allows AQP2 to contribute to cell motility and epithelial morphogenesis and may allow AQP2 to play an important role in the development and maintenance of tubular structure. These findings may also explain why AQP2-null mice have abnormal tubule development and neonatal mortality, in contrast to other AQP-null mice. The piecing together of the uniquely abnormal phenotype of AQP2-null mice and the integrin binding site, and then demonstrating the functional consequences of the AQP2–β1 integrin interaction, provides a significant advance in our understanding of AQP2 biology and suggests a previously unrecognized role for AQP2 in tubule development.

Although AQP2-null mice demonstrate neonatal mortality, there are humans with AQP2 mutations who do survive to adulthood. At first glance, this may suggest that the abnormalities in the AQP2-null mice do not occur in people. However, there is an important difference between AQP2-null mice and humans with AQP2 mutations: the mice completely lack AQP2, whereas the humans have a mutated form of AQP2 that does not transport water. Because the RGD motif that binds β1 integrin is located in the second extracellular loop of AQP2, one wonders whether the mutant AQP2 proteins present in humans maintain this newly identified role of AQP2 in regulating epithelial cell migration through interaction with β1 integrin, even if they cannot transport water? It would be interesting to test whether known disease-causing AQP2 mutations interact with β1 integrin and maintain a promigratory effect on epithelial cell mobility.

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DISCLOSURES

None.

REFERENCES


See related article, “Aquaporin 2 Promotes Cell Migration and Epithelial Morphogenesis,” on pages 1506–1517.

Lifetime Risk of ESRD: A Meaningful Concept?

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Turin and colleagues present some fascinating estimates of both the lifetime and short-term risks of ESRD in this issue of JASN, exploiting the excellent epidemiologic database in Alberta, Canada. Based on a total population of nearly 2.9 million persons with nearly 26 million person-years of follow-up, they have been able to calculate actual lifetime event rates of ESRD (2.6% and 1.8% for men and women, respectively) rather than the synthetic estimates based on observed incidence rates applied to hypothetical populations. The advantage of this approach is not so much in increased accuracy of the estimate as in the ability to array the predictions.
by starting levels of kidney function. For example, for men 40 years of age, an estimated GFR (eGFR) of 45–59 ml/min per 1.73 m² increases the lifetime risk of ESRD by almost 7-fold over men with an initial eGFR of 60–89 ml/min per 1.73 m². The other useful addition of initial eGFR is the relative effect of moderately impaired renal function by age. For example, for young men with a starting eGFR of 45–59 ml/min per 1.73 m², the short- and long-term probability of progressing to ESRD is substantial (3.4% at 10 years and 8.6% lifetime risk). However, for men who have attained the age of 70, an eGFR of 45–59 ml/min per 1.73 m² confers less than one-third the short- and long-term risk.¹

This should be exceedingly useful in counseling patients. Moderately decreased kidney function should not be cause for panic in elderly patients. However, a similar level of kidney function in young patients needs to be taken very seriously. One hopes the authors will continue to expand their analyses to include other risk variables such as diabetes, presence of albuminuria, BP levels, and other clinical indicators.

In this study, the authors use the well-accepted definition of ESRD as the initiation of renal replacement therapy, either dialysis or transplantation. In both the United States and Canada, the rates of treated renal failure have stabilized in the last decade. However, the rate of treated renal failure in the United States is well over twice as large as in Canada (371 and 159 per million, respectively).²,³ Even among Caucasians, the rate of treatment in the United States is nearly twice that of Canada. Thus, the estimates of lifetime risk of ESRD generated by Kiberd and Clase⁴ based on the United States are still probably more relevant to the United States renal community, particularly in light of the nearly 3-fold greater incidence of ESRD among African Americans and the 50% increased risk of ESRD in Hispanic Americans.

As the authors note, this is a treatment-defined event and will be subject to changes in practice patterns over time, as well as differences in acceptance criteria between countries or geographic areas. The authors themselves use a different definition of ESRD in their recent JAMA article on treatment rates for ESRD, in which case they use eGFR of ≤15 ml/min per 1.73 m² to define ESRD.⁵ Based on the eGFR criteria, about one-half of the persons in Canada who arrive at ESRD actually receive renal replacement therapy. This varies greatly by age, from almost 90% of persons <45 years of age to about 7% of persons >75 years of age. Untreated ESRD in the elderly is the subject of considerable debate within the renal community,⁶,⁷ and will not be addressed here except to note that "treated ESRD" is a somewhat slippery concept and will inevitably affect both short- and long-term risk estimates.

Is lifetime risk a valuable tool for risk estimation or for patient counseling? The advantage of such estimations is to illustrate the fact that even rare events such as ESRD, which we typically express as number of cases per million population, add up over a lifetime. The downside of such estimates is that they can lead to unnecessary worry.⁸ Although ESRD does not carry the same fear factor as does cancer, a lifetime sentence to a thrice weekly dialysis regimen can be a scary thing. It sounds somewhat remote to say that one's risk of ESRD is 160 in 1,000,000 in the next year. That sounds like a long shot lottery. No chance it is going to happen. However, a 2%–3% chance of ESRD is definitely within the realm of possibility. That almost sounds like a real thing. Others have noted the difficulty in interpreting lifetime estimates of disease incidence for patients and have recommended the short-term age conditional estimates of a 10– or even 20-year time horizon.⁹

The problem with lifetime risk is its relevance to the average person. Everyone has a 100% lifetime risk of dying of something. The public health advances of the early and mid-20th century largely eliminated infectious diseases as primary causes of mortality. This in turn led to remarkable increases in life expectancy. Now, people live long enough to die of something else, primarily cancer and cardiovascular diseases. This is evidenced by the very high lifetime risks associated with cancer (45% and 38% for men and women, respectively),¹⁰ coronary disease (49% and 31% for men and women, respectively),¹¹ and diabetes (33% and 39% for men and women, respectively).¹² Basically, if you live long enough, one of the major chronic diseases is going to get you. We can now add ESRD to that list of inevitable end-of-life problems.

Lifetime risk also does not quite necessarily parallel short-term risk. For example, although African Americans have higher rates of invasive incident cancer, their lifetime risk is actually lower than that of Caucasians, because of their lower life expectancy.¹³ This is further evidence that the shorter-term estimates are of more clinical value to clinicians and patients.

In the United States, it has been estimated that >20 million persons have CKD, which is >10% of the adult population.¹⁴ The vast majority of these persons will not progress to ESRD, either in terms of a treatment-defined or an eGFR-defined end point. Studies such as that presented by Turin et al. need to be expanded to include additional risk factors to help quantify the most important predictors of CKD progression so that scarce health resources can be directed where they will do the most good.

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DISCLOSURES

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REFERENCES

Randomized Trial of Pre-Emptive or Prophylactic Valganciclovir Therapy for Prevention of Cytomegalovirus Infection in Renal Transplantation

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In this issue of JASN, Reischig et al.'s 1 report important information on a randomized trial of pre-emptive or prophylactic valganciclovir therapy in renal transplant recipients. It is the follow-up of a prospective trial of 70 initial patients transplanted between October 2003 and August 2006 who were randomized to receive either preemptive valganciclovir (VGC; n = 36), 900 mg twice daily for 2–3 weeks, on detection of significant cytomegalovirus (CMV) viremia (>2000 copies per milliliter of blood) or prophylactic valacyclovir (VACV; n = 34), 2 g four times daily for 3 months, adjusted for renal function as necessary.2 The study used an intention-to-treat analysis. This is important because 32% of the patients needed a dose reduction or discontinuation of VACV because of hallucinations, other neurologic difficulties, and cytopenias. Another important finding in the initial study was that patients in the VACV prophylaxis arm experienced significantly less early acute rejection by 1 year (16% versus 36%) and less subclinical rejection (6% versus 11%).

The lower incidence of acute rejection in the VACV prophylaxis-treated group was surprising, but confirmed the authors' previous work comparing VACV to oral ganciclovir (OGCV) prophylaxis and deferred therapy in which they found acute rejection rates by 1 year of 12%, 34%, and 58%, respectively.3 The lower rejection rate partially confirmed the work of others showing that VACV was associated with less acute rejection in the CMV donor seropositive/recipient seronegative group (CMV D+/R−), but not when the recipient was CMV seropositive (R+).4 The relationship with CMV and rejection is complex. Others have previously shown that symptomless CMV may appear histologically as acute rejection that responds to intravenous ganciclovir rather than increased immunosuppression in patients with late acute rejection occurring 2–7 years after transplant.3 Important differences between these studies, however, are that in the present study there were only two patients in the preemptive group with CMV disease after 1 year and only three patients in the prophylactic group with CMV disease. Furthermore, there was only one patient in the prophylactic group with an acute rejection episode after 1 year in the present study.1

At first glance, these remarkable findings suggest that VACV may be one of the best immunosuppressants introduced in the last two decades. Alternatively, control of CMV, especially early, by whatever means, may lessen the rate of acute rejection. The present paper provides a nuance to what it means to control CMV.

In this follow-up study, 55 patients were available to undergo protocol biopsies at 3 years, but only 49 actually underwent biopsies and had enough tissue for mRNA analyses.1 At 3 years, the intrarenal allograft biopsies showed that the incidence of moderate to severe interstitial fibrosis and tubular atrophy (IFTA) was 38% in the VACV prophylaxis arm and 19% in the VGCV pre-emptive group (odds ratio, 2.50; 95% confidence interval [CI], 0.74–8.43; P = 0.222), and IFTA with inflammation was seen in 42% and 19% (P = 0.082), respectively. These were not statistically significant because the sample size was small, particularly because of graft loss in the VACV arm (two deaths and seven graft failures, which may