' that is linked to the cyst phenotype.

Recognition that cell-specific inhibition of cAMP action ameliorates PKD has opened therapeutic opportunities. Specifically targeting the AVP-V2R axis will likely be more effective and produce less problematic secondary effects than targeting the complete range of hormones and autacoids that affect cAMP levels within cyst epithelial cells. In this respect nature is on the side of AVP, in contradistinction to prostaglandins, parathyroid hormone, vaso-intestinal-polypeptide, adenosine and β-adrenergic agonists and forskolin (12,16,17). The biology of terrestrial animals is rigged to minimize the intake of fluids, leaving them to function with plasma levels of AVP sufficient to concentrate the urine most of the time. In PKD, circulating AVP is increased above normal (18,19) and V2R is over-expressed (2–4). AVP, acting on V2R, is the main agonist of adenylyl cyclase in tubular segments where cystogenesis is particularly active, possibly because of higher baseline proliferation rates. Clinical trials of V2R antagonists for the treatment of hyponatremia and congestive heart failure have shown that these drugs are relatively safe, likely because of the restricted expression of V2R, mainly in the CDs, distal nephron, and a few other tissues (20–22).

Regulation of AVP Release and Thirst

AVP is synthesized in paraventricular magnocellular neurons and supraoptic nuclei located in the hypothalamus. Axons from these neurons project into the pituitary axis and reach the neural lobe of the hypophysis where AVP is stored. The precursor of AVP is a 164 amino acid peptide that is cleaved into three peptides, the mature AVP nonapeptide, neurophysin, and copeptin, during its descent along the axons of the pituitary stalk. The hormone and associated peptides are released into the blood in response to increased effective osmotic pressure of plasma or decreased effective blood volume (23,24).

Plasma osmolality (P_{osm}), due primarily to solutes that do not freely cross cell membranes (mainly sodium chloride), is the most important stimulus for AVP release under physiologic conditions. Osmoreceptor neurons in the circumventricular organum vasculosum of the lamina terminalis and in the anterior wall of the third ventricle detect changes in osmotic pressure and send projections to the magnocellular AVP neurons and to the insular and cingulate cortex responsible for the sensation of thirst. AVP secretion is more sensitive than thirst to small changes in osmolality (less than one mosm/kg H_2O) (Figure 1). This difference in thresholds ensures that AVP is almost constantly present in the plasma except when fluids are ingested abundantly to quench thirst (25).

Arterial stretch, sensed by neurons (baroreceptors) in the

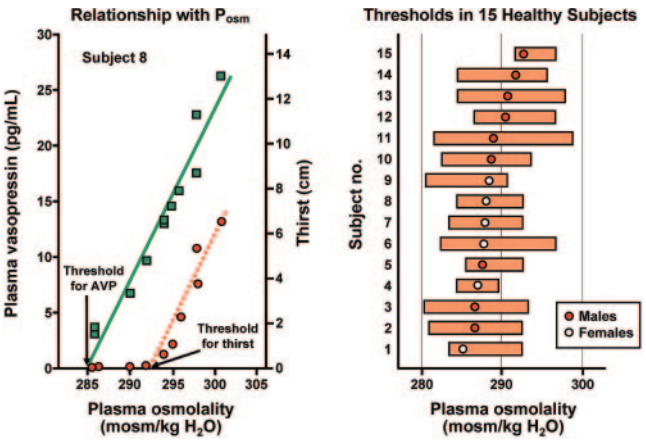

Figure 1. Plasma arginine-vasopressin (AVP) and thirst thresholds. Relationship between plasma osmolality (P_{osm}) and plasma AVP level or intensity of thirst in normal subjects. P_{osm} was lowered or raised by intravenous infusions of either hypotonic or hypertonic sodium chloride solutions. Left: A representative subject separately defines P_{osm} thresholds and slopes for AVP release (green squares) and for sense of thirst (red circles). Right: Thresholds for AVP secretion and thirst (left and right ends of the horizontal bars, respectively) in 15 different subjects. The closed and open circles represent the resting P_{osm} for males and females. Note the large interindividual differences in the distances between the two thresholds and in the resting P_{osm}. (Adapted from Robertson GL, Kidney Int. 25:460 to 480, 1984.)

aortic arch and carotid sinus and transmitted to the central nervous system by the vagus and glossopharyngeal nerves, tonically inhibits AVP release. Arterial underfilling, caused by volume contraction, low-output cardiac failure, or peripheral vasodilatation, eliminates this inhibition and causes AVP release. AVP secretion is much less sensitive to changes in blood volume than to changes in P_{osm} (26).

Plasma AVP concentrations under physiologic conditions range from undetectable to 2 to 3 pg/ml (approximately 10^{-12} M). Changes in plasma AVP concentration below the detection limit (0.5 pg/ml) can, nonetheless, cause significant changes in urine osmolality (U_{osm}) and flow rate (27). Copeptin is released into the blood in amounts equimolar to AVP but has a longer half life and is easier to measure (28). This new marker could become a useful surrogate for AVP in clinical studies in which it is important to assess small changes in hormone concentration.

Effects of AVP on Renal Water Conservation

Solute-free water is generated in the ascending loop of Henle and distal tubule and reabsorbed in the cortical, medullary, and papillary segments of the CD when AVP is present in the blood. AVP acts on three G protein-coupled receptors: V2 (cAMP second messenger) and V1a and V1b (also called V3) (calcium second messenger). Several actions of AVP on V2R contribute to the urinary concentrating process (possibly with different hormone concentration thresholds): (*1*) insertion of aquaporin 2 (AQP-2) water channels into the apical cell membrane of CDs (within minutes) to increase water permeability, followed by up-regulation of *AQP-2* gene expression (on a longer term); (29,30) (*2*) activation of the urea transporters UT-A1 and UT-A3 to increase in urea permeability of the terminal part of the inner medullary CD (this allows urea delivery to the tip of the papilla and favors urea accumulation in the inner medulla); (31,32) (*3*) stimulation of the epithelial sodium channel ENaC to increase sodium reabsorption by the cortical and outer medullary CDs (this allows more water to be reabsorbed in the early part of the CD, thus reducing the amount of fluid entering the medullary CD); (33,34) (*4*) stimulation of sodium reabsorption and increased Na-K-2Cl cotransporter expression in the thick ascending limb (TAL). Working in concert, these actions of AVP allow variable amounts of water to be absorbed into the cortical and medullary interstitium, thereby concentrating urinary solutes to a variable degree. In the absence of AVP, the permeability to water of the CD segments is very low, and solute-free water generated in the TAL and distal tubule flows into the renal pelvis at an osmolality as low as 60 mosm/kg H_2O.

Relationship Between Osmolar Excretion, Urine Osmolality, and Urine Volume in Healthy Individuals

The kidneys regulate the excretion of water and solutes to maintain P_{osm} and extracellular fluid volume. Under normal conditions, there is wide interindividual variability in the daily osmolar excretion ($U_{osm}V$) among healthy subjects. Under steady-state metabolic conditions, osmolar excretion reflects the intake of protein and electrolytes minus losses via bowel and skin. A survey of daily dietary solute intake in healthy individuals aged 2 to 59 yr provides estimates of individual and total solutes destined for urinary excretion (Table 1). Adults ingest more solutes than children and adult males more than females.

Daily solute excretion data compiled from nine international studies (Table 2) are in general agreement with the potential solute intakes shown in Table 1. The mean osmolality of urine over the full 24-h period in these subjects was uniformly greater than that of plasma. Urine osmolality throughout the day has been determined over the course of sequential 24 h periods. In

Table 1. Daily dietary solute intake in healthy individuals aged 2 to 59 yr

Sex	Age Range (yr)	Protein (g)	Urea[a] (mmol)	Na (mEq)	K (mEq)	Osmoles[b] (mosm)
Males	2 to 5	58	331	105	56	653
	6 to 11	77	440	144	60	847
	12 to 19	94	537	176	70	1031
	20 to 29	111	634	198	80	1190
	30 to 39	109	623	198	84	1188
	40 to 49	103	589	188	84	1132
	50 to 59	95	543	169	81	1044
Females	2 to 5	61	349	114	57	692
	6 to 11	65	371	131	55	744
	12 to 19	68	389	131	54	758
	20 to 29	75	429	138	60	825
	30 to 39	72	411	137	62	809
	40 to 49	68	389	127	61	766
	50 to 59	67	383	121	59	743

Adapted from What We Eat in America, NHANES, 2003-2004. Table 1 Nutrient Intakes from Food: Mean Amounts Consumed per Individual, One Day, 2003-2004 U.S. Department of Agriculture, Agricultural Research Service. 2007. www.ars.usda.gov/ba/bhnrc/fsrg

[a]Urea (mmol) = protein (g) ÷ 0.175. [b]Sum of urea and 2 × (Na + K).

Table 2. Mean daily solute and water excretion in normal adult men and women (from nine international studies) and in adult ADPKD patients with normal GFR (from three studies)

	Healthy Individuals			ADPKD Patients		
	Men	Women	Men and women	Men and women		
Subjects (n)	78	763	46	87	33	241
V (L)	1.40	1.84	1.83	1.97	2.25	2.43
Na (mEq)	170	144	155	NA	168	183
K (mEq)	70	59	53	NA	66	57
Urea (mmol)	402	359	351	NA	NA	358[b]
U_{osm} V (mosm)	1013	909	978	833	1458	836[a]
U_{osm} (mosm/L)	724	494	534	423[a]	648	344[a]
References	(36, 82, 83, 84, 85)	(36, 84, 86)	(87–89)	(45)	(46)	(44,47)

NA, not available.
[a]Calculated osmolality. [b]Calculated from urine urea nitrogen.

normal recumbent men, overnight U_{osm} averaged 708 mosm/kg H_2O (35). The mean U_{osm} fell to 564, 370 and 414 mosm/kg H_2O in the morning, afternoon and evening, respectively over several days of study. Thus, AVP operates to promote the continuous reabsorption of solute-free water by CDs throughout the day and night.

Osmolar loads are excreted by kidneys in varying volumes of urine depending on the availability of water, drinking habit, and genetic and environmental factors that control thirst (36). Under normal conditions, urine volume is determined by the obligatory excretion of the osmolar load, by the plasma level of AVP, and by the capacity of the kidneys to concentrate or dilute the urine. When U_{osm} exceeds P_{osm}, the osmolar clearance ($C_{osm} = U_{osm}V/P_{osm}$) exceeds urine flow (V) and solute-free water is "saved" for the body. In contrast, when P_{osm} exceeds U_{osm}, urine flow exceeds the osmolar clearance and solute-free water is cleared ($C_{H20} = V - C_{osm}$) from the body. For a given osmolar excretion, the reciprocal relationship between U_{osm} and urine volume is not linear (Figure 2) (37). For each doubling of U_{osm}, the reduction in daily urine volume becomes smaller by one-half. Consequently, concentrating the urine saves proportionally small amounts, whereas urine dilution can generate relatively large amounts of solute-free water.

The capacity to conserve solute-free water and generate maximally concentrated urine (approximately 1200 mosm/kg H_2O) depends on intact AVP secretion, kidney structure, and renal concentrating mechanisms. The maximal capacity to excrete a water load depends on appropriate osmolar excretion, complete suppression of AVP release, and intact renal diluting mechanisms to produce urine osmolalities as low as 60 mosm/kg H_2O. To illustrate the important role of osmolar excretion, (38) Figure 3 shows that the excretion of 300 or 900 mosm in 60 mosm/kg H_2O urine generates 4 L of solute-free water (in 5 L of urine) or 12 L of solute-free water (in 15 L of urine), respectively. Osmolar excretion, U_{osm}, and urine volume are affected by gender and race. Men eat more than women (Table 1) and excrete higher daily osmolar loads (Table 2) in similar urine volumes by raising U_{osm} (36). African Americans excrete similar daily osmolar loads as Caucasians, but with a higher U_{osm} and in a lower urine volume (39). Men tend to have higher plasma AVP concentrations than women and African Americans higher than Caucasians, possibly contributing to their greater susceptibility to renal disease progression and salt-sensitive hypertension (36,40).

Urinary Concentrating and Diluting Capacities in Chronic Kidney Disease

In chronic kidney disease (CKD), compensatory mechanisms cause the GFR in residual nephrons to rise, causing an increase

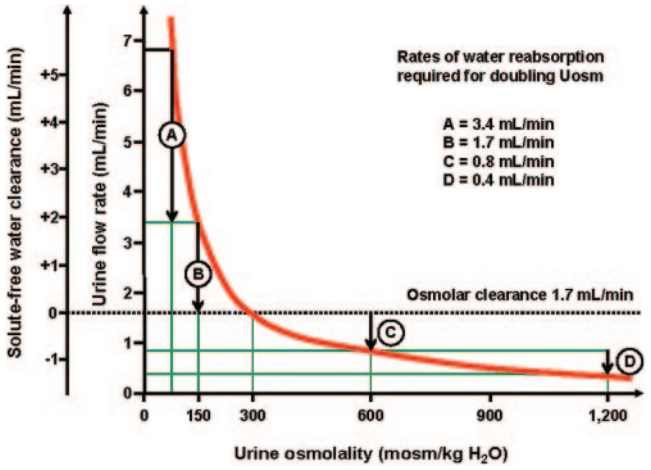

Figure 2. Relationship between urine flow rate and osmolality for a fixed osmolar excretion of 735 mosm/d (corresponding to an osmolar clearance of 1.7 ml/min when plasma osmolality [P_{osm}] = 300 mosm/kg H_2O). Ordinate: Urine flow rate or solute-free water clearance (C_{H20}). When $U_{osm} = P_{osm}$, urine flow rate = osmolar clearance and solute-free water clearance = 0. The rates of water reabsorption required to successively double U_{osm} from 75 to 1200 mosm/kg H_2O are shown by vertical arrows and quantified in the insert. The amount of water "saved" by the effects of AVP is relatively large when the starting U_{osm} is less than that of plasma (hypo-osmotic); however, the amount "saved" declines sharply when urine is concentrated above that of plasma (hyperosmotic). (Adapted from Bankir L. Cardiovasc Res 51:372–390, 2001.)

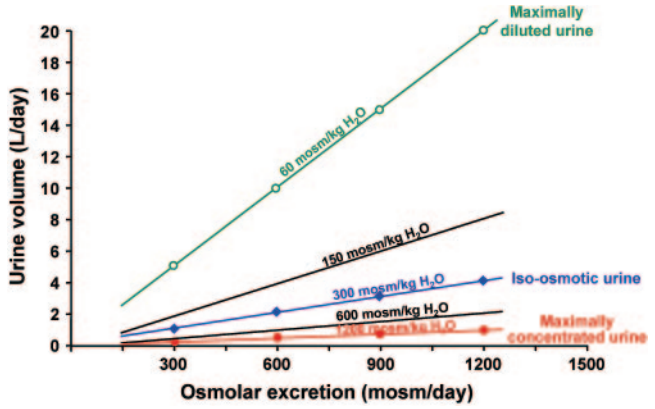

Figure 3. Osmolar excretion and urine volume; influence of daily osmolar load (osmolar excretion) on daily urine volume at different urine osmolalities. The iso-osmotic urine line divides the graph into urine dilution and urine concentration. The osmolar load sets limits on the amounts of urine that can be excreted when the kidney produces maximally dilute urine (60 mosm/kg H_2O). The excretion of 300 or 900 mosm in maximally dilute urine (60 mosm/kg H_2O) would generate 4 L of solute-free water (in 5 L of urine) or 12 L of solute-free water (in 15 L of urine), respectively. For someone excreting only 180 mosm/d solute-free water excretion would fall to 2.4 L in 3 L of maximally dilute urine, placing the patient at a higher risk for developing hyponatremia.

in the filtered solute load presented to individual tubules. Adjustments in the fractional reabsorption of sodium by the tubules (mainly in the distal nephron and CD and possibly in the proximal tubule at advanced stages of CKD) maintain urinary solute excretion equal to dietary intake. As CKD progresses, the compensatory process accelerates the flow of filtered solutes within surviving nephron units to the point that tubule solute reabsorptive transport mechanisms are eventually exceeded. When this point is reached, the osmolality of the final urine is clamped close to that of the plasma because of the osmotic effect of the increased solute excretion per nephron (isosthenuria) (41,42).

The concentrating mechanism appears to malfunction before the diluting mechanism in CKD. Damage to the medullary architecture undermines countercurrent multiplication mechanisms, thereby impairing the capacity to maximally concentrate the urine. AVP-resistant hyposthenuria can also occur in certain renal diseases and in advanced renal failure (43). In contrast, the diluting capacity, which depends primarily on the function of the cortical TALs and distal tubules, continues to generate solute-free water until the solute reabsorptive capacities of those tubule segments are exceeded. In advanced renal insufficiency, the capacity to excrete free water, at equal solute excretion rates, remains similar to normal if it is expressed per unit of glomerular filtrate. However, the absolute reduction in GFR reduces the overall capacity of the kidney to excrete a water load.

The foregoing principles are illustrated by calculations summarized in Table 3. When the GFR declines progressively from 60 to 5 ml/min, let us assume that the distal delivery of filtrate is 30% for GFR 60 to 10 ml/min, 40% for GFR 10 ml/min, and 50% for GFR 5 ml/min. The table shows the minimal achievable U_{osm} (increasing as a result of osmotic diuresis per nephron), maximal urine volume (estimated from osmolar excretions and minimal U_{osm}), and solute-free water excretion (estimated from urine volumes and osmolar excretions) for a range of daily osmolar excretions (osmolar load is assumed to decrease as the GFR falls below 10 ml/min). This analysis illustrates that a minimal U_{osm} of 60 mosm/kg H_2O could be achieved and extracellular volume tonicity maintained in the normal range until GFR fell below 40 ml/min, thereby permitting urine volumes up to 20 L/d for individuals excreting a relatively high osmolar load of 1200 mosm/d. The maximum urine volume falls by one-half when the osmolar load is reduced to 600 mosm/d.

Daily Urine Volume and Solute Excretion in ADPKD Patients

Table 2 lists average values for 24-h urine sodium, potassium, urea, osmolar excretion, volume, and mean U_{osm} from three studies of adult ADPKD patients with GFRs in the normal range (44–47). Mean daily urine volumes ranged from 1.97 to 2.43 L, levels that tended to be higher than in normal individuals drawn from the United States and Europe (Table 2). It should be noted, however, that a direct comparison of patients

Table 3. Hypothetical values for distal delivery of filtrate, minimal achievable U_{osm}, maximal achievable urine volumes, and solute-free water excretions for daily osmolar excretions ranging from 600 to 1,200 mosm.

GFR (ml/min)	GFR (L/day)	Distal Delivery % of GFR	Distal Delivery (L/day)	Osmolar Excretion (mosm)	Minimum U_{osm} (mosm /kg H_2O)	Maximum Urine Volume (L/day)	Maximum Solute-Free H_2O (L/day)
60	86.4	30	25.9	600–1200	60	10–20	8–16
50	72.0	30	21.6	600–1200	60	10–20	8–16
40	57.6	30	17.3	600–1200	60	10–20	8–16
30	43.2	30	13.0	600–900	100	6–9	4–6
20	28.8	30	8.6	600–900	150	4–6	2–3
10	14.4	40	5.8	600	200	3	1
5	7.2	50	3.6	600	200	3	1

*See text for assumptions made to construct this table

and their unaffected relatives found no difference in the mean daily urine volumes (45).

The average daily excretion of individual solutes appears to be similar in ADPKD patients and healthy controls. The range of U_{osm} (344 to 648 mosm/kg H_2O) over the full 24-h period was greater than that of plasma in ADPKD, although slightly lower than that observed in healthy controls (Table 2). Considered together, these data indicate that ADPKD patients with GFRs in the normal range conserve water, but perhaps less effectively than healthy individuals of the same age.

Urine Concentrating and Diluting Capacities in ADPKD

Impaired urinary-concentrating capacity was identified as a common feature in early descriptions of ADPKD, even in patients with normal GFR (45,48–52) Sixty-three of 71 patients (48) were unable to concentrate the urine to a specific gravity ≥ 1.022 during a concentration test (normal range, 1.002 to 1.030). Eleven of 13 patients (50) with a mean GFR of 103 ml/min/1.73 m^2 failed to concentrate the urine to >700 mosm/kg H_2O after 24 h of dehydration and AVP administration. In the largest study to date, 87 ADPKD patients with a mean creatinine clearance of 102 ml/min/1.73 m^2 had a mean U_{osm} of 680 ± 14 mosm/kg H_2O after overnight dehydration and AVP administration, as compared with 812 ± 13 mosm/kg H_2O in 106 nonaffected relatives (45). In this cohort, there was an inverse correlation between maximal U_{osm} and renal volume. The inability to concentrate the urine maximally occurs early, as it can be detected in children with ADPKD (53–55).

The cause of the AVP-resistant concentrating defect in some patients is not known. Increased plasma AVP levels suggest a relative renal resistance to the effects of AVP (18,19). Although a few patients may have AVP-resistant hyposthenuria (50,43), in most cases U_{osm} after dehydration and AVP administration is higher than P_{osm}. Decreased generation of cAMP or reduced expression of CD genes associated with urinary concentration do not explain the concentrating defect, as they are increased in animal models of PKD (2–4,13). It is interesting to note that *Pkd1*$^{+/-}$ mice have few renal cysts and the urine-concentrating capacity is not reduced, or is even slightly increased (56), making it unlikely that the gene mutation, represented in every renal cell and responsible for the most common type of ADPKD, is the proximate cause of the concentrating defect.

In contrast, a cellular defect associated with the cystic phenotype cannot be entirely ruled out. Overexpression of concentration-associated genes in CDs accompanies the development of polyuria and precedes the development of cysts in the *cpk* mouse, a model of rapidly progressive PKD (2). Polyuria precedes the dilation of the CDs in models of PKD induced by diphenylamine or diphenylthiazole (57,58). Impaired renal concentrating capacity is an early manifestation of other renal ciliopathies where macroscopic cysts are less prominent than in ADPKD (*e.g.*, autosomal recessive PKD, nephronophthisis, and Bardet-Biedl syndrome). In some studies, AQP2 is found throughout the principal cells in cystic CDs, whereas it is mainly restricted to the apical portion of normal CDs, suggesting an abnormal trafficking or recycling of AQP2 in PKD (2,59). In the final analysis, metabolic disturbances within CD cells paired with cystic distortion of the countercurrent mechanism, probably underlie the urine-concentrating defect.

In contrast to the interest in urinary concentration in ADPKD, few studies have examined renal diluting capacity. Martinez-Maldonado *et al.* administered a water load of 20 ml/kg body weight, followed by replacement of urine and insensible water losses, to two groups of ADPKD patients with GFRs 60 to 165 ml/min and 5 to 10 ml/min, respectively, and to a group of unaffected family members (50). The ingested water uniformly lowered U_{osm} to <100 mosm/kg H_2O. When the urine flow and U_{osm} stabilized, 0.45% saline was infused at increasing rates from 4 to 16 ml/min to enhance distal delivery of sodium and to ascertain the functional integrity of the TAL. In the healthy controls and in the ADPKD patients with normal renal function, the relationship between urine volume (3% to 18% of GFR) and solute-free water clearance (1% to 12% of GFR) as a percentage of GFR was linear, without evidence of a limit. In the ADPKD patients with advanced renal insufficiency, there was a similar relationship as urine volume increased from 28% to 50% of GFR and solute-free water clearance increased from 8% to 25% of GFR. Other studies also found that urine-diluting mechanisms are intact in ADPKD, at least in patients with normal renal function (49,60).

Factors that potentially limit water intake in ADPKD

The marketing of increased water intake as a health benefit has awakened nephrologists to the potential adverse effects of too much water (61). Although normal kidneys have the capacity to generate and excrete many liters of free water, there are situations (when delivery of solutes to the diluting segments of the nephron is inadequate or when the release or effect of AVP is inappropriately enhanced) in which patients may drink more free water than the kidneys can excrete (38,62). The importance of solute intake on the formation of dilute urine and the excretion of solute-free water was recently re-examined (38). The total excretion of solutes (electrolytes and urea) sets the ceiling as to how much free water can be excreted. Adequate dietary sodium chloride is necessary for the generation of free water in the cortical TAL. Salt depletion as a result of stringent diets, gastrointestinal disorders, or overuse of diuretics renders individuals who drink moderately increased amounts of water more susceptible to hyponatremia. Loop of Henle diuretics and thiazides reduce renal diluting capacity by inhibiting the reabsorption of sodium chloride without water in the water-impermeable TAL and distal convoluted tubule, respectively.

In ADPKD, hypertension is treated with moderate salt restriction and, less often, with diuretics (63). Limitation of dietary protein intake to less than 1.0 g/kg is frequently recommended as well. Such interventions do not reduce the capacity to excrete solute-free water to a dangerous level. However, patients who follow diets severely restricted in salt and protein or who use large doses of diuretics will be at risk for the development of hyponatremia if water intake exceeds the reduced diluting capacity.

Plasma AVP levels may be increased in ADPKD patients, possibly as a result of the decrease in urine-concentrating capacity, although disturbances in P_{osm} are not a feature of the

disease. AVP levels can be appropriately suppressed when free water intake is increased since ADPKD patients with normal GFR excrete solute-free water without difficulty. Nonetheless, a variety of drugs can inappropriately stimulate the release of AVP or potentiate its action. Some of them, for example, serotonin reuptake inhibitors and tricyclic antidepressants, (64,65) are commonly used by ADPKD patients. The excretion of water may also be impaired when arterial underfilling, caused by extracellular fluid volume contraction, low-output cardiac failure, or peripheral vasodilatation eliminates the tonic inhibition of baroreceptors and causes AVP release.

Concerns About Increased Urine Flow

In the Modification of Diet in Renal Disease study, a *post hoc* analysis of ADPKD subjects with GFR values less than 55 ml/min/1.73 m^2 found that high daily urine volumes were associated with increased rates of GFR decline (66). This finding in the late stage of ADPKD was interpreted to indicate that increased urine flow rate had a deleterious effect on disease progression. However, we submit that given the data in hand, it is impossible to adduce whether the high urine flow rate was a cause or a consequence of the decline in GFR or whether another independent factor influenced the two variables simultaneously. The association between high urine volume and GFR decline is not unexpected, as defective urine concentrating-capacity is a manifestation of CKD (see above).

The Modification of Diet in Renal Disease investigators supposed that these patients were "pushing fluids" because the serum sodium concentrations tended to be reduced. However, a large fraction of the patients in that study used diuretics, which not only could modify urine volumes (thus inducing a bias in the studied variable), but also are known to increase AVP secretion (67,68) and by this mechanism possibly contribute to CKD progression. The conclusion that high urine flow rates promote more rapid renal failure is not in agreement with studies in which large volumes of solute-free water ingested for several weeks by rats and mice ameliorated hereditary cystic (14) and other types of renal disease (69–73). In the ongoing prospective CRISP study of ADPKD subjects over a 3-yr period (referenced in Table 2), urine flow rates were relatively high, and in a preliminary analysis, there was no correlation between structural or functional progression and urine flow rate (47,74).

Renal transplantation has shown that one kidney can process the solute and fluid loads usually handled by two kidneys without developing structural or functional defects in the renal pelvis or ureter. Although severe polyuria associated with central and nephrogenic diabetes insipidus, or less often with psychogenic polydipsia, can result in urinary bladder distension, intramural obstruction of the distal ureters, ureteral dilation, and hydronephrosis, (75) this is unlikely to occur with moderate degrees of polyuria. The advice to increase fluid intake by 1.5 L given to 55- to 75-yr-old men with moderate low urinary tract symptoms had no negative effects in a randomized trial (76). ADPKD patients, therefore, should be able to increase daily urine volume to 4 L/d (approximately 1.5 L over the average urine output of an adult with ADPKD) without causing urologic problems as long as they remember to void more frequently than usual and avoid drugs that interfere with bladder contractility.

Which ADPKD Patients Can Safely Increase Water Intake and How Much Extra Water Is Reasonable?

Increased water intake should be recommended only to those ADPKD patients who can safely excrete the load (Table 4). The capacity to generate and excrete solute-free water is intact in patients with ADPKD and normal or moderately reduced GFR. Those with a GFR $>$ 60 ml/min (CKD 1 or 2), who follow a diet not severely restricted in protein ($>$0.6 g/kg ideal body weight/d) or sodium ($>$60 mEq/d), are not edematous or volume contracted, do not take medications that interfere with the reabsorption of sodium chloride in diluting segments of the nephron (*e.g.*, loop diuretics or thiazides) or enhance the release or effect of AVP (*e.g.*, serotonin reuptake inhibitors, tricyclic antidepressants), and have normal voiding mechanics can handle moderate increases in urine volume ($\leq$4 L daily) without untoward effect. Measuring the osmolar excretion over a 24-h period can help to estimate how much water to drink to lower the average U_{osm} to 250 mosm/kg H_2O. It would be wise to measure the plasma sodium concentration after several days to exclude hyponatremia.

The administration of this amount of fluid is probably safe in patients with a GFR between 30 and 60 ml/min (CKD 3), but it would be reasonable to monitor the plasma sodium concentration after increased water intake is prescribed. More frequent monitoring of plasma sodium is also sensible in patients using certain water-retaining medications. Water intake beyond that needed to quench thirst is not recommended for patients with more advanced CKD.

The goal of increasing the water intake is to reduce the effect of AVP on the distal nephron and CD cysts as continuously as possible. The additional water should be free of caffeine (77) and sugar (78) and contain vanishingly low amounts of dichloroacetate (79) and fluoride (80). A reasonable goal is to drink fluids as evenly as possible throughout waking hours and immediately before going to bed. More than likely patients will experience nocturia at least once, and water should be drunk after voiding. However, individuals who do not tolerate interruptions in sleep should omit water drinking immediately before bedtime and during the night.

An amount of water sufficient to maintain an average 24-h U_{osm} of 250 mosm/kg H_2O is a reasonable goal. The total fluid intake to reach this goal will depend on the usual daily mean osmolar excretion of the individual patient. For example, assuming a daily osmolar excretion of 750 or 1000 mosm, 3 or 4 L of urine, respectively, would yield a mean osmolality of 250 mosm/kg H_2O (specific gravity approximately 1008). The use of dipsticks for measuring specific gravity may help patients reach this goal (81). If the daily fluid intake was evenly spaced, the mean plasma AVP level would decrease proportionately with the mean U_{osm}. Urinary bladders should be emptied frequently throughout the day. Patients who are unable to maintain high water intakes would be advised to increase fluid intake to whatever degree they can achieve, as any sustained decrease in plasma AVP would help mitigate cyst enlargement.

Table 4. Recommendations for intake of water in patients with ADPKD

	GFR $\geq$ 60 ml/min/1.73 m^2	60 > GFR > 30 ml/min/1.73 m^2	GFR $\leq$ 30 ml/min/1.73 m^2
Recommendation	Enough to achieve an average U_{osm} of 250 mosm/kg H_2O, usually 2.5–4 L per day	Enough to achieve an average U_{osm} of 250 mosm/kg H_2O, usually 2.5–4 L per day	Not recommended, follow thirst
Risk	Minimal	Low	NA
Benefit	Likely reduction in the rate of cyst growth by suppressing the secretion of AVP and its effect on tubular cell proliferation and fluid secretion	Likely reduction in the rate of cyst growth by suppressing the secretion of AVP and its effect on tubular cell proliferation and fluid secretion	NA
Follow-Up	Recheck serum sodium within 1–3 wk after increasing water intake, more frequently in patients on drugs which may enhance AVP secretion or effect	Recheck serum sodium within 1–3 wk after increasing water intake and regularly thereafter	NA
Exclusions	Severe protein or sodium restriction, volume contraction or reduced effective intravascular volume, diuretics or drugs enhancing the release or effect of AVP, abnormal voiding mechanisms	Severe protein or sodium restriction, volume contraction or reduced effective intravascular volume, diuretics or drugs enhancing the release or effect of AVP, abnormal voiding mechanisms	NA

NA, not applicable.

These recommendations are based on a wealth of preclinical data rather than the results of a prospective, randomized clinical trial, and some will question this advice in the light of the current emphasis on evidence-based medicine. Moreover, we can not be certain that reducing plasma AVP levels will mitigate disease progression in human patients. Financial support for a trial of increased hydration in ADPKD seems unlikely, because present regulations make a trial mandatory for a drug such as tolvaptan, but not for water, a natural product consumed in variable amounts. The results of the TEMPO trial are not likely to prove or disprove the value of increased water intake because tolvaptan and increased water intake are not equivalent, even if they both reduce cAMP in the CDs. Tolvaptan tends to increase P_{osm} and AVP, whereas increased water intake tends to decrease P_{osm} and AVP (and thus V1a effects). Lacking a clinical trial to directly assess the value of increased hydration, recommendations for water intake have to rest on a critical analysis of potential benefits (reduction in the rate of disease progression) and risks (hyponatremia if solute intake or GFR is too low or if drugs limiting the ability to dilute the urine are administered, negative effects of chronically increased urine volume on urinary tract or kidney function, unforeseen psychologic disturbances from polyuria or nocturia). The increase in water intake needed to reach the target indicated in this review is moderate, and physicians who recommend such an increase will need to monitor their patients at reasonable intervals.

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Disclosures

None.

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