The commonly accepted manifestations of renal insufficiency are usually not recognized in patients with autosomal dominant polycystic kidney disease (ADPKD) until the fourth decade of life (1). However, many ADPKD patients with GFRs indistinguishable from normal are unable to increase the osmolality of urine above 800 mosm/kg H$_2$O after overnight dehydration or after the parenteral administration of supplementary vasopressin. This “concentrating defect” can be detected in some young children and young adults decades before the GFR noticeably declines, indicating that parenchymal malfunction begins very early in the course of renal cystic disease (2). In an excellent study reported in this issue of CJASN, Zittema et al. (3) confirm that maximal urine concentration capacity is lost in ADPKD patients compared with normal controls. Still at issue is the mechanism(s) by which ADPKD impairs the maximal concentration of the urine.

The baseline urine volumes, osmotic excretion rates, and plasma arginine vasopressin (AVP) and copeptin concentrations were not appreciably different between ADPKD patients and controls in this study; however, after overnight dehydration, the plasma levels of AVP and copeptin were significantly and persistently higher in the ADPKD subjects, and the urine osmolarity was persistently lower than in the controls. The authors found evidence of an intact hypothalamic mechanism for the osmotic release of vasopressin, meaning that the defect must lie in the kidneys. Interestingly, ADPKD patients had higher plasma and lower urine concentrations of urea after achieving the highest elevation of urine osmolarity, suggesting that urea clearance was decreased in the ADPKD patients even though eGFR was not different between study patients and control subjects. The urea excretion rate after dehydration was not reported; however, the similar baseline osmolar excretion rates make it unlikely that the urea excretion rates in the ADPKD patients were different from normal.

The plasma urea levels were elevated in the ADPKD patients, possibly reflecting a decreased renal urea clearance. Because plasma sodium levels were equal in patients and control subjects, the increased urea concentration probably accounts for the consistent elevation of plasma osmolality in ADPKD patients compared with control subjects. Because urea distributes relatively freely in body water, it is unlikely that the small increase in plasma osmolality caused by increased urea concentration was responsible for the increased plasma concentrations of AVP and copeptin in the ADPKD patients. On the other hand, the restriction of water intake unquestionably increased plasma levels of vasopressin and copeptin and the reabsorption of free water in the patients, although to a lesser degree than in control subjects. A nonosmotic vasopressin releasing mechanism, e.g., extracellular fluid volume contraction, is a reasonable possibility and, in this regard, careful measurements of changes in body weight and urine volume before and after water restriction would probably have confirmed that body water content had decreased overnight.

The 24-hour urine volume did not differ between ADPKD and normal subjects in the baseline collection, indicating that overall water balance of the patients was appropriately regulated despite the inability to maximally concentrate the urine to normal maximal levels. In other words, the ADPKD subjects did not manifest any outward signs of a urine concentration defect. The baseline osmolar loads excreted by ADPKD (1096 mosm/d) and normal (1039 mosm/kg H$_2$O) subjects were also similar and typical of most individuals at large (4). Consequently, polyuria and polydipsia would not be expected in these ADPKD subjects with excellent estimated GFR (eGFR) unless the solute load was increased by dietary excesses of salt and protein. Interesting in this regard, in much larger cohorts of patients, daily solute loads tended to be higher and urine volumes greater owing to increased dietary intake of protein and salt (5,6).

The cause of the limited concentrating capacity of the “early”-stage polycystic kidneys reported in this study appears to reside within the kidneys and, more specifically, within the medulla. There, the prime candidates to account for the reduction in maximal Uosm are (1) a decreased responsiveness of the collecting ducts to vasopressin and (2) the failure to generate and maintain a hyperosmotic interstitial milieu. A decreased expression of AVP-V2 receptors has been reported at the end stage of the 5/6 nephrectomy model of ESRD in rats (7); consequently, renal insufficiency from any cause could underlie reduced collecting duct responses to AVP. Contrary to that possibility, however, is the finding that AVP-V2 receptor RNA was increased in the kidneys of a murine Pkd2 model, and aquaporin 2 RNA was elevated and the protein expressed in the apical plasma membranes of mice with Pkd1 (8). It seems
unlikely, therefore, that responsiveness to AVP limits the equilibration of water between the tubule fluid and the interstitium; alternatively, a faulty medullary hyperosmolarity gradient would seem to be a more likely cause of the diminished concentrating capacity. Urea is a major contributor to the hyperosmotic renal interstitium and, after overnight dehydration, the urinary concentration of this solute was reduced by an amount nearly equal to the urinary osmolality difference between the patients and the normal controls. Because the osmolar loads at baseline were nearly equal, it is unlikely that protein depletion and a reduced urea load accounted for the low urinary urea levels in the cystic patients. The low urine and elevated plasma urea levels are consistent with an impairment in urea clearance, supporting the suggestion that some of the urine concentrating defect demonstrated in the current study is probably caused by the failure to generate a maximally hyperosmotic medullary interstitium.

Physical disruption of the renal parenchyma by cysts has commonly been advanced as an explanation for the renal insufficiency that eventually develops in most patients. Gabow et al. (2) observed an inverse relationship between renal volume and the capacity to concentrate the urine; similar observations have been made in children with ADPKD (9). The potential for cysts that develop in medullary collecting ducts to affect the function of hundreds of upstream nephrons has recently been advanced as an overlooked mechanism for causing kidneys to fail in ADPKD (10). As functioning nephrons are lost in the course of progressive nephropathies, the solutes and fluid acquired in the diet must be excreted by the surviving functional units. This increased filtered load per residual nephron can probably be handled for a while by glomerular hyperfiltration and tubule hypertrophy, but, as more nephrons are lost, a point may eventually be reached when the increased amount of solute-rich urine leaving cortical tubules overwhelms the reabsorptive capacity of the loop of Henle, leading to a washout of the interstitial papilla to cortex osmolality gradient. Near the end stage of renal disease, plasma vasopressin concentrations rise to high levels, yet even AVP-V2–responsive collecting duct segments cannot elevate urine osmolality above that of the interstitium. Consequently, urine at the end stage becomes isohygric.

Zittema et al. suggest that the “early” loss of maximal concentrating capacity in young patients with apparently normal eGFR levels indicates that significant underlying renal injury is extant. I would only disagree with the definition of what “early” or “mild” may imply in this context. The conventional definition of “mild” or “early,” based on Kidney Disease Outcomes Quality Initiative criteria, would include an eGFR as low as 60 ml/min per 1.73 m² (www.kidney.org/professionals/kdoqi/pdf/ckd_evaluation_classification_stratification).

Evidence is building to indicate that ADPKD patients experience renal insufficiency long before a change in iothalomate clearance or eGFR can be reliably detected (10,11). Hypertension is detected in some children before significant increases in renal volume can be reliably measured (12,13), consistent with the view that injury may be caused by innumerable renal cysts too small to be detected by ultrasound, computed tomography, and magnetic resonance (13). Renal blood flow is decreased and renal vascular resistance is increased in ADPKD before changes in GFR can be detected (1,11,14). Moreover, the hyperfiltration documented early in the course of ADPKD (15) suggests that radical readjustments in renal hemodynamics may occur as the cysts disturb the delicate anatomy of the cortex and, especially, the medulla. In this light, it is not unreasonable to suppose that renal insufficiency, broadly defined, may occur very early in the course of the disease and that hypertension, hyperfiltration, and impaired maximal urine concentration are the tangible manifestations of cyst mayhem.

The human kidney has a remarkable capacity to compensate for the loss of functioning nephrons, so remarkable in fact that we use donor kidneys from normal individuals to preserve the lives of many with ESRD. Within 1 year of nephrectomy, a normal donor can expect to have a GFR only ~10 ml/min per 1.73 m² less than what the two original kidneys would have produced (16). It is time we acknowledge that living renal donors, by definition, have “renal insufficiency,” except the insufficiency is effectively camouflaged by glomerular hyperfiltration and tubule hypertrophy, which hide the nephron debt left by a surgeon. Interestingly, human renal donors with otherwise excellent numerical GFR values exhibit a “mild” defect in maximal urine concentration, as do uninephrectomized animals (17,18). Perhaps the most elegant model illustrating the long-term consequences of a solitary kidney is a study of uninephrectomized fetal sheep that were studied 6 months and 4 years after birth (19). Uninephrectomized animals had lower maximal urine osmolalities than normal animals after 30 hours of dehydration and supplementary infusion of AVP. Plasma AVP levels rose equally in nephrectomized and sham animals after dehydration, leading the authors to conclude that uninephrectomy leads to a decreased concentrating capacity. Unlike the surgical removal of a kidney, in disorders such as ADPKD, nephrons are removed piecemeal for years on end. The residual functioning nephrons are signaled to do increasing amounts of renal work until they, too, are driven out by the cysts, causing the GFR to fall sharply.

In summary, the study of Zittema et al. helps in the understanding of the basis of the diminished capacity to concentrate the urine in ADPKD, but perhaps even more important, it awakens us to the high probability that renal insufficiency, redefined as the loss of functioning nephrons sufficient to promote compensatory adjustments, begins much earlier in ADPKD patients than we might have ever imagined.

Disclosures
J.J.G. serves as a consultant to Otsuka Corp.

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