Assessment of Glomerular Filtration Rate and End-Stage Kidney Disease Risk in Living Kidney Donor Candidates: A Paradigm for Evaluation, Selection, and Counseling

Lesley A. Inker, Farrukh M. Koraishy, Nitender Goyal, and Krista L. Lentine

Living donor kidney transplantation is the preferred treatment option for ESRD. However, recent data suggest a small increase in the long-term risk of kidney failure in living kidney donors when compared to healthy nondonors. These data have led to a need for reconsideration of how donor candidates are evaluated and selected for donation. A Kidney Disease: Improving Global Outcomes (KDIGO) work group completed a comprehensive clinical practice guideline for evaluation of living kidney donor candidates in 2017, based on systematic evidence review, de novo evidence generation, and expert opinion. Central to the evaluation framework is assessment of glomerular filtration rate (GFR), which is used to screen for kidney disease and aid the prediction of long-term kidney failure risk after donation. Accurate estimation of the level of GFR and risk of kidney failure, and communication of estimated risks, can support evidence-based donor selection and shared decision-making. In this review, we discuss approaches to optimal GFR estimation in the donor evaluation process, long-term risk projection, and risk communication to donor candidates, integrating recommendations from the new KDIGO guideline, other recent literature, and experience from our own research and practice. We conclude by highlighting topics for further research in this important area of transplant medicine.

Key Words: Evaluation, Glomerular filtration rate, Kidney failure, Living kidney donation, Risk assessment

INTRODUCTION

Living donor kidney transplantation provides the best outcomes for patients with ESRD.[1,2] Traditionally, kidney donation was considered safe with a relatively low early surgical risk (0.03% mortality and less than 1% risk of major morbidity)[3] and without increased long-term risks compared to the general population.[4-6] However, recent studies incorporating comparisons to healthy nondonors outcomes suggest low, but increased, risks of ESRD and other medical conditions in donors over intermediate-term follow-up.[7,8] These data have led to a need for reconsideration of how donor candidates are evaluated and selected for donation.[9] In August 2017, Kidney Disease: Improving Global Outcomes (KDIGO) published a comprehensive clinical practice guideline for evaluation of living kidney donor candidates.[10,11] Glomerular filtration rate (GFR), defined as the volume of fluid filtered by the kidney glomeruli into the Bowman's spaces per unit time, is the best assessment of overall kidney function. Assessment of GFR is a critical component of the donor candidate evaluation and is used to detect the presence of kidney disease and aid the prediction of long-term kidney failure risk. In this article, we focus on best methods to assess GFR and current evidence for how GFR portends long-term risk, and conclude with recommendations for counseling and selecting donor candidates. The article integrates recommendations from the new KDIGO guideline, other recent literature, and experience from our own research and practice.

THE KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES FRAMEWORK FOR DONOR RISK ASSESSMENT

The KDIGO living donor guideline advances a framework for evaluating and selecting donor candidates based on long-term risk for adverse outcomes estimated from simultaneous consideration of a profile of demographic and health characteristics, rather than a single factor in isolation. For example, prior to the new guideline, most programs excluded donors with a body mass index (BMI) exceeding a predetermined threshold, usually between 30 and 35 kg/m^2, without explicit consideration of additional donor characteristics or risk factors. By comparison, the KDIGO guideline endorses individualizing the decision to approve donation in obese candidates based on their predicted long-term risk in relation to the transplant program's acceptance threshold.[10,11] A central goal of this new guideline is to promote "consistent, transparent, and defensible decision-making" based on comparison of

From the Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, MA; Renal Section, St. Louis VA Medical Center, St. Louis, MO; Saint Louis University Center for Abdominal Transplantation, St. Louis, MO; and Division of Nephrology, Department of Medicine, Saint Louis University School of Medicine, St. Louis, MO.

Financial Disclosure: L.A.I reports funding to Tufts Medical Center for research and contracts with the National Institutes of Health, National Kidney Foundation, Pharmalink AB, Gilead Sciences, and Otsuka and has a provisional patent (Coresh, Inker, and Levey) filed 8/15/2014—"Precise estimation of glomerular filtration rate from multiple biomarkers" PCT/US2015/044567. The technology is not licensed in whole or in part to any company. Tufts Medical Center, John Hopkins University, and Metabolon Inc have a collaboration agreement to develop a product to estimate GFR from a panel of markers. F.M.K and N.G. do not have any conflicts of interest. K.L.L. receives support from the NIH/NIDDK, "Long-Term Health Outcomes After Live Kidney Donation in African-Americans" grant R01-DK096008 and is co-chair of the KDIGO "Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors" work group.

Address correspondence to Krista L. Lentine, MD, PhD, Saint Louis University Center for Abdominal Transplantation, 1402 S. Grand Blvd., St. Louis, MO, 63104. E-mail: krista.lentine@health.slu.edu

1548-5595/$36.00

https://doi.org/10.1053/j.ackd.2017.09.002

individualized, quantitative estimates of donor risks "to a transplant program's acceptable risk threshold".[11] Risk threshold is defined as the upper limit of acceptable risk established by a program for donor candidate selection. Under the KDIGO framework, when a candidate's estimated risk is above the acceptable threshold, the transplant program is justified in declining the candidate and can ground its decision in a quantitative framework. When a donor candidate's estimated risk is below the acceptable risk threshold, the transplant program should accept a donor candidate, and it should be the candidate's decision whether to proceed with living kidney donation after being informed of the risks. Once established, acceptable risk thresholds should be applied consistently and transparently for all donor candidates evaluated at a program.

There are several outcomes to consider after kidney donation, but the KDIGO framework focuses on the postdonation development of kidney failure requiring dialysis or transplantation because it is a central outcome after removal of one kidney and has a biologically plausible link to donation (Fig. 1).[11] This framework conceptualizes the candidate's long-term postdonation risk as the combination of risks conferred by his or her demographic and health characteristics at the time of evaluation plus the risk attributable to donation. The level of GFR predonation is a key clinical characteristic that impacts the donor candidate's estimated risk, and thus, the accurate assessment of GFR is a critical step in the donor evaluation. The KDIGO framework was informed by a systematic evidence review.[10,11] In response to lack of data for a quantitative framework, the guideline development methodology also included a de novo meta-analysis of data from nearly 5 million healthy persons identified from 7 general population cohorts who are similar to kidney donor candidates, calibrated to annual ESRD incidence in the US healthy population, to develop a tool for projection of 15-year and lifetime risks of ESRD based on level of predonation GFR and other baseline demographic and health factors.[12]

CLINICAL SUMMARY

- Recent data suggest a small increase in the long-term risk of kidney failure in living kidney donors compared to healthy non-donor controls, prompting a need for reconsideration of how donor candidates are evaluated and selected.
- Assessment of GFR is central to the framework for evaluating living donor candidates, being used to screen for kidney disease and aid the prediction of long-term ESRD risk after donation.
- Accurate estimation of the level of GFR and risk of kidney failure, and communication of estimated risks, can support evidence-based donor selection and shared decision-making.

THE KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES RECOMMENDATIONS FOR EVALUATION OF KIDNEY FUNCTION IN LIVING DONOR CANDIDATES

The purpose of GFR evaluation in kidney donor candidates is to detect acute or chronic kidney disease and to support prediction of long-term risk for the candidate donor. The KDIGO guideline recommends that GFR ≥90 mL/min per 1.73 m^2 (normal) is acceptable for donation in the absence of other markers of kidney disease (eg, proteinuria, hematuria, or anatomic abnormalities noted on kidney imaging), whereas candidates with GFR <60 mL/min per 1.73 m^2) should not donate.[11,13] The guideline suggests that the decision to approve donor candidates with GFR 60 to 89 mL/min per 1.73 m^2 should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold, including projected ESRD risk. The rationale for this stratified approach is based on GFR levels defining normal (≥90 mL/min per 1.73 m^2) and chronic kidney disease (CKD) (<60 mL/min per 1.73 m^2) in the general population, with a wide intermediate range of GFR (60-89 mL/min per 1.73 m^2) in which transplant programs can individualize decisions based on other risk factors (Fig. 2).

Normal Levels of Kidney Function

GFR is considered as the best overall measure of kidney function because the degree of GFR reduction is closely correlated with alterations in kidney structure and with complications related to CKD. In the general population[14] as well as in patients with CKD,[15] decreased GFR is associated with a higher risk of kidney failure, cardiovascular disease, and death. In adults younger than age 40 years, the normal range of GFR in men is 100-130 mL/min per 1.73 m^2 and slightly lower in women (90 mL/min per 1.73 m^2 to 120 mL/min per 1.73 m^2).[16] After age 40 years, there is a progressive decline in GFR of approximately 6-8 mL/min per 1.73 m^2 with each decade of aging.[17] A GFR of 90 mL/min per 1.73 m^2 or greater is considered "normal," while a GFR <60 mL/min per 1.73 m^2 is considered low in adults of any age. Controversy exists in differentiating disease from normal variation when GFR is in the 60 to 89 mL/min/1.73 m^2 range, especially in persons over the age of 40 years and without significant proteinuria.[16,18]

Measured Glomerular Filtration Rate

The urinary clearance of an "ideal" filtration marker is considered the "gold standard" for the measurement of GFR.[19] An ideal filtration marker is defined as a substance that is freely filtered at the glomerulus, is neither reabsorbed, secreted, synthesized, or metabolized by the tubules, and for exogenous markers (substances not synthesized within the human body), does not alter the function of the kidney. However, these measurements are challenging to perform, and therefore, measured GFR (mGFR) contains an element of error, differentiating it from the "true" physiological GFR.[20] Since the use of exogenous filtration markers (eg, inulin and iohexol) to calculate mGFR is expensive and not universally available, the measurement of creatinine clearance (mCrCl) using a 24-hour urine collection is often used as a confirmatory test of