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Benjamin R. Morgan & Hassan N. Ibrahim

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REVIEW ARTICLE

Long-term outcomes of kidney donors

Benjamin R. Morgan, Hassan N. Ibrahim *

Division of Renal Diseases and Hypertension, University of Minnesota, MN, USA

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KEYWORDS

Kidney;
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ABBREVIATIONS

ESRD, end-stage renal disease; BMI, body mass index; DM, diabetes mellitus; RR, relative risk; UNOS, United Network for Organ Sharing; HRQL, health-related quality of life; SF, short form; GI, impaired glucose tolerance

Abstract As the demand for kidney transplantation, particularly from living donors, continues to rise, there is increasing and much needed interest in accurately quantifying the long-term risks of kidney donation. We review the outcomes of kidney donors in the domains of survival, perioperative mortality, risk of end-stage renal disease, quality of life, course of diabetes mellitus in donors, pregnancy after donation, obesity, and prevalence of other health conditions.

* Corresponding author. Address: University of Minnesota, Division of Renal Diseases and Hypertension, 717 Delaware Street, SE, Suite 353, Mail Delivery Code 1932, MN 55414, USA. Tel.: +1 612 624 9444; fax: +1 612 626 3840.
E-mail address: ibrah007@umn.edu (H.N. Ibrahim).

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Epidemiology of live donation in the USA and internationally

The number of live kidney donations in 2009 rose to 6387 as compared to 5968 in 2008, marking the first reported annual increase in living donor transplantation in the USA since its peak in 2004. While this increase is encouraging, the rapidly growing waiting-list for kidney transplantation outstrips this rise. Since the end of 2008, the number listed has increased by >13%, with the current active waiting list standing at >72,000 [1]. Waiting times also continue to increase nationwide. In fact, for candidates entering the list in 2005, the most recent year in which half of the listed waiting patients had been transplanted, the estimated median waiting time was 3 years. Sadly, 16% of those listed died within 5 years of being placed on the list [2].

The number of living kidney donations has also shown a general increase internationally [3]. Of 69 countries reporting transplantation statistics, 62% reported a >50% increase in living kidney donations over the past decade. The most annual living donor kidney transplants were in the USA (6435), Brazil (1768), Iran (1615), Mexico (1459) and Japan (939). The highest per capita rate of transplantation was reported in Saudi Arabia, at 32 procedures per million population, followed by Jordan (29), Iceland (26), Iran (23), and the USA (21). Some of these values should of course be viewed in the context that deceased donor kidney transplantation is minimal in some of the countries that reported high live-donation rates.

These increasing rates of living-donor transplantation, both in the USA and internationally, along with the growing prevalence of end-stage renal disease (ESRD), have justifiably generated increased interest in the long-term outcomes of kidney donors, which we discuss here.

Survival of kidney donors

Four large studies affirm that kidney donors do not incur any shortened survival. Fehrman-Ekholm et al. [4] found that kidney donors live longer than Swedish controls in the general population. In their analysis of 459 donors who donated between 1964 and 1994, 41 donors died 1.25–31 years after donation. The 20-year survival was 85%, in contrast to 66% in controls. Okamoto et al. [5] reported similar findings for 601 Japanese donors who donated between 1970 and 2006, with a 20-year survival rate of 86.4%, which is nearly the same as that reported by Fehrman-Ekholm et al. [4]. The University of Minnesota reported an extensive single-centre study of nearly 3700 kidney donors, spanning four decades [6]. In that study the 20-year survival rate was 93.5% for donors, compared to 89.5% in age-matched controls. At 30 years, these proportions were 82.5% vs 76.2%, and at 40 years they were 50.1% vs 55.8% in controls. Finally, Segev et al. [7] further substantiated these results by reporting long-term survival obtained from mandated national USA registry data. Between 1994 and 2009, 80,000 kidney donors were compared to age and comorbidity-matched controls, stratified by age, sex, and race. Considerable efforts were made to identify a suitable control population that closely matched the relatively healthy status of kidney donors, and no difference was found in overall long-term mortality rates after a median follow-up of 6.3 years [7].

Perioperative morbidity and surgical mortality associated with donor nephrectomy

By contrast with most surgical interventions, no degrees of physical or symptomatic improvements are expected for the donor, and the very nature of kidney donation serves as an act of donor self-sacrifice. Given these circumstances, efforts to ensure that perioperative morbidity and mortality remain minimized have paid off. Matas et al. [8] compared the living-donor morbidity and mortality for open nephrectomy, hand-assisted laparoscopic nephrectomy and non-hand-assisted laparoscopic nephrectomy. In a survey of 2828 living-donor nephrectomies, 52.3% were open, 20.7% were hand-assisted and 27% were not hand-assisted. Two donors died from surgical complications and one was in a persistent vegetative state, all after laparoscopic nephrectomy. Re-operation was necessary in 0.4% of open cases, 1% of hand-assisted cases and 0.9% of non-hand-assisted ones; complications not requiring re-operations were reported for 0.3%, 1% and 0.8%, respectively. Overall, the re-admission rate was higher for laparoscopic nephrectomy (1.6% vs 6%), almost entirely as a result of an increase in gastrointestinal complications in laparoscopic nephrectomy donors.

More recently, Patel et al. [9] studied the factors associated with perioperative complications in 3074 donors from 28 centres during 2004–2005. The overall complication rate was 10.6%, there were no deaths, and 1.4% of donors were re-admitted. Age >50 years, obesity, tobacco use and annual centre volume <50 transplants/year were significantly associated with overall morbidity and the latter was significantly associated with major complications. For tobacco use and kidney-donor outcomes, by contrast, Taber et al. [10], in their studies of 221 donors who underwent laparoscopic nephrectomy, of whom 81 were current or former smokers, found no difference between smokers and non-smokers in mean operative duration, length of stay, estimated blood loss, narcotic use or postoperative complications.

In the analysis by Segev et al. [7], the mortality rates after nephrectomy in the USA were also analysed. There were 25 deaths within 90 days of kidney donation during the study period. Surgical mortality from kidney donation was 3.1 per 10,000 donor nephrectomies (95% CI, 2.0–4.6). Surgical mortality was higher in men than in women (5.1 vs 1.7 per 10,000 donors; risk ratio, RR, 3.0; 95% CI, 1.3–6.9; $P = 0.007$), in black vs white and Hispanic individuals (7.6 vs 2.6 and 2.0 per 10,000 donors; RR, 3.1; 95% CI, 1.3–7.1; $P = 0.01$), and in donors with hypertension vs without hypertension (36.7 vs 1.3 per 10,000 donors; RR, 27.4; 95% CI, 5.0–149.5; $P < 0.001$).

Uninephrectomy and future renal function in nondonors

Evidence that a reduction in renal mass might lead to progressive renal failure has come primarily from studies of children born with a reduced number of functioning nephrons, and reports of the development of focal sclerosis in patients with unilateral renal agenesis [11,12]. However, many long-term follow-up studies after nephrectomy for unilateral disease have not shown progressive deterioration in renal function [13,14]. Baudoin et al. [15] studied subjects who had undergone uninephrectomy in childhood. In general, their kidney function was maintained. However, those followed for >25 years had

a higher incidence of kidney failure, proteinuria and hypertension. In another study, Narkun-Burgess et al. [16] assessed 56 World War II veterans 45 years after they had lost a kidney due to trauma during the war, and compared them to other World War II veterans of the same age. Their mortality was not increased and of the 28 living, none had serious renal insufficiency. Of particular interest are the case reports of patients with partial loss of a solitary kidney. Of 35 such patients studied, 31 were reported to have stable renal function [17,18]. However, in a larger series of 14 patients who were assessed 5–17 years after partial nephrectomy of a solitary kidney, 12 had stable renal function, two developed renal failure and nine had proteinuria [19]. The extent of proteinuria correlated directly with the length of follow-up and inversely with the amount of remaining renal tissue.

ESRD risk in kidney donors

Given its very low prevalence among kidney donors, little was previously known about the risk of developing ESRD, although evidence suggested that there was no greater risk of ESRD. Estimates have considerably improved as a result of several recent studies, including both single-centre and national retrospective analyses. Fehrman-Ekholm et al. [4] reported six cases of ESRD in 1112 donors who donated between 1965 and 2000, a rate of 0.5%, which is similar to the general Swedish population. Okamoto et al. [5] discovered three out of 601 cases within their Japanese centre. Ibrahim et al. [6], at the University of Minnesota, reported 11 previous donors developing ESRD, or 0.2% of the studied donor population. ESRD developed 22.5 ± 10.4 years after donation. Eight donors were white, one was black, one was Asian, and one was Native American. The corresponding total numbers of donors from these three minority groups were 93, 39 and 76, yielding an incidence of 1%, 2.6% and 1.3%, rates that are higher than those noted in Caucasian donors, but the number of donors in these ethnic categories is too small to draw conclusions.

Conclusions about the long-term risk of ESRD in kidney donors are limited, mainly due to either the relative infrequency of ESRD cases in the studied donors or the over-representation of Caucasians. In the study by Ibrahim et al. [6] for example, 98.8% of the donor sample was Caucasian. Concerns were raised about the risk of ESRD development in traditionally higher-risk subgroup populations, primarily African-Americans and Hispanics [6]. Gibney et al. [20] queried the United Network for Organ Sharing (UNOS) Organ Procurement Transplantation Network database for former donors who were subsequently placed on the kidney transplant waiting list. They noted that, although African-Americans comprised only 14.3% of all living kidney donors, they comprised 44% of donors on the waiting list. In a following study, Gibney et al. [21] identified 126 previous donors who had been placed on the waiting list, including 50 African-Americans. Risk factors for developing ESRD included male sex and those who donated before age 35 years; males comprised 44% of donors, but 58% of those with ESRD.

Lentine et al. [22] also recently investigated this question of the risk of ESRD in understudied minority USA populations. They used a retrospective analysis linking former UNOS kidney donors to an insurance company administrative database. Among donors, 76.3% were white, 13.1% black, 8.2% Hispanic, and 2.4% another race or ethnic group. Black and Hispanics donors, as compared to white donors, had a greater risk of hypertension, diabetes mellitus (DM) requiring drug therapy, and chronic kidney disease (hazard ratio 2.32; 95% CI, 1.48–3.62). Overall, 5.2% of donors had a medical diagnosis claim of chronic kidney disease with no designation of stage. No cases of ESRD were identified in any of the 1786 white donors, but ESRD developed in two of 271 black donors (0.7%) and one of 197 Hispanic donors (0.5%). These results raise concern that the risk of uninephrectomy might not be similar in all ethnic subgroups, and highlight the need for strict long-term follow-up studies of non-Caucasian living donors to accurately determine the risk of ESRD.

Hypertension in kidney donors

Boudville et al. [23] described in detail the epidemiology of hypertension in kidney donors. The average systolic and diastolic blood pressures were 121 and 77 mmHg, respectively. Beyond the first 5 years after donation, blood pressure in the donors was 5 mmHg higher in kidney donors than controls. Okamoto et al. [5] reported that 31.1% of Japanese donors were hypertensive after 7–406 months of follow-up, a proportion similar to that reported by Fehrman-Ekholm [4]. Ibrahim et al. [6] also assessed the prevalence of hypertension, defined as the requirement for antihypertensive medications or by an average blood pressure of >140/90 mmHg in those not taking antihypertensive medications, in 255 kidney donors 3–45 years after donation. The mean (SD) systolic blood pressure in the 255 donors was 122.2 (14.9) mmHg, the diastolic was 73.3 (9.0) mmHg, 63 (24.7%) donors required antihypertensive medications, and 19 (7.4%) donors were found to have a blood pressure of >140/90 mmHg, which was the first time they knew they might have hypertension; yielding a prevalence of 32.1%. The risk for hypertension increased with age (odds ratio 1.09; 95% CI, 1.04–1.13) and with higher body mass index (BMI, odds ratio 1.12; 95% CI 1.04–1.21). Most importantly, when donors were matched by age, gender, ethnicity and BMI with controls, their prevalence of hypertension was comparable, in contrast to previously held opinion that donation is associated with hypertension.

Health-related quality of life (HRQL) after kidney donation

Collectively, living donors report a similar, or better, HRQL than the general population. However, risk factors for less positive outcomes have also been identified, and include a poor donor or recipient physical outcome, a negative personal donor-recipient relationship, and financial hardship [24]. Recently, HRQL data were obtained from 240 Minnesota donors who completed either the Short Form (SF)-12 (204) or SF-36 (41). Of the donors, ≈60% rated their physical health higher than average for their age-gender peers in the USA general population. Similar results for mental health were also reported; 62% of the donors rated their mental health higher than their age-gender peers in the USA general population [6]. Shrestha et al. [25] investigated differences before and after donation among 66 donors compared with a control group of potential donors who did not proceed with donation, by using the Medical Outcome Survey SF-36. The SF-36 scores after donation of the donors were not significantly different from

those of the control group, except in one of eight dimensions, the physical role. Reassuringly, 83% of the donors would have donated again if possible, and 90.9% wished to encourage living-kidney donation.

More recently, Mjoen et al. [26] reported on the largest study to date on HRQL among living donors. In that study, 1414 Norwegian living donors, spanning four decades of donation, completed both the SF-36 survey and a questionnaire specifically targeting kidney donation. This sample represented 76% of the 1984 living donors still alive within the Norwegian Renal Registry. When asked whether they would consent to undergoing donation again, 81% responded as 'definitely' and 14% as 'probably.' This study also highlighted the same statistically significant predictors for poor donor HRQL as previously described, mainly recipient graft loss (odds ratio 3.1), medical problems after donation (odds ratio 3.7), unrelated donor (odds ratio 2.2), and < 12 years since donation (odds ratio 1.8). Importantly, Norwegian donors receive full medical reimbursement and are provided with life-long follow-up care, considerations that might hinder comparing these results to other differing donor situations.

DM after kidney donation

Limited research has been reported to directly study the question of kidney donation and future development of type 2 DM or the effect of donation on the course of DM in a single kidney. Ibrahim et al. [27] surveyed 2919 donors, of whom 114 developed type 2 DM at a mean (SD) of 16.8 (8.7) years after donation. Male gender, BMI > 30 kg/m^2, family history of type 2 DM, and hypertension were associated with the development of type 2 DM. Of the diabetic donors, 67% were hypertensive and 17.5% were albuminuric, and in a subset with serial creatinine measurements, the annual estimated GFR change in diabetic donors (-1.8 ± 8.3 mL/min/1.73 m^2) was comparable to the rates in two control groups, i.e. non-diabetic donors (with a similar duration after the uninephrectomy) and the published rates in microalbuminuric diabetics with two kidneys [28].

In efforts to potentially expand the eligibility of living donation, Okamoto et al. [29] investigated the potential effect of kidney donation on individuals with pre-existing impaired fasting blood sugar levels. In all, 444 live kidney donors from one Japanese centre were divided into two groups based on the results of a 75-g oral glucose tolerance test; 71 had an impaired glucose tolerance pattern (GI), and 373 did not. The incidence of perioperative complications was no higher in the GI group than in the non-GI group (4.3% vs 5.4%, respectively). Survival rates in the GI group at 5, 10 and 20 years were 98.3%, 95.1% and 89.2%, respectively, whereas those in the non-GI group were 98.0%, 96.1% and 91.5%, with no statistical significance [29]. Although these single-centre study results suggest that individuals with identified early stages of glucose impairment might have no long-term consequences from donation, the current standard is to discourage any individual with a known history of glucose impairment, overt type 2 DM, or those with a strong family history of diabetic kidney disease, from donation. Further research is needed to better determine if individuals with impaired fasting glucose levels are appropriate candidates for donation.

Pregnancy after kidney donation

Previous small studies of kidney donors suggested no significant differences in maternal or fetal outcomes compared with the general population [30]. However, none compared pregnancies before and after donation in the same donor. A more recent and a larger study from Norway showed that the adjusted risk of pre-eclampsia was significantly higher in pregnancies after donation, at 5.7%, compared with before donation, at 2.6%. This finding raises concerns, given that pre-eclampsia might have long-term renal consequences [31,32]. Ibrahim et al. [33] reported on the largest experience to date on pregnancy in kidney donors, by survey sampling 1785 female donors. Fetal and maternal outcomes in pregnancies after donation were comparable to published rates in the general population.

Women who had both pregnancies both before and after donation were more likely to have adverse maternal outcomes (gestational diabetes, hypertension, proteinuria, and pre-eclampsia) but no adverse fetal outcomes in their pregnancies after donation. After adjusting for age, parity and other demographic characteristics, having a pregnancy after donation remained a risk factor for both adverse fetal and maternal outcomes. Moreover, donors who had pre-eclampsia had an increased prevalence of proteinuria and hypertension. A proteinuria prevalence of 40% in women who had hypertension or pre-eclampsia is comparable to the 20–40% reported rate of microalbuminuria 3–5 years after pregnancies seen with pre-eclampsia or gestational hypertension in women with two kidneys [34]. However, these rates of hypertension and proteinuria in donors with complicated pregnancies are significantly higher that those reported in kidney donors in general. Given that women of childbearing age are the largest group of kidney donors, the effects of donation on maternal and fetal outcomes should be part of the routine discussion of donation risk. Women should routinely be asked at the time of donor evaluation about their history of gestational complications, and those with pregnancy-induced hypertension or pre-eclampsia should probably be discouraged from donation, particularly if they wish to have children after donation.

Unresolved issues related to kidney donation

Obesity

The realm of living kidney donation is not immune to the global epidemic of obesity within the developed world. It is well appreciated that individuals with this condition are more prone to develop functional and structural changes in the kidneys [35]. Of most significance is the observation that obesity can lead to a marked increase in the GFR, higher likelihood of systemic hypertension, proteinuria, and ESRD. Heimbach et al. [36], at the Mayo Clinic, investigated perioperative complications rates and renal function after donation in 553 healthy obese donors who had a laparoscopic nephrectomy, compared to non-obese controls. Although the duration of surgery was longer by 19 min and the total number of perioperative complications (mainly minor wound infections) was greater in obese donors, there was no significant difference in major surgical complications. Similarly, after 12 months, there was no significant difference in either iothalamate-based GFR or microalbuminuria. Importantly, in this study, careful selection criteria were ap-

plied to obese donors, based on the absence of hypertension, family history of DM, or cardiovascular disease.

Noguiera et al. [37] reported the renal outcomes of 36 obese donors with mean follow-up of 6.8 years after donation. In 17 of the donors the estimated GFR was 30–59 mL/min, 15 had developed hypertension, and seven had evidence of microalbuminuria. Although limited by only 36% of invited subjects participating in the study, and potential confounding via over-representation of African-Americans, (46%), these results raise important questions about the long-term renal outcomes in obese donors. Given these concerns about renal function and surgical risk, obese donors have generally been precluded, at least the severest of cases, from becoming kidney donors. A recent survey of transplant centres indicates that 52% of programmes use a BMI threshold of 35 kg/m^2, while 10% of programmes decline donors with a BMI of >30 kg/m^2 [38].

Controlled hypertension before kidney donation

Traditionally, patients with diagnosed hypertension are excluded as potential kidney donors. However, it is very clear that the criteria for excluding hypertension have become less rigorous over the years. In a recent survey, 47% of programmes excluded donors on any antihypertensive medication, 41% excluded donors on more than one medication and 8% excluded them if they were taking more than two antihypertensives [38]. Recommendations from the Amsterdam Forum on the Care of the Live Kidney Donor [39] for hypertension in the donors are as follows: patients with a blood pressure of $>140/90$ mmHg by ambulatory blood pressure should generally not be accepted as donors, and the preferred method of measurement is ambulatory blood pressure monitoring, particularly in those aged >55 years and those with high office-based blood pressure readings. For those with easily controlled hypertension, age must be >50 years, the GFR should be $\geqslant 80$ mL/min and they should be normoalbuminuric. Donors with hypertension should be regularly followed up by a physician.

Appropriate controls for kidney donor studies

Traditionally, to assess health outcomes, kidney donors have been compared to the general population. Given that kidney donors undergo careful screening procedures and need to meet specific eligibility criteria, comparisons to the general population are unlikely to be valid. More recent studies have attempted to account for this dilemma by using control groups adjusted for age, sex and comorbidity. Inclusion of donors from minority groups also poses a problem for selecting appropriate control groups, especially given the relative under-representation of USA minority groups in most previous studies.

Conclusion

As the prevalence of ESRD continues to rise both within the USA and internationally, live kidney donation will remain a favorable treatment option. It is of primary importance to remain cognisant of this growing demand for living donation, and yet still maintain stringent and evidence-based standards for donor eligibility and selection. Donor nephrectomy is associated with well-defined surgical risks and it is important to continue to study the long-term risks. Every effort should be made to protect living kidney donors who are risking undergoing a major surgical procedure that is not without consequences. Continued surveillance and research is needed to study the long-term health status and outcomes of living kidney donors.

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