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Opinion and Hypothesis Section

Moving closer to understanding the risks of living kidney donation

Steiner RW. Moving closer to understanding the risks of living kidney donation.

Abstract: Recent studies from the United States and Norway have suggested an unexpected 8- to 11-fold relative risk of ESRD after kidney donation, but a low long-term absolute risk. Abundant renal epidemiologic data predict that these studies have underestimated long-term risk. The 1% lifetime post-donation risk in the US study requires medical screening to predict ESRD in 96 of 100 candidates. This is particularly unlikely in the 30–35% of candidates under age 35, half of whose lifetime ESRD will occur after age 64. Many experts have attributed the increased relative risks in these studies to loss of GFR at donation, which ultimately means that high–normal pre-donation GFRs will reduce absolute post-donation risks. The 8- to 11-fold relative risks predict implausible risks of uninephrectomy in the general population, but lower estimates still result in very high risks for black donors. Young vs. older age, low vs. high–normal pre-donation GFRs, black race, and an increased relative risk of donation all predict highly variable individual risks, not a single "low" or "1%" risk as these studies suggest. A uniform, ethically defensible donor selection protocol would accept older donors with many minor medical abnormalities but protect from donation many currently acceptable younger, black, and/or low GFR candidates.

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Two recent studies have suggested an increased risk for end-stage renal disease (ESRD) attributable to living kidney donation. These findings concerned transplant specialists, who had good reason to believe that risk was not increased by donation (1–3). In US kidney donors (the "US study"), the incidence of ESRD over a median post-donation interval of 7.6 yr was compared to new-onset ESRD in well-matched, two-kidney controls (4). A second study (the "Norwegian study") performed a similar analysis in Norwegian donors over a median 15.1-yr post-donation interval (5). The US study found a post-donation incidence of ESRD that was about eight times that of controls, and the Norwegian study found an 11-fold relative risk of donation. The US study estimated a 1% post-donation lifetime risk of ESRD for kidney donors. The Norwegian study did not offer a lifetime risk. The authors of both studies advocated that we largely continue current donor selection practices, because the overall incidence of ESRD in their donors was very low. Editorial comment and a lively correspondence criticized the statistical methods and the control groups, which were defended by the authors (6–15). The profession and a wider press have largely endorsed their estimates of very low long-term absolute ESRD risk for kidney donors and accepted an increase in relative risk that these studies may or may not have precisely defined (6–25). At bottom, these important registry studies have determined ESRD rates in donors and controls over given intervals; they provide associations, not conclusions. Part of the interpretation of their data requires an awareness of the natural histories of the kidney diseases that these studies seek to capture. This perspective provides several insights into the strengths and limitations of these studies and the risks of living kidney donors.

During these studies, donors and controls will develop more kidney diseases than they will ESRD

Both studies tracked ESRD rates over finite study intervals in donors and well-matched healthy controls. But a large cohort of initially normal individuals will not bifurcate into those who quickly develop ESRD and others who remain entirely normal. A certain number of kidney diseases will begin at various intervals after donation, and they will progress at various rates (26–30). Abundant data confirm that ESRD will be "the thin edge of the wedge," accompanied by a larger array of new-onset renal risk factors and kidney diseases that will not reach ESRD during the study interval. The majority of proteinuric diseases, for example, do not lose GFR at more than a few mL/min/1.73 m^2/year (27, 30). In the general population, the low ratio of new-onset ESRD to the prevalence of moderate to severe kidney diseases illustrates this point. For individuals aged 30–64 who develop ESRD each year, there are about 5- to 6-fold more with a GFR <30 mL/min/1.73 m^2 and 10–15 fold more with a GFR <45 mL/min/1.73 m^2 (26).

The US and Norwegian studies do not capture the long-term post-donation risks of ESRD

The 1% lifetime risk for ESRD in kidney donors in the US study was substantially lower than the approximate 3% lifetime risk of unselected individuals in the general population. The "lifetime risk" of ESRD is formally defined as the chance of being diagnosed with ESRD during one's lifetime (31). It is the ratio of ESRD deaths to total deaths each year in the general population, with death usually occurring at some point after starting dialysis or after transplantation. It does not predict the age at which ESRD will be diagnosed or how long one will live afterward, although those data are known. For the general population, several independent studies have divided lifetime risk into about 2.5–3% for non-blacks and 7–8% for blacks (27, 28, 31). As kidney diseases progress, very low GFRs appear to increase mortality across diagnoses and racial groups (32–35). The high probability of dying at this stage makes lifetime risks of near ESRD (e.g., CKD stage 4) higher than those for ESRD. Patients with diabetes often have non-renal comorbidities that further increase pre-ESRD mortality (32, 33). Paradoxically, patients with lower mortality risks will have higher lifetime rates of ESRD because they more often will live to see it.

The US study did not attempt to calculate a lifetime risk of ESRD by following its donors and controls until they died. To attempt to capture ESRD that occurred after its 7.6-yr study period ended, it derived a composite absolute lifetime risk by "splicing together" ESRD rates in subcohorts of successively older donors, beginning at age 20, to attempt to total ESRD rates over a hypothetical 80-yr lifespan. Thus, if an individual who was 40 yr old at donation developed glomerulonephritis 4 yr later and reached ESRD outside the study interval at age 55, 15 yr after donation, this was intended to be reflected by the ESRD rates in other 55 yr olds who were still within their study intervals, for example, those who donated at ages 48–54 and were followed for 7.6 yr. However, surrogates for donors or controls who did not reach ESRD during the study interval, but only developed hematuria at 2 yr, diabetes at 3 yr, 2 + proteinuria at 4 yr, or a serum creatinine of 2 mg/dL at 5 yr would not be included in the successively older subcohorts, because those cohorts by definition had to start out normal. As kidney diseases always had to occur de novo after donation, the ESRD they produced within the study interval would be a fraction of lifetime ESRD in the donor cohort. Younger donors would have 40–50 yr for these untracked kidney diseases to produce uncaptured ESRD. The Norwegian study would have the same problem and would also miss all ESRD that arose from kidney diseases that began outside its study interval. A 25-yr-old donor, for example, might stay normal within a 15-yr study interval, develop a kidney disease at age 45, and reach ESRD at age 60. This is also a problem with our previous outcome studies (2, 3) and disproportionately underestimates the risks of young donors in the United States, because half of their lifetime ESRD will occur after age 64 (36).

The US and Norwegian studies captured only ESRD from rapidly progressing kidney diseases. That may be the reason that seven of nine ill-fated Norwegian donors had glomerular diseases, which are capable of rapid progression. But such rapid progression is distinctly uncommon. Most glomerular and other kidney diseases progress slowly. In one study, only about 25% of 5627 individuals with 1+ to 4+ proteinuria who were unselected for GFR at screening reached dialysis by 17 yr (30). It may seem counter-intuitive to call 8- to 15-yr studies "short term," but it is the donors who are followed for 8–15 yr, not the diseases. The average interval from donation to ESRD in the US study was 8.6 $\pm$ 3.6 yr, and most kidney diseases would not have begun immediately after donation. Others have also been concerned that the low incidence of ESRD in the US and Norwegian studies was only temporary (9, 10, 37). The ESRD rates in

both studies indeed seemed reassuringly low. In the US study, 96 217 donors produced only 99 cases of ESRD, and 1901 donors in the Norwegian study produced only nine cases. But low initial rates are consistent with significant long-term risks. For example, the unselected, two-kidney US population under age 44, at full lifetime risk, produces ESRD at a rate of only 8/10 0000/yr. But almost 90% of lifetime ESRD lies ahead.

Diabetes merits special attention because it is such an important cause of ESRD and advanced lifetime CKD. Neither the US study, the Norwegian study, nor our older outcome studies allow time for long-lived donors to develop diabetic ESRD. Diabetic ESRD has a well-characterized pathogenesis and epidemiology (38–42); type II diabetes accounts for about half of all ESRD in the United States (36), and its prevalence increases markedly from ages 30 to 40 (38). Donor screening seems not to markedly reduce its risk (2, 43, 44), so its prevalence will likely increase with time after donation. Despite improved medical therapies, the prevalence of diabetic nephropathy in the general population is increasing and may be underdiagnosed (40–42). In a sense, diabetic nephropathy does not tangibly "progress" at all during the first 15 yr of diabetes. It is only then that dipstick-positive proteinuria and/or progressive loss of GFR occurs. On the average, ESRD will ensue in another 10–15 yr (39–41), far too late to register in either the US or Norwegian studies. The renal consequences of diabetes that arose in younger donors would not be reflected in older "spliced" cohorts, as diabetes would always have been screened out at entry. However, if the same young individuals were followed as they aged, diabetic ESRD would appear at increasing rates. Just as most young donors with kidney diseases would take decades to reach ESRD, so would older donors. But because of their limited life expectancy, the low ESRD rates in both studies would be closer to the real lifetime risks of older candidates. As discussed below, screening is more effective in older candidates, which also lowers their risks.

The risk estimates in the US study place an impossible burden on medical screening of donor candidates

The US study concluded that although kidney donation increased ESRD risks about eightfold, the lifetime post-donation risk of ESRD was a low 1%, about a third of the 3% risk for the general population. The reduction of pre-donation risk by donor screening that is needed to satisfy those two conditions can be calculated algebraically to be 1/24th of an unselected individual's lifetime risk of ESRD. This would mean that 96 of 100 candidates who were fated to develop ESRD in their lifetimes would have to be excluded at the time of donation to achieve these low risks. Most certainly in young candidates, we cannot expect screening to be this effective. The inability of current screening protocols to exclude post-donation diabetes (2, 43, 44) would by itself prevent a substantial reduction in long-term risks. Diabetes aside, in the United States, if donor screening improbably excluded all the 25-yr-old candidates who would develop ESRD just in their next 20 years, almost 90% of lifetime ESRD would remain (37). A recent Swedish study found strong 20- to 30-yr predictors for ESRD only in a small minority of military age adolescents (45). The Organ and Procurement Transplantation Network currently advises that the donor medical evaluation will not predict the lifetime risks of young candidates, most certainly not 96 of 100 of them (46). Underestimation of absolute long-term risk in the US and the Norwegian studies would seem greatest for the 30–35% of individuals who are below age 35 at donation (47).

Black donor risks are high, even with more plausible relative risk estimates

For young black candidates at an "unselected" 7% lifetime ESRD risk to have the US study's eightfold relative risk and a post-donation 1% absolute lifetime risk, screening would need to exclude 550 of 560 candidates who were fated to develop ESRD, again suggesting that the 1% absolute post-donation risk that was estimated in the US study is implausibly low and difficult to meaningfully apply in donor counseling or selection. Moreover, another straightforward application suggests that the 8- to 11-fold relative risk of nephrectomy in the US and Norwegian studies is overestimated. With a 10-fold relative risk, uninephrectomy in unselected young black individuals at full lifetime risk would increase a "two-kidney" 7% risk of ESRD to 70%. It would increase the 2.5% lifetime ESRD risk of a similar non-black individual to 25%. As lifetime ESRD risks for the general population are so well established, these implausible results are attributable to overestimation of relative risk, suggesting that we have more to learn about deriving and applying them. However, if relative risks were increased only fivefold and medical screening reduced pre-donation 7–8% population-based risks by as much as half, lifetime ESRD risks for young black donors would still be 15–20%. These high risks would be consistent with the high ESRD rates currently observed in black donors

(3–5). As discussed below, current acceptance of young black donors creates ethical problems when other candidates at lower risk are denied because they are "too risky."

Each study demonstrates an increased relative risk associated with loss of GFR at donation

Most critics acknowledged that the US and Norwegian studies demonstrated an increased relative risk associated with donation, although the precision of their estimates was questioned (6–11). Donors may have had undiagnosed familial diseases that could have reached ESRD relatively rapidly (6). Over a longer time, as more common, non-familial ESRD accumulated in both cohorts, differences might narrow. But differences did not narrow: The Norwegian study followed donors twice as long as the US study and showed no less a relative risk of donation, and in the US study, an effect of familial diseases was unlikely (4). In neither study would "virtual" screening of controls have been as effective as actual screening of donors. The 22 control subjects who developed ESRD in the Norwegian study were not afforded a formal history, a physical examination, a urinalysis, or even an estimation of GFR. For example, five cases of congenital cystic disease might have been excluded with renal imaging, which would have increased the relative risks of donors even more.

What is most certain is that in a well-controlled study, the 30% loss of GFR at donation would be the major difference between donors and controls, a difference that could account for more donors reaching ESRD at any point than their two-kidney comparators. For more donors to reach ESRD, they would not need to develop more kidney diseases than controls, and their diseases would not have to progress more rapidly. Simply because of donation, their GFRs would be lower at the point that further, disease-driven losses of GFR began, and more of them would reach ESRD during the study interval. Several experts have cited this reduced "renal reserve" to explain the relative risks suggested by these studies (6–8).

Loss of GFR at donation would change what would have been advanced lifetime CKD without donation to lifetime ESRD. As an example, a 25-yr non-donor with a GFR of 110 mL/min/1.73 m^2 may lose 40 mL/min/1.73 m^2 over his lifetime with normal aging and another 40 mL/min/1.73 m^2 after a kidney disease begins in later life, making his end of life GFR 30 mL/min/1.73 m^2. Lifetime CKD of this severity is about threefold more likely than lifetime ESRD (28). But were he to donate at age 25, all else equal, his immediate post-donation GFR would be 70 mL/min/1.73 m^2, and he would reach ESRD before he died. This makes diabetes even more important as a donor risk factor, because in the two-kidney population, it produces much more lifetime advanced CKD than ESRD. In the macroalbuminuric phase, diabetes causes about 40 mL/min/1.73 m^2 of GFR to be lost per decade (27). Assuming that mortality was not increased, if donation sacrificed 40 mL/min/1.73 m^2 of GFR, diabetic ESRD would occur 10 yr earlier in a donor's life. With more slowly progressing kidney diseases, donation would result in even more life-yr with ESRD. This would particularly impact donors with long life expectancies who developed slowly progressive diseases shortly after donation. Very rapidly progressing diseases that began after donation (i.e., the ones captured by the US and Norwegian studies) would involve only small increases in life-years with ESRD. This analysis assumes that a donor's life will not be shortened when advanced CKD and ESRD occur at an earlier age. It also assumes that kidney diseases will progress at the same rates after donation as they do without it. This question is not entirely settled, but another broad consequence of the US and Norwegian studies is that donor nephrectomy does not protect against progression of kidney diseases. Importantly, GFR-related risks of donation would decrease over time if donors who have not yet acquired kidney diseases lose only 3–4 mL/min/1.73 of GFR per decade (2, 48, 49), as compared to normal control age-related losses of 7–10 mL/min/1.73 m^2 per decade (27, 50).

The US and Norwegian studies suggest that donor candidates with higher pre-donation GFRs will have lower absolute lifetime risks

As discussed above, the 30% loss of GFR at nephrectomy can explain the increased relative risk of donation, because it would result in more new-onset, progressive kidney diseases reaching ESRD during any study interval. Restated, this means that the absolute post-donation GFR—before disease begins – is an important donor risk factor. But this is directly determined by pre-donation GFR, which makes pre-donation GFR the fundamental risk factor. To explain this point in more detail, the range of currently acceptable pre-donation GFRs is quite wide (51–53). Some candidates will have predonation GFRs that are so high that their post-nephrectomy GFRs will be comparable to the average GFRs in non-donor control groups. Even allowing for a significant relative risk of donation, these candidates with high- normal pre-donation GFRs would have relatively low

absolute postdonation risks that were similar to the average risks of non-donor controls. In this way, a high–normal pre-donation GFR will mitigate the effects of donation on absolute risk. The US and Norwegian studies therefore indirectly suggest that pre-donation kidney function throughout the normal range is a powerful but underappreciated determinant of long-term ESRD risk. Currently, 25-yr-old candidates with GFRs or creatinine clearances that differ by 40 mL/min are treated similarly (51–54), even though the pre-donation GFR of one will approximate the post-donation GFR of the other. However, candidates are routinely refused for hypertension or microalbuminuria (51–53), which predict far less GFR loss over several decades (27, 55). Besides being intuitively valid, low GFR has been shown to be an ESRD risk factor in many population studies (27, 29). GFR-related risks of course involve more that defining a cutoff of 80–90 mL/min, below which donation is refused (54). Rather the point is that currently acceptable young candidates with low–normal GFRs will be at long-term risk that is particularly high and may merit exclusion from donation (56).

The individual lifetime risk of ESRD will vary significantly among normal candidates

Donors and the transplant community have customarily been presented with "the" risk of living kidney donation, whether it is said to be "very low" or "1%" as estimated in the US study. Older outcome studies express "it" as ESRD/patient/year (2, 3). But lifetime risk of ESRD will depend on a number of donor characteristics, including race, pre-donation GFR, and age, and cannot be expressed that way. Older candidates will have their ESRD risks markedly reduced by current screening protocols. In the general population, ill-fated individuals will typically exhibit long pre-ESRD "prodromes," reaching ESRD at a median age of about 64 (36). Those 55 yr olds with such "prodromes" as diabetes, dipstick-positive proteinuria, and/or gradually rising serum creatinine values will be excluded from donation, leaving acceptable donor candidates at well below the average ESRD risk for the unselected population. The current practice of excluding GFRs or creatinine clearances below 80 mL/min/1.73 m^2 (50–54) allows virtually the entire normal range in young donors, but excludes the lowest third of normal GFRs in 55 yr olds (56). The lower GFR-related risks of the acceptable older candidates will further reduce their lifetime ESRD risks, even below those of normal individuals in the general population. Differences in pre-donation risk between young and middle-aged candidates may be small, for example, 2% vs. 0.5% in non-blacks (56, 57), but the newly described relative risks make them more important. A 2% pre-donation risk in a normal young donor and a hypothetical relative risk multiple of 5 would produce a 10% lifetime risk. Risks for many black candidates will be higher, and some may well merit exclusion from donation (56). At the same time, it is not clear that these newly formulated, individualized risks have to be extremely low to be acceptable, as long as donors understand them and the transplant community can countenance them. Many of us, for example, might want to take a 5% or even a 10% risk of ESRD later in life to help a loved one, but an ethically defensible threshold for unacceptable risk can be determined by consensus. The standard for exclusion must be uniform: We cannot responsibly refuse a candidate as "too risky" and then accept another who is at the same or higher risk. A reasonably inclusive, uniform standard would allow many minor medical risk factors when present in older, high GFR, and/or non-black candidates (55–57). Responsibly denying donor candidates is in its own way as important an ethical issue as accepting them (58).

Studies that focus on the ESRD risks of donors must be designed differently

The risk of ESRD from common, post-donation kidney diseases is distinctly different from the risks of hyperfiltration itself or so-called uremia from loss of GFR with nephrectomy. These possible risks may well be meaningfully addressed in smaller cohorts over shorter intervals. Recent well-done studies that address these risks are reassuring (48, 49, 59), but out of an abundance of caution, they should be continued. But the risks of common kidney diseases are an entirely different matter. We do not need longer studies out of an abundance of caution; studies that follow donors for 8–15 yr are inherently unable to capture their long-term risks for ESRD. That is because such studies cannot capture the risks of delayed onset and/or typically slowly progressing kidney diseases, particularly in young individuals.

"Definitive" prospective studies that focus specifically on post-donation kidney diseases would take decades to fill and would need to extend for decades more. Over the course of these studies, medical practices and demographic risks of obesity and diabetes would change. Many donors would be lost to follow-up, and confidence limits would be wide; risk specialists would not be

satisfied. The well-done US and Norwegian studies have encountered similar criticisms, even of their analyses of relative risk, which is their strongest feature. These studies have also clearly distinguished the concepts of pre-donation "baseline" risks from relative risks and post-donation absolute risks. To address these risks, we can apply a different methodology rooted in the abundant epidemiologic data that we currently have. We can focus on risks of lifetime ESRD and near-ESRD risks in the general population and how they are reduced by donor exclusion protocols and increased by nephrectomy (56, 57). Saying that we have "no idea of risk" and continuing business as usual is wrong for two reasons. First, we do in fact know a great deal about risk and need to apply it. Second, if we truly have no idea of risk, living kidney donation becomes a phase one study, that is, having the highest possible risks. To protect the donor when we are truly uncertain about donor risk, the default position has never been to proceed (60). Advocates of the status quo must convincingly defend it, or donor selection practices must change. We must always be open to examining and revising risk estimates, so that we do not inappropriately counsel, deny, or accept donor candidates.

Conclusions

1. The recent Norwegian and US studies cannot capture long-term ESRD risks in living kidney donors, because most donors will predictably reach ESRD outside of their study intervals. Both studies demonstrate an increased relative risk of donation, which they are best designed to capture.
2. Both studies indirectly suggest that high–normal pre-donation GFR is an important, heretofore-unappreciated factor that will mitigate an increased absolute risk of post-donation ESRD.
3. Low–normal pre-donation GFR, young age, and black race determine sometimes high long-term individual risks, not a single "low" or "1%" risk of donation as these studies suggest. A uniform, ethically defensible donor selection protocol should allow donation to older candidates with many minor medical abnormalities and protect –by exclusion from donation– younger, low GFR, and/or black candidates at high lifetime risk.

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References

1. Ramos E, Vijayan A, Vella J. Evaluation of the living kidney donor and risk of donor nephrectomy. In: Brennan DC ed. Retrieved from http://www.uptodate.com (Accessed 2 May 2013).
2. Ibrahim HN, Foley R, Tan LP et al. Long-term consequences of kidney donation. N Engl J Med 2009: 360: 449.
3. Cherikh WS, Young CJ, Kramer BF, Taranto SE, Randall HB, Fan PY. Ethnic and gender related differences in the risk of end stage renal disease after living kidney donation. Am J Transplant 2011: 11: 1650.
4. Muzaale AD, Massie AB, Wang MC et al. Risk of end-stage renal disease following live kidney donation. JAMA 2014: 311: 579.
5. Mjoen G, Hallan S, Hartmann A et al. Long-term risks for kidney donors. Kidney Int 2014: 86: 162.
6. Gill JS, Tonelli M. Understanding rare adverse outcomes following living kidney donation. JAMA 2014: 311: 577.
7. Boudville N, Garg AX. End-stage renal disease in living kidney donors. Kidney Int 2014: 86: 20.
8. Kaplan B, Ilahe A. Quantifying risk of kidney donation: the truth is not out there (Yet). Am J Transplant 2014: 14: 1715.
9. Gaston RS, Kumar V, Matas AJ. Reassessing medical risk in living kidney donors. J Am Soc Nephrol 2014: 26: 1.
10. Lam NN, Lentine KL, Garg AX. End-stage renal disease risk in live kidney donors: what have we learned from two recent studies? Curr Opin Nephrol Hypertens 2014: 23: 592.
11. Kasiske B. Outcomes after living kidney donation: what we still need to know and why. Am J Kid Dis 2014: 64: 335.
12. Mjøen G. Author Reply. Kidney Int 2014: 85: 1469.
13. Mjøen G, Holdaas H. Author Reply. Kidney Int. 2014: 86: 447
14. Mjøen G, Hallan S, Dekker FW, Holdaas H. Author Reply.Kidney Int 2014: 86:650.
15. Massie AB, Segev DL. Comment: The US study AD. JAMA 2014: 312: 93.
16. Research Finds Low Risk of Renal Failure for Kidney Donors. *ASN In The Loop*. KidneyDaily@asn.custombriefings.com, February 13, 2014.
17. Healy M. Is there a cost to kidney donation? Yes, but. . .says study. *Los Angeles Times, Science Now*. 2014 Feb 12. http://articles.latimes.com/2014/feb/12/science/la-sci-sn-kidney-donation-health
18. Allegretti AS, Yeung MY, Riella LV. Counseling potential donors to the risk of ESRD after kidney donation: glass half-full or half-empty? Am J Transplant 2014: 14: 2434.
19. Berns JS, Reese PP. Risks to live kidney donors: what to tell patients. Medscape Nephrol.
20. Gill J, Reese PP. Potential Risks of Living Kidney Donation. American Society of Transplantation, *AST Desktop: Conversation with the President*. Posted by Kneewell. 20 October 2014.
21. Charnow JA. Kidney Donors Face Higher ESRD Risk. *Renal & Urology News*. 11 July 2014.
22. Kidney Donors at Long-Term Risk? Should We Change Our Practice? *Astellas Symposia, World Transplant Congress*. 28 July 2014.
23. Yard DH. Live Kidney Donors Face Elevated ESRD Risk. *Renal & Urology News*. 13 February 2014.
24. Study Finds Low Risk of ESRD For Living Kidney Donors. Nephrology News & Issues, *Kidney Transplant*. 11 March 2014.

25. A Discussion of Risk in Living Kidney Donors. *AST* Timely Topics in Transplantation Webcast Series; April 22, 2014.
26. Hoerger TJ, Simpson SA, Yarnoff BO et al. The future burden of CKD in the United States: a simulation model for the CDC CKD initative. Am J Kidney Dis 2015: 65: 403.
27. Hoerger TJ, Wittenborn JS, Segel JE et al. A health policy model of CKD: 1. model construction, assumptions, and validation of health consequences. Centers for Disease Control and Prevention CKD Initiative. Am J Kidney Dis 2010: 55: 452.
28. Grams ME, Chow EK, Segev DL, Coresh J. Lifetime incidence of CKD stages 3-5 in the United States. Am J Kidney Dis 2013: 62: 245.
29. Hallan Sl, Ritz E, Lydersen S, Romundstad S, Kvenild K, Orth SR. Combining GFR and albuminuria to classify CKD improves prediction of ESRD. J Am Soc Nephrol 2009: 20: 1069
30. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. Kidney Int 2003: 63: 1468.
31. Kiberd BA, Clase CM. Cumulative risk for developing end-stage renal disease in the US population. J Am Soc Nephrol 2002: 13: 1635.
32. Afkarian M, Sachs MC, Kestenbaum B et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol 2013: 24: 302.
33. Haynes R, Staplin N, Emberson J et al., SHARP Collaborative Group. Evaluating the contribution of the cause of kidney disease to prognosis in CKD: results from the Study of Heart and Renal Protection (SHARP). Am J Kidney Dis 2014: 64: 40.
34. Wen CP, Matsushita K, Coresh J et al. Chronic Kidney Disease Prognosis Consortium. Relative risks of chronic kidney disease for mortality and end-stage renal disease across races are similar. Kidney Int 2014: 86: 819.
35. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004: 351: 1296.
36. United States Renal Data System (*USRDS*). www.USRDS.org
37. Kiberd B, Tennankore K. Comment. JAMA 2014: 312:93.
38. Narayan KM, Boyle JP, Thompson TJ, Sorensen SW. Williamson DF lifetime risk for diabetes mellitus in the United States. JAMA 2003: 290: 1884.
39. Ibrahim HN, Hostetter TH. Diabetic nephropathy. J Am Soc Nephrol 1997: 8: 487.
40. Harjutsalo V, Per-Henrik G. Epidemiology and risk factors for diabetic kidney disease. Adv Chronic Kidney Dis 2014: 21: 260.
41. Plantinga LC, Crews DC, Coresh J et al. Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. Clin J Am Soc Nephrol 2010: 5: 673.
42. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA 2011: 305: 2532.
43. Lentine KL, Schnitzler MA, Xiao H et al. Racial variation in medical outcomes among living kidney donors. N Engl J Med 2010: 363: 724.
44. Boyarsky BJ, Van Arendonk K, Deshpande NA, James NT, Montgomery RA, Segev DL. Johns Hopkins WHOLE-DONOR Study. Race is associated with new onset hypertension and diabetes after living kidney donation. Abstract presented at American Transplant Congress, Boston, MA, June 6–12, 2012.
45. Sundin P, Udumyan R, Sjostrom P, Montgomery S. Predictors in adolescence of ESRD in middle-aged men. Am J Kid Dis 2014: 64: 723.
46. Living Donor Informed Consent Checklist www.optn.transplant.hrsa.govs
47. www.unos.org
48. Lenihan CR, Busque S, Derby G, Blouch K, Meyers BD, Tan JC. Longitudinal study of living kidney donor glomerular dynamics after nephrectomy. J Clin Invest 2015: 125: 1311.
49. Kasiske BL, Anderson-Haag T, Israni A et al. A prospective controlled study of living kidney donors: three year follow –up. Am J Kidney Dis 2015: 66: 114.
50. NKF KDOQI Guidelines-Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Part 4. Definition and Classification of Stages of Chronic Kidney Disease. Guideline 1. Definition and Stages of Chronic Kidney Disease. www.kidney.org. National Kidney Foundation, 2002.
51. Tong A, Chapman JR, Wong G, de Bruijn J, Craig JC. Screening and follow-up of living kidney donors: a systematic review of clinical practice guidelines. Transplantation 2011: 92: 962.
52. Mandelbrot DA, Pavlakis M. Living donor practices in the United States. Adv Chronic Kidney Dis. 2012: 19: 212.
53. Delmonico F. Council of the Transplantation Society. A Report of the Amsterdam Forum on the Care of the live kidney donor: data and medical guidelines. Transplantation 2005: 2S: S53.
54. Poggio ED, Rule AD, Tanchanco R et al. Demographic and clinical characteristics associated with glomerular filtration rates in living kidney donors. Kidney Int 2009: 75: 1079.
55. Steiner RW. Risk appreciation for living kidney donors: another new subspecialty? Am J Transplant 2004: 5: 694.
56. Steiner RW, Ix JH, Rifkin DE, Gert B. Estimating risks of de novo kidney diseases after living kidney donation. Am J Transplant 2014: 20: 1.
57. Steiner RW. Normal for now or at future risk: a double standard for selecting young and older living kidney donors. Am J Transplant 2010: 10: 737.
58. Allen MB, Abt PL, Reese PP. What are the harms of refusing to allow living kidney donation? An expanded view of risks and benefits Am J Transplant 2014: 14: 531.
59. Delayane P, Mariat C, Glassock RJ. Safety of living donation: another brick in the wall. . .and a solid (physiologic) one. Am J Kidney Dis 2015: 66: 1.
60. Reese PP, Caplan AL, Kesselheim AS, Bloom RD. Creating a medical, ethical, and legal framework for complex living kidney donors. Clin J Am Soc Nephrol 2006: 1: 628.