Size Matters in Renal Allograft Survival

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The clinical importance of nephron mass is a widely recognized determinant of renal fate and function. Those who are born with adequate numbers of nephrons get through life with less risk for cardiovascular and chronic kidney disease. Size also matters when it comes to selecting a donor for renal allograft transplantation. In their interesting and provocative article in this issue of JASN, Giral et al.2 describe a new clinical marker of allograft success: The ratio of the weight of the renal allograft before implantation to the recipient weight, or Kw/Rw.

Recipients of a kidney with a Kw/Rw of <2.3 g/kg had worse long-term graft survival, worse long-term graft function as measured by the GFR, more proteinuria, more hypertension, and more glomerulosclerosis than recipients of a kidney with a Kw/Rw of >2.3 g/kg. These investigators describe this risk for deterioration in graft function as occurring late, beyond 7 years after transplantation. They based their observations on an analysis of more than 1000 adult patients, virtually all deceased-donor kidney recipients. Not surprising, more female donors and male recipients were associated with lower ratios. The occurrence of acute rejection also had a more detrimental effect in patients with a low Kw/Rw.

These observations represent a new and elegant way of quantifying the potentially negative effect of nephron underdosing and make the additional point that this effect takes a longer time to appear after transplantation than we once thought. Most studies of outcomes after kidney transplantation suffer from the problem of insufficient follow-up, and, in fact, the authors’ previous publication on this subject showed no impact of Kw/Rw on 3-year outcomes.

There are some caveats to consider. Because living donors made up <1% of the case material, it is not clear that these observations hold true in anyone other than recipients of deceased-donor kidneys. Kidneys from very young pediatric donors might also be associated with different outcomes, particularly when transplanted en bloc.3 No data in this article address these issues.

One may also speculate whether the current observation would hold true for recipients who were not receiving long-term calcineurin inhibitors. If calcineurin inhibitor–sparing or other avoidance regimens are used in an increasing percentage of patients, it will be interesting to see whether these observations on weight ratios remain relevant. Finally, it will be important to replicate these provocative observations of Giral et al.2 in other large cohorts of patients with sufficiently long follow-up. In the meantime, the authors are to be congratulated for describing a novel measure that may have important implications for long-term outcomes in renal allograft recipients.

DISCLOSURES

None.

REFERENCES


See related article, “Kidneys from Donors after Cardiac Death Provide Survival Benefit,” on pages 1015–1021.


Randomized Intervention Studies in Human Polycystic Kidney and Liver Disease

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Autosomal dominant polycystic disease (ADPKD) is the most common life-threatening genetic disease in the United States. ADPKD is more common than Huntington disease, hemophilia, cystic fibrosis, sickle cell disease, Down syndrome, and myotonic dystrophy combined.1 The increase in kidney cyst volume over time correlates with hypertension and progressive renal dysfunction, yet, to date, there is no established intervention to slow or prevent the renal cyst growth. Increased proliferation accompanies renal cyst growth, and recent research in nonorthologous experimental animals and patients with ADPKD suggests aberrant activation of the Ser/Thr kinase mammalian target of rapamycin (mTOR), which modulates cell growth and proliferation.2–5 Recently, rapamycin was shown to have dramatic effects on liver cyst volumes in humans6 and in an orthologous rodent model with conditional inactivation of the PKD1 gene.7 The results demonstrate that mTOR inhibition with rapamycin decreases cyst growth, fibrosis, and proliferation and improves renal function. Of interest, there was regression of cyst burden, which may have been due to increased apoptosis among the cystic epithelium.

Perico et al.8 in this issue of JASN performed a renal safety and efficacy study to examine further this potential pathogenetic ADPKD pathway in humans. This randomized crossover study examined the effect of sirolimus (rapamycin) over 6 months on progression of ADPKD compared with conventional therapy. The main efficacy variable was the effect on total kidney volume, but renal cyst and parenchymal volumes were also measured. The effect of sirolimus on GFR was also examined relative to kidney volume and structure changes. The kidney volumes were measured by spiral computerized tomography and GFR by the iothexol plasma clearance techniques. There were no differences in the increase in total renal volume or change in GFR between sirolimus and conventional treatment; however, the absolute cyst volume was virtually stable in the sirolimus arm, whereas it increased with conventional treatment (mean 4.5 versus 54.9 ml; P < 0.06). When relative cyst volume changes were compared, the increase in cyst volume with sirolimus was significantly less than with conventional therapy (P = 0.02). The most impressive change was that parenchymal volume actually increased significantly with sirolimus and was stable with conventional therapy (mean 26.0 versus −2.7 ml; P < 0.009). One potential explanation for this latter finding, suggested by the authors, was that less cystic compression of renal parenchyma and vasculature with sirolimus treatment led to increased parenchymal volume.

There are several caveats regarding this 6-month study. There was a 28% dropout rate (six of 21), and the statistical analysis was not by intention-to-treat. Ten of the remaining 15 patients developed aphthous stomatitis. In this 6-month study, sirolimus treatment was associated with statistically significant increases in liver enzymes (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase) and lipids (total cholesterol, LDL cholesterol, and triglycerides), a decrease in hematocrit, and an increase in urinary albumin/protein excretion, none of which was observed with conventional therapy. This is potentially bothersome regarding possible lifelong therapy for ADPKD. Thus, results of larger and longer follow-up studies of mTOR inhibitors in patients with ADPKD will be very important.

In this issue of JASN, another interventional study examined the effects of a somatostatin analogue in patients with polycystic liver and kidney diseases.8 There is considerable evidence for a role of cAMP in epithelial proliferation and fluid secretion in experimental renal and hepatic cystic disease. In that regard, somatostatin blunts hepatic cyst expansion by blocking secretin-induced cAMP generation and fluid secretion by cholangiocytes.10 Hogan et al.9 performed a 1-year randomized, blinded study to examine whether octreotide, a long-acting somatostatin, would decrease liver volume compared with placebo in 42 patients with severe polycystic liver disease (34 with ADPKD and eight with autosomal dominant polycystic liver disease). By magnetic resonance imaging, the mean liver volume decreased from 5907 to 5557 ml (4.95 ± 7.00%) in the octreotide group (n = 28) compared with 5374 to 5361 ml (0.92 ± 7.00%) in the placebo group (n = 14). This differ-