Medical Risks in Living Kidney Donors: Absence of Proof Is Not Proof of Absence

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Living-kidney donation has become increasingly widespread, yet there has been little critical analysis of existing studies of long-term medical outcomes in living donors. This review analyzes issues in study design that affect the quality of the evidence and summarizes possible risk factors in living donors. Virtually all studies of long-term outcomes in donors are retrospective, many with large losses to follow-up, and therefore are subject to selection bias. Most studies have small sample sizes and are underpowered to detect clinically meaningful differences between donors and comparison groups. Many studies compare donors with the general population, but donors are screened to be healthier than the general population and this may not be a valid comparison group. Difficulties in measurement of BP and renal function may underestimate the impact of donation on these outcomes. Several studies have identified possible risk factors for development of hypertension, proteinuria, and ESRD, but potential vulnerability factors in donors have not been well explored and there is a paucity of data on cardiovascular risk factors in donors. Prospective registration of living kidney donors and prospective studies of diverse populations of donors are essential to protect living donors and preserve living-kidney donation.

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In 1954, the first successful kidney transplantation was performed using a kidney from a living donor: the identical twin of the recipient. Living kidney donation continued to be performed because of a good-faith belief that it would do no harm to the donor. Enthusiasm for living donation waned somewhat in the early 1980s with experimental reports of hyperfiltration after uninephrectomy and fear that living kidney donation would cause proteinuria, hypertension, and eventual glomerulosclerosis. However, these data were not borne out in human studies, and living kidney donation has steadily increased in the past several years. The number of living donors has more than doubled, from 3009 in 1994 to 6467 in 2003, and in 2001 surpassed the number of cadaveric donors (1). In addition, data showing that living-unrelated transplants have similar graft and patient survival to living-related transplants (2) have increased the number of unrelated donors, including emotionally unrelated donors. Emotionally unrelated donors have increased from 2.5% of all living donors in 1994 to 21.4% in 2004 (1).

All involved in the area of transplantation acknowledge the great contribution of living donors, and there are many safeguards in place to protect donors. However, medical exclusion criteria are variable from center to center, reflecting the uncertainty of the importance of these criteria on donor outcomes (3). In the past few years, there has been a trend in some centers to expand the eligible donor pool beyond traditional limits, motivated by and explained as a response to the increased demand for kidneys (4–8). Short-term studies have found no data contraindicating these policies, and indeed there are few specific data for many of the existing exclusion criteria for donation. However, evidence-based policies must be based on appropriate and valid studies. There has been little critical analysis of existing studies of long-term medical outcomes in living kidney donors and little examination of whether these studies meet current methodologic, epidemiologic, and statistical standards. In this review, we analyze the existing data in the context of five major issues in study design that affect the quality of the evidence—retrospective studies, power and sample size, choice of appropriate controls, inclusion of racial and ethnic minorities, and measurement limitations—summarize possible risk factors in living donors, and make recommendations for future directions.

Retrospective Nature of Existing Studies

Virtually all studies that report medical outcomes of living kidney donors at >1 yr from donation are retrospective. Although practical for evaluation of long-term outcomes, retrospective studies are vulnerable to certain methodologic pitfalls and biases that may limit their interpretability. Most important is the potential for selection bias, which may alter findings if there is a difference between included and nonincluded donors either as a result of nonparticipation or because the study investigators are unable to locate the subject. In studies that follow living kidney donors, donors in good health may be more likely to participate because of greater survival or greater ability to meet the requirements of participation. Selection bias is of greatest concern when the percentage of eligible subjects who are included is small. Table 1 illustrates the low inclusion

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Table 1. Studies of living kidney donor outcomes[a]

Author, Year	Years of Follow-Up, Mean (Range)	Postnephrectomy Findings *versus* Comparison (Statistical Significance)	N[b]	Participation Rate (%)[b]
Bertolatus *et al.*, 1985 (50)	1.2 (0.1 to 3)	SBP: 130 *versus* 118 predonation ($P < 0.05$)[c] DBP: 87 *versus* 76 predonation ($P < 0.05$)[c] Urinary albumin excretion (24-h urine collection): 9.9 *versus* 6.3 mg predonation (NS) Urinary protein excretion (24-h urine collection): 64 *versus* 78 mg predonation (NS)	21	N/A
Siebels *et al.*, 2003 (83)	3 (0.04 to 5)	Serum creatinine: 1.2 *versus* 1.2 mg/dl 1 yr postdonation (NS) Hypertension (not defined): 7 *versus* 5% predonation (N/A) Proteinuria (positive urine dipstick): 6 *versus* 0% predonation (N/A)	100	63
Rizvi *et al.*, 2005 (47)	3 (0.5 to 18)	CrCl (24-h urine collection): 87 *versus* 101 mg predonation ($P = 0.0001$)[c] Serum creatinine: 1.0 *versus* 0.8 mg/dl predonation ($P = 0.0001$)[c] Hypertension (>140/90): 10 *versus* 0% predonation (N/A) Proteinuria (>150 mg/24 h): 24 *versus* 0% predonation (N/A)	736	57
Dunn *et al.*, 1986 (13)	4.4 (0.5 to 15)	Serum creatinine: 1.18 *versus* 1.01 mg/dl predonation ($P < 0.001$)[c]	180	57
		CrCl: 85.2 *versus* 128.2 ml/min predonation ($P < 0.001$)[c]	98	31
		Hypertension (≥150/90 by questionnaire): 14.4 *versus* 0% predonation (N/A)	250	80
		Proteinuria (positive urine dipstick): 4 *versus* 0% predonation (N/A)	137	44
		Serum creatinine: 1.16 *versus* 1.02 mg/dl in age/gender-matched potential donors ($P < 0.001$)[c] CrCl (24-h urine collection): 87.7 *versus* 131.6 ml/min in age/gender-matched potential donors ($P < 0.001$)[c] SBP: 122 *versus* 123 in age/gender-matched potential donors ($P = 0.50$) DBP: 77 *versus* 78 in age/gender-matched potential donors ($P = 0.63$)	71	23
Tapson *et al.*, 1984 (64)	Short-term: 4.7 (1 to 10)	Serum creatinine: 104.0 *versus* 88.4 μmol/L predonation ($P < 0.001$)[c] CrCl (24-h urine collection): 78.3 *versus* 105.1 ml/min predonation ($P < 0.001$)[c] SBP: 133 *versus* 128 predonation ($P < 0.05$)[c] DBP: 84 *versus* 78 predonation ($P < 0.01$)[c] Hypertension (not defined): 13 *versus* 0% predonation (N/A) Proteinuria (not defined, based on 24-h urine collection): 3 *versus* 0% predonation (NS)	38	N/A
	Long-term: 13.5 (10 to 21)	Serum creatinine: 98.6 *versus* 87.2 μmol/L predonation ($P < 0.01$)[c] Cr l (24-h urine collection): 83.3 *versus* 101.4 ml/min predonation ($P < 0.01$)[c] SBP: 144 *versus* 130 predonation ($P < 0.01$)[c] DBP: 90 *versus* 80 predonation ($P < 0.01$)[c] Hypertension (not defined): 38 *versus* 0% predonation ($P < 0.05$)[c] Proteinuria (not defined, based on 24-h urine collection): 0 *versus* 0% predonation (NS)	37	N/A
Miller *et al.*, 1985 (18)	6	Hypertension (≥160/90 or on antihypertensives): 31 *versus* 0% predonation (N/A)	29	14
		Hypertension (≥160/90 or on antihypertensives): 40 *versus* 13% in race/age/gender-matched controls ($P = 0.11$)	15	7
		Serum creatinine: 1.2 *versus* 1.0 mg/dl predonation ($P < 0.001$)[c]; 1.19 *versus* 1.05 in race/age/gender-matched controls ($P < 0.001$)[c]	45	22
Borchardt *et al.*, 1996 (21)	6.4 (0.7 to 24)	Hypertension (SBP >140 or on antihypertensives): 23 *versus* 42% in age-matched general Austrian population (N/A)	22	19
Chavers *et al.*, 1985 (10)	7 (1 to 22)	Urinary albumin excretion (24-h urine collection): 6 *versus* 7.7 mg in potential donors (NS)	129	80
Fehrman-Ekholm and Thiel, 2005 (84)	7	Hypertension (DBP > 90): 34 *versus* 13% predonation (N/A) Albuminuria (>5 mg albumin/mmol creatinine): 9 *versus* 3% predonation (N/A)	91	70

Table 1. Continued

Author, Year	Years of Follow-Up, Mean (Range)	Postnephrectomy Findings *versus* Comparison (Statistical Significance)	N^b	Participation Rate (%)[b]
Wiesel *et al.*, 1997 (42)	8	Serum creatinine: 1.3 *versus* 1.0 mg/dl predonation (N/A) Hypertension (not defined): 27 *versus* 0% predonation (N/A) Proteinuria (not defined): 19 *versus* 0% predonation (N/A)	67	57
Toronyi *et al.*, 1998 (63)	8.9	Hypertension (not defined): 17 *versus* 0% predonation (N/A)	30	38
Bahous *et al.*, 2005 (15)	9.3 (4 to 18)	CrCl (calculated by Cockroft-Gault equation): 86.2 *versus* 107.6 ml/min per 1.73 m^2 predonation ($P < 0.0001$)[c] SBP: 130 *versus* 114 predonation ($P < 0.0001$)[c] DBP: 82 *versus* 69 predonation ($P < 0.0001$)[c] Hypertension (140/90): 18.8 *versus* 0% predonation ($P < 0.0001$)[c]	101	41
Hakim *et al.*, 1984 (11)	>10	Urinary protein excretion (24-h urine collection): 188 *versus* <50 mg in age/gender-matched potential donors ($P < 0.01$)[c]; men: 212 *versus* 63 mg in outpatient controls ($P < 0.01$)[c]; women: no difference *versus* outpatient controls, means not given	52	87
		Hypertension (DBP >90): Men: 60 *versus* 18% predonation ($P < 0.003$)[c] *versus* 28% in age/gender-matched potential donors ($P < 0.02$)[c] *versus* 17% in normal controls (N/A); women: 30 *versus* 10% predonation (NS) *versus* 14% in age/gender-matched potential donors (NS) *versus* 20% in normal controls (NS)	51	87
Torres *et al.*, 1987 (26)	>10	Hypertension (combined "borderline" >140/90 and "definite" >160/95): 35 *versus* 26% predonation (N/A)	90	63
Talseth *et al.*, 1986 (12)	11 (10 to 12)	CrCl (24-h urine collection): 87 *versus* 108 ml/min per 1.73 m^2 predonation (N/A) SBP: 140 *versus* 132 predonation ($P < 0.003$)[c] DBP: 90 *versus* 82 predonation ($P < 0.001$)[c] Proteinuria (urine dipstick positive for albumin): 13 *versus* 0% predonation (N/A)	68	92
		SBP: 140 *versus* 132 in controls (NS) DBP: 90 *versus* 85 in controls ($P < 0.05$)[c] Urinary protein excretion (24-h urine): 105 *versus* 94 mg in controls (NS) Urinary albumin excretion (24-h urine): 7.7 *versus* 4.7 mg in controls ($P < 0.002$)[c] Albumin excretion rate: 4 *versus* 3.3 μg/min in controls ($P < 0.002$)[c]	32	43
Gossman *et al.*, 2005 (9)	11.7 (1 to 28)	Serum creatinine: 85.7 *versus* 72.5 mmol/L predonation ($P < 0.001$)[c] CrCl (24 h urine): 99 *versus* 119 ml/min per 1.73 m^2 predonation[c] Estimated GFR (modified MDRD equation): 71 *versus* 92 ml/min per 1.73 m^2 predonation SBP: 134 *versus* 125 mmHg predonation ($P < 0.001$)[c] DBP: 81 *versus* 79 mmHg predonation (NS) Hypertension (>140/90 or on antihypertensives): 30 *versus* 7% predonation	135	93
		Proteinuria (>150 mg on 24-h urine collection): 56 *versus* 0% predonation[c] Albuminuria (>50 mg/L on 24-h urine collection): 10 *versus* 0% predonation[c]	115	79
Fehrman-Ekholm *et al.*, 2001 (14)	12 (2 to 33)	Hypertension (DBP >90 or on antihypertensives): 38%, similar to age/gender-matched general population (NS)	348	87
		Mild proteinuria (<1.0 g/L on urine dipstick): 9 *versus* 0% predonation (N/A) Significant proteinuria (>1.0 g/L on urine dipstick): 3 *versus* 0% predonation (N/A)	331	82
Anderson *et al.*, 1985 (23)	12.6	Hypertension (>160/95 or on antihypertensives): 19 *versus* 21 to 27% in general Minnesota population (NS)	89	61
Watnick *et al.*, 1988 (24)	(9 to 18)	Serum creatinine: 1.06 *versus* 0.86 mg/dl in race/age/gender-matched controls ($P < 0.025$)[c] CrCl (24 h urine): 85 *versus* 109 ml/min per 1.73 m^2 in race/age/gender-matched controls ($P < 0.025$)[c] Inulin Cl: 66 *versus* 78 ml/min per 1.73 m^2 in race/age/gender-matched controls ($P < 0.025$)[c] Hypertension (>140/90 or on antihypertensives): 62 *versus* 42% in adults >50 yr old in Connecticut ($P < 0.05$)[c] *versus* 32% in race/age/gender-matched controls ($P < 0.05$)[c] Urinary albumin excretion (24-h urine): 61 *versus* 4 mg in race/age/gender-matched controls ($P < 0.05$)[c]	29	71

Table 1. Continued

Author, Year	Years of Follow-Up, Mean (Range)	Postnephrectomy Findings *versus* Comparison (Statistical Significance)	*N*[b]	Participation Rate (%)[b]
Williams *et al.*, 1986 (25)	12.6 (10 to 18)	Serum creatinine: 20% higher *versus* siblings, age-adjusted[c] CrCl: 20% lower *versus* siblings, age-adjusted[c] Hypertension (≥140/90 or on antihypertensives): 47 *versus* 35% siblings ($P = 0.41$); men: 42 *versus* 42% in age/race/gender-matched control group ($P > 0.50$); women: 50 *versus* 31% in age/race/gender-matched control group ($P = 0.16$)	38	68
		Urinary protein excretion (24-h urine collection): mean increase of 100 mg *versus* predonation[c]	19	34
		Urinary protein excretion (24-h urine collection): men: 190 *versus* 40 mg in siblings ($P = 0.001$)[c]; women: 80 *versus* 20 mg in siblings ($P = 0.08$)	38	68
Vincenti *et al.*, 1983 (20)	16 (15 to 19)	BP: 122/77 *versus* 124/78 predonation (NS) Urinary protein excretion (24-h urine collection): 141 *versus* 74 mg in age/gender-matched controls ($P < 0.005$)[c]	20	31
Iglesias-Marquez *et al.*, 2001 (41)	>20	Serum creatinine: 1.01 *versus* 0.87 mg predonation ($P = 0.10$) CrCl (24-h urine): 98.2 *versus* 125.3 ml/min predonation ($P = 0.10$) Prevalence of hypertension (not defined): 25 *versus* 22% in general population (N/A) MAP: 104.7 *versus* 89.8 predonation ($P < 0.003$)[c] Proteinuria by urinalysis: 5 *versus* 0% predonation (N/A)	20	N/A
Saran *et al.*, 1997 (49)	20 (12.5 to 31)	Prevalence of hypertension (>140/90 or on antihypertensives): 74.5 *versus* 51% in age/gender-stratified population controls ($P < 0.001$)[c] Albumin excretion rate >20 μg/min (timed overnight collection): 34 *versus* 0% in age/gender-stratified population controls ($P = 0.0003$)[c] Albumin excretion rate: median increase of 2.7 mg *versus* early postdonation ($P < 0.001$)[c]	47	62
Najarian *et al.*, 1992 (19)	24 (21 to 29)	Serum creatinine: 1.1 *versus* 1.1 mg/dl in siblings (NS) CrCl (24 h urine): 82 *versus* 89 ml/min in siblings (NS)	57	42
		Prevalence of antihypertensive medication (by questionnaire): 32 *versus* 44% in siblings (NS) SBP of those not on antihypertensives: 130 *versus* 116 predonation ($P < 0.01$)[c] *versus* 122 in siblings (NS) DBP of those not on antihypertensives: 79 *versus* 74 predonation (NS) *versus* 79 in siblings (NS)	63	47
		Proteinuria (>150 mg on 24-h collection): 23 *versus* 22% in siblings (NS) Abnormal albumin excretion (not defined): 6 *versus* 7% in siblings (NS)	52	38
Goldfarb *et al.*, 2001 (17)	25 (>20)	Serum creatinine: 1.2 *versus* 1.0 mg/dl predonation ($P < 0.001$)[c] CrCl (24-h urine): 73 *versus* 102 mg/ml per 1.73 m^2 predonation ($P < 0.001$)[c] Prevalence of hypertension (>140/90 or on antihypertensives): 48 *versus* 0% predonation ($P < 0.001$)[c] Urinary protein excretion (24-h urine collection): 230 *versus* 80 mg predonation ($P = 0.05$)	70	39

[a]CrCl, creatinine clearance; DBP, diastolic BP; MAP, mean arterial pressure; MDRD, Modification of Diet in Renal Disease; N/A, data not available; SBP, systolic BP.
[b]Numbers may vary for different comparisons within a study.
[c]Significant at $P = 0.05$.

rate of most studies: the majority have a participation rate of <80%, and seven have lower than a 50% participation rate (9–21). The results of these studies must be accepted with caution.

Power and Statistical Significance

Studies that fail to demonstrate statistical significance may do so because they are underpowered to reveal a true difference between groups. As can be seen in Table 1, the majority of

studies of long-term outcomes of living donors have relatively small sample sizes; therefore, studies with "negative" results may simply be underpowered.

One way to evaluate the adequacy of the sample size in a study is to determine the minimum detectable difference, which is the smallest difference in outcomes between two groups that could be statistically significant given the magnitude of the outcome and the number of subjects in the study. If the minimum detectable difference is larger than what would constitute a clinically important difference in outcomes, then the study is underpowered to detect clinically important differences.

Table 2 applies this approach to those living donor cohort studies with negative results. Only studies that compared donors with a control group were included, to eliminate the confounding effect of increasing BP and proteinuria with age. (Outcomes that evaluated kidney function were not included, because it is expected that function will be lower in donors than nondonors.) Minimal detectable differences were calculated using the Power Calculator offered on the UCLA Department of Statistics' web site (http://calculators.stat.ucla.edu/powercalc/). By convention, α was set to 0.05 and power was set to 80%. As is shown in Table 2, with only two exceptions, the negative studies evaluated had minimum detectable differences that were larger than the differences that were seen between donors and control subjects. This suggests insufficient power in these studies. More striking, the minimum detectable difference in most studies is far greater than what would be deemed clinically important.

Underpowered studies may provide invalid information to physicians and potential donors and undercut the need for future study. It is not possible, of course, to know whether the negative studies in Table 2 would find differences in BP or proteinuria outcomes if a larger sample of donors were included. The purpose of this analysis is simply to demonstrate that many of the "negative" studies of living donor outcomes do not rule out a true and meaningful effect of living donation on these outcomes.

Comparisons and Controls

Studies that measure outcomes without providing a comparison value for context may contribute to the body of knowledge on living donor outcomes, but they cannot be used to evaluate changes or associations in a meaningful way. The majority of studies in living donors compare postdonation to predonation values. Those that compare renal function postdonation with predonation provide little information, given the expected decrease in function with donation. Studies that compare early and late postdonation function also may be limited because of an expected age-related decline in GFR (22). Similarly, the prevalence of hypertension increases with age, making comparisons over time less informative. A separate control group may provide a more meaningful comparison, but to be valid, a

Table 2. Minimum detectable difference[a]

Study	Finding of No Difference	Minimum Detectable Difference
Dunn *et al.*, 1986 (13)	SBP: 122 *versus* 123 in age/gender-matched potential donors	7 mmHg
	DBP: 77 *versus* 78 in age/gender-matched potential donors	5 mmHg
Miller *et al.*, 1985 (18)	Prevalence of hypertension (>160/90): 40 *versus* 13% in race/gender/age-matched controls	54%
Chavers, 1985 (10)	**24-h urinary albumin excretion: 6 *versus* 7.7 mg in potential donor controls**	**3.5 mg**
Hakim *et al.*, 1984 (11)	Prevalence of hypertension (DBP >90):	
	Women: 30 *versus* 20% in outpatient controls	44%
	Women: 30 *versus* 14% in matched potential donors	43%
Anderson *et al.*, 1985 (23)	**Prevalence of hypertension (>160/95 or on medication): 19 *versus* 21 to 27% in general Minnesota population**	**12 to 13%**
Williams *et al.*, 1986 (25)	Prevalence of hypertension (≥140/90 or on medication): 47 *versus* 35% in siblings	34%
	47 *versus* 34% in age/race/gender-matched general population	34%
	Men: 42 *versus* 42% in age/race/gender-matched control group	57%
	Women: 50 *versus* 31% in age/race/gender-matched control group	42%
Najarian, 1992 (19)	Prevalence of antihypertensive medication: 32 *versus* 44% in siblings	26%
	SBP of those not on antihypertensives: 130 *versus* 122 in siblings	10 mmHg
	DBP of those not on antihypertensives: 79 *versus* 79 in siblings	**4 mmHg**
	Proteinuria (>150 mg on 24-h collection): 23 *versus* 22% in siblings	28%
	Abnormal albumin excretion (not defined): 6 *versus* 7% in siblings	23%

[a]The smallest difference in outcomes between donors and comparison group that could be statistically significant in studies with negative findings. Studies whose minimum detectable difference is within the difference found are in bold.

control group should be as similar as possible to the donor group in other characteristics that may influence outcomes. Unfortunately, several studies compare donor outcomes with those in the general population (9,21,23,24); because donors are screened carefully, they are expected to be healthier than the general population and therefore have a lower risk for developing other health problems. Studies that find outcomes in living donors to be similar to or even better than those in the general population, then, cannot be used to show that living donation does not increase medical risk among donors.

The most valid control group in studies of living donors would be composed of siblings or potential donors who are excluded for nonmedical reasons. Either of these groups would be expected to have age, race, and family history of renal disease similar to that in donors. Five studies have compared donors with siblings or potential kidney donors, and these have shown conflicting results for the impact of donation on BP, renal function, and proteinuria outcomes (10,11,13,19,25). The sum of the results of these five studies can be interpreted as showing that there is likely an increase in hypertension and proteinuria in male donors and, not unexpected, a loss of renal function of at least 20% in both genders. However, given small sample sizes and low participation rates, it cannot be determined from these studies whether similar hypertension and proteinuria risks apply to women as well or more subtle differences in BP exist in donors.

Race and Ethnicity

There is a paucity of data regarding long-term outcomes in living donors from minority populations. In 2003, 14.3% of living donors were black and 12.6% were Hispanic (1), yet few studies that evaluate medical outcomes of donors describe race or ethnicity of the study participants, and US studies that do reveal that their donors are almost exclusively white (8,24–26). There are clear racial and ethnic disparities in the development, progression, and control of disease, including those that may be especially relevant to living kidney donors.

The incidence rate of ESRD in black individuals is four times higher than in white individuals (27) and in Hispanic individuals is 1.5 times higher than in non-Hispanic individuals (28). The prevalence of hypertension in black individuals is 41% compared with 28% in white individuals (29), and black individuals with hypertension show a six-fold greater progression to ESRD than hypertensive white individuals (30). Although hypertension in Hispanic individuals is lower than that in other groups, the prevalence may be increasing (31), and Hispanic individuals have the lowest rates of controlled hypertension (32). In women, who constitute the majority of living donors, the prevalence of overweight and obesity is >50% in black and Hispanic women, compared with 34% in white women (33); obesity increases the risks for proteinuria, hypertension, cardiovascular (CV) events, and ESRD (34). Black individuals in general have a 50% higher rate of abnormal microalbumin excretion than white individuals (35) and are particularly prone to certain renal diseases, including focal segmental glomerulosclerosis and HIV nephropathy, a variant of focal segmental glomerulosclerosis that affects black individuals almost exclusively. There also are several reports of familial clustering of renal disease in black individuals with a family history of ESRD as a result of diabetes, hypertension, HIV, and systemic lupus erythematous (27,36–38).

It is possible, then, that living donors, especially living-related donors, from minority populations form a group at increased risk for developing hypertension or renal disease. Given the limited inclusion of minorities in studies of living donors and given the increased rates of renal disease in these populations in general, basing risk assessments in black and Hispanic potential donors on existing studies may be misleading.

Limitations in Measurement

Measurement difficulties limit our ability to interpret studies of BP outcomes. In several studies, measurement was not standardized, or results were determined by patient self-report (13,17,19,24,39,40), thereby increasing chances of measurement errors and decreasing the chance of detecting a true difference in BP or hypertension in donors. The definition of hypertension has changed over time, and early studies (11,12,14,18,23) used cutoff points for hypertension that would not be considered acceptable today, whereas other studies (14,41,42) provided no definition of hypertension. Further complicating these studies is a prevalence of white-coat hypertension of 20 to 43% in potential kidney donors (4,43,44). BP that is measured during donor evaluation, which may be a time of considerable stress, may not reflect a donor's true BP, and BP that is measured long after donation may underestimate changes in true BP. This may explain the finding in some studies that donors who were hypertensive at the time of donation were normotensive on follow-up (11,45).

The majority of transplant centers use creatinine clearance as determined by 24-h urine collection to estimate GFR. However, 24-h urine samples are vulnerable to under- or overcollection, and prediction equations using body weight to determine the adequacy of a collection may not be useful (46). Furthermore, because of tubular secretion of creatinine, both serum creatinine and creatinine clearance will overestimate GFR to a greater degree as renal function declines. This may lead to underestimation of decreases in renal function and the degree of renal dysfunction after donation in studies that rely on these measurements, as the majority do (11,12,17–20,23,25,40,45,47). This is demonstrated in a study by Watnick *et al.* (24), in which postdonation creatinine clearance was only modestly decreased at 85 ml/min per 1.73 m^2, whereas inulin clearance was 44% lower at 66 ml/min per 1.73 m^2.

Summary of Risk Factors

Several risk factors for bad outcomes have been identified in the existing literature and deserve special emphasis

Hypertension

BP does tend to increase after donation, and pretransplantation BP may be a determining factor. Despite the possibility of white-coat effect in potential donors, higher values of BP before donation have been shown to be associated with a greater rate

of hypertension after donation, even when BP is within normal limits (12,23,47). In one study, donors who were hypertensive at follow-up had a predonation mean BP of 133/82 mmHg, as compared with 123/79 mmHg in those who were normotensive at follow-up (12,23,47). There are few studies of the effects of donation on established hypertensive donors, but the few data that do exist suggest that it is associated with worse BP control (8,10–12,26,48).

Renal Failure

Studies that have compared early with late postdonation function have found no difference in mean function in the sample of donors (49,50). In fact, a study by Saran *et al.* (49), which compared ^{51}Cr EDTA early postdonation and then 10 yr later, found that the mean GFR had actually improved slightly at a follow-up of 20 yr. However, there is evidence that some donors may be at risk for renal failure. Studies by Talseth *et al.* (12) and Hakim *et al.* (11) identified a small group of donors, 9 and 12% respectively, whose renal function declined by >50% at least 10 yr after donation. In a study by Ramcharan and Matas (40), 2% of donors who responded to a questionnaire had advanced renal disease or had required kidney transplantation. Ellison *et al.* (51) used the Organ Procurement and Transplantation Network database to identify former living donors who had received or were awaiting kidney transplant. This analysis revealed an incidence of ESRD of 0.04% as compared with a 0.03% incidence in the general US population (52); this study likely underestimates the true rate of renal failure in donors because it does not include donors with less advanced renal failure or those who had ESRD and were not listed for transplant. These studies suggest an increased risk for important renal dysfunction after donation in certain donors.

Particular donor characteristics that confer vulnerability to renal failure in the general population have been examined in a few studies of living donors. Talseth *et al.* (12) found that the degree of renal decline after donation was inversely and independently associated with predonation systolic and diastolic BP, suggesting that higher levels of BP either interfere with compensatory hyperfiltration or promote decline in renal function. However, a recent study that evaluated renal function after donation in donors with established hypertension found no difference in serum creatinine compared with normotensive donors at a mean follow-up of 11 mo (8), although most hypertensive donors were taking an angiotensin receptor blocker, which may have offered renal protection. Najarian *et al.* (19) reported that donors with "below normal" (not defined) creatinine clearance were more likely to have siblings with "below normal" clearance than were donors with "normal" creatinine clearance, indicating a familial propensity to renal disease in these donors.

Proteinuria

Most studies that compare urinary protein with values predonation or in a control group reveal an increased amount of urinary protein or increased frequency of abnormal excretion (9,11,12,17,20,24,25,49), although the amount of urinary protein usually is small. However, studies use varying definitions of "abnormal," and rates vary widely among studies (9–12,16,17, 19–21,24,25,42,45,49,50,53). One recent study that included 18 donors with established hypertension found that none had developed proteinuria at a median follow-up of 30 mo (48). However, studies with at least 7 yr of follow-up have shown greater levels of protein excretion in donors with higher BP or established hypertension (9–11). Four studies of donors, including a meta-analysis by Kasiske *et al*. (53), have shown a greater rate of proteinuria in men as compared with women (11,25,49,53).

CV Events

Living kidney donors live longer than the general population, as shown in an often-cited study by Fehrman-Ekholm *et al.* (39). Although, as the authors pointed out, this is because living donors are healthier than the general population, the study does demonstrate that donor nephrectomy does not increase mortality beyond that in the general population. Nonetheless, uninephrectomy may increase certain CV risk factors and therefore raise the risk for CV events in otherwise healthy living donors. This topic has not been studied specifically and has not been well explored in the literature on living kidney donation.

Most living donors are left with creatinine clearances of between 70 and 90 ml/min after donation, whereas older donors or those with other CV risk factors may have a GFR of 60 ml/min or less (4,8,54,55). Given this decreased renal function in conjunction with the presence of a solitary kidney, many donors would be considered to meet criteria for chronic kidney disease (CKD). Several large studies have established that mortality and CV risk rise with even mild CKD and increase in a graded manner as renal function decreases (56–59). In the Second National Health and Nutrition Examination Survey, people with an estimated GFR of <70 ml/min had a 64% greater risk for CV death than those with a GFR of ≥90 ml/min (56).

Risk for CV events increases with increasing BP, even when BP is below hypertensive levels (60–62). In a study of the Framingham cohort, women and men with high-normal BP (130 to 139/85 to 89) had a 60 and 150% greater rate, respectively, of CV events than those with BP <120/80 (61). Several studies have found that BP not only increases after donation but also increases with time after donation; in several of these studies, increases in BP were independent of age (13,14, 47,63,64).

Most living donor studies have shown a small increase in urinary protein or albumin. Even low levels of proteinuria and microalbuminuria have been shown to be important risk factors for CV events, independent of BP, diabetes, or other cardiac risk factors (65–68). In one population study, an increase in the risk for death was seen beginning at an albumin-to-creatinine ratio of 6.7 μg/mg (68).

Abnormal serum lipid profile is a long-established marker of CV risk. Elevations in LDL and triglycerides (TG) and declines in HDL each increase CV risk by approximately two-fold in healthy adults (69). LDL and TG typically increase and HDL typically decreases as renal function declines, although it is unclear whether there is a threshold GFR below which the lipid

profile significantly worsens (70). Animal models may suggest an increase in lipids as a result of nephrectomy itself: apolipoprotein E–deficient hyperlipidemic mice that underwent uninephrectomy were found to have significantly increased total cholesterol despite similar serum creatinines (71). Although most transplant centers include serum lipid profile in their donor evaluation, there has been little study of risks that are associated with abnormal lipid levels in donors.

Obesity is an important modifiable risk factor for CV events and death (72–74). As the prevalence of obesity in the US population continues to increase (75) and more transplant centers accept obese living donors, the number of donors who face this health risk has increased. Individual risk for developing obesity increases with time (76), and this holds true for living donors as well (15,23,26,77). In a study that followed donors for at least 10 yr, there was a significant weight gain, and the mean weight at follow-up was in the obese range. The greatest weight gain was seen in donors who were already overweight at the time of donation (26). Although consensus statements encourage weight loss and healthy lifestyle education in obese donors (78), there is no evidence that this lowers obesity risks in living donors. In one prospective study of living donors, there was no change in body mas index among overweight, obese, or extremely obese donors at 1 yr after donation (5).

The effects of donor nephrectomy may impart an increase in relative risk for CV events in living donors. Although this may translate into slight increases in absolute risk in most donors, it nonetheless necessitates careful follow-up of living donors for identification of the development of risk factors and timely initiation of risk factor modification.

Discussion

The Council on Ethical and Judicial Affairs of the American Medical Association issued a report on the transplantation of organs from living donors that stated, "The risks to a kidney donor . . . are fairly well understood, have a relatively low incidence, and are considered minimal beyond the regular risks of surgery" (79). This sense of understanding, at first glance, may seem justifiable given the number of studies on living donor outcomes and the long duration of follow-up of several of these studies. When we examine many studies closely, however, we find limitations that weaken our confidence. Early in the history of living donation, it was necessary and appropriate to obtain fairly quickly data that would provide us with preliminary reassurance that donation posed no great harm. Retrospective study designs that included small numbers of subjects and comparisons with the general population were reasonable approaches at that time and have advanced the field. We should be reassured that there have been no consistent increases in BP or large decreases in GFR. However, we have not considered adequately small changes in GFR, proteinuria, and hypertension and the evidence that risk in certain donors may be enhanced by nephrectomy. We also must consider the potential long-term CV risk that is associated with such changes. Moreover, we have not evaluated these issues in donors from minority populations. The history of clinical research has taught us that extrapolation of results in white individuals to other racial and ethnic groups may underestimate the risks in a more diverse group of donors.

Moving forward, it no longer seems sufficient to base practices and consensus statements on the existing studies and the existing methods. It is time for the transplant community to call for prospective registration of living kidney donors and prospective studies of diverse populations of donors that may be compared with groups with similar compositions of race, ethnicity, and family history.

The United Network for Organ Sharing maintains a database on outcomes of living kidney donors. However, an analysis of the completeness of these data found that only 60% of 6-mo follow-up forms were returned to the United Network for Organ Sharing from transplant centers, and those forms that were returned revealed that 36% of donors already were lost to follow-up (51). It is understandably difficult to maintain a relationship with donors who wish to think of themselves as healthy individuals. However, the South-Eastern Organ Procurement Foundation reported on efforts to follow living donors with questionnaires and found an overall response rate of 90% (80). The authors attributed the maintenance of a high response rate to the fact that donors were enrolled prospectively and knew that participation was a part of their follow-up care. It is likely that registries or programs that involve hospital visits and blood tests, which are necessary to ensure adequate and accurate data, would have a lower rate of donor participation than seen in this study. However, it also is likely that if donors understand that the risks of donation are not completely clear and understand from the outset that follow-up of their health is part of the donation process, then we will be able to obtain sufficient information to gain a better understanding of risks of living donation.

How, then, in the era before the creation of a national donor registry and before the development of long-term prospective studies in diverse donor populations should we evaluate and counsel potential living kidney donors? The transplant community continues to revisit this question, most recently at the international Amsterdam Forum in 2004. The report that was generated from this meeting was published in 2005, and we direct the readers to this article for a comprehensive discussion of the currently accepted guidelines for living donation (81). As discussed in this article, however, the data on which these guidelines are based are not complete. Given these circumstances, prudence suggests the exclusion of "marginal living donors"—prospective donors with medical abnormalities that have been shown to increase overall medical risk in the general population. We should recognize that the use of marginal living donors as a response to the growing number of patients who have ESRD and are dying while awaiting renal transplantation may be in direct conflict with our responsibility to potential donors to "do no harm." A recent multicenter study of potential living donors in Canada found that acceptance of potential donors who were excluded for mild hypertension or proteinuria would have resulted in only a 3% increase in the number of patients who receive a transplant (82). Liberalization of these exclusion criteria would have a minimal impact on the waiting list and would not offset its steady growth. However, the

impact would be great for the potential donor who has hypertension and is eager to donate to his or her child. The evaluation of potential donors therefore must balance our respect for donor autonomy with our level of comfort with the risk involved. It is not paternalism but protection of our own core beliefs that prevents us from facilitating a donation that we have reason to believe may cause substantial harm to the donor. Perhaps the most compelling argument for maintenance of cautious donor acceptance criteria and for proceeding with registries and research studies is our dependence on public trust and goodwill for continuation of living-donor transplantation. If certain donor characteristics, including medical abnormalities, confer greater medical risks, then it likely will be discovered many years in the future. If the transplant community has not made appropriate efforts, through registries and research, to understand potential risks, then living-donor transplantation and the health care system will be irreparably damaged.

As Henry David Thoreau said, "To know that we know what we know, and that we do not know what we do not know, that is true knowledge." We must acknowledge to ourselves and to potential donors the limits of our knowledge and request of our donors another gift: That of continued participation in research and in registries. It is only by further study that we may truly protect our living donors and preserve the practice of living donation.

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