Medical Risks of Becoming a Living Kidney Donor

What is known and what needs to be known

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SUMMARY

- Living organ donation remains a complex ethical, moral and medical issue. The premise for accepting living donors is that "minimal" medical, psychological and financial risks of harm realized by the donor are outweighed by the definite advantages to the recipient and potential psychological benefits of altruism to the donor.

- This report focuses on the medical risks of living kidney donation for the healthy donor. There is little information on the long-term medical risks for those individuals who are not in perfect health prior to the time of being accepted for donation (i.e. those who have high blood pressure or slightly reduced kidney function prior to donation). Such 'extended criteria' donors are not considered here.

- Short-term peri-operative medical consequences are relatively well established. The peri-operative risk of death is less than 0.03%, appreciating that some donor deaths have occurred in Canada. The pulmonary embolism rate is less than 2%, and morbidity such as minor wound infections, urinary tract infections, and low-grade fever occurs in less than 10% of patients. Overall, an average hospitalization lasts less than a week and most patients feel fit enough to return to work within a month after the procedure.

- The long-term medical risks faced by living kidney donors remain uncertain and studies conducted to date have important methodological limitations. There are considerably different estimates in the literature on the long-term medical risks. Currently, in the various transplant programs in Canada and across the world, donors are provided different information on the long-term risks of this procedure.

- Based on a detailed critical review of the literature, and recognizing limitations in the existing literature:

    - It would seem that one's blood pressure increases 5 mmHg after donating a kidney above the natural increase which occurs with normal aging. A two-fold increase in the risk of developing hypertension after donation was described in one study, but not others (over 10 years approximately 18% of middle aged adults in the general population develop hypertension).

    - Kidney function (glomerular filtration rate; GFR) decreases 10 mL/min after donation, and subsequent reductions in kidney function are as anticipated with normal aging. In follow-up, approximately 13% of donors developed a GFR between 30 and 59 mL/min and 0.4% a GFR less than 30 mL/min. There have been rare cases of kidney failure after kidney donation. In cases of reduced kidney function or kidney failure after kidney donation, the extent to which donating a kidney per se was a contributing factor is uncertain. A small proportion of these individuals would have developed these outcomes even if they had not donated a kidney.

- Kidney donation results in small increases in urine albumin (increase in 66 mg/day of urine protein; in follow-up, the average urine protein was 83 mg/day in controls and 147 mg/day in donors). Higher amounts of protein are seen in donors who are followed for longer periods of time.

- No study to date, using appropriate controls, has examined whether donating a kidney increases the risk of premature death or cardiovascular disease over the long-term.

- The prognostic significance of changes in blood pressure, renal function or urinary protein after kidney donation is uncertain. In the general population, every 10 mmHg increase in systolic blood pressure and 5 mmHg increase in diastolic blood pressure is associated with a one and a half fold increase in mortality from both ischemic heart disease and stroke. Similarly, in the general population, reduced kidney function and proteinuria may be signs of systemic atherosclerosis, and both are associated with concurrent metabolic disturbances, future premature mortality, cardiovascular disease, and kidney failure. For this reason, some, but not all, consider a GFR of 30 to 59 mL/min as the pathologic state of stage 3 chronic kidney disease. However, kidney donors develop reduced kidney function or low grade proteinuria through a different mechanism, and their prognostic significance in this segment of the population remains uncertain. Likewise, whether an increase in blood pressure from kidney donation is similarly prognostic requires future consideration, as closer surveillance and early intervention in these otherwise healthy adults could offset any such risk.

- These considerations not withstanding, it may be prudent to counsel and follow all donors on modifiable risk factors which prevent hypertension, kidney disease and future cardiovascular disease.

- Unlike blood pressure measurements, routinely screening the general population to detect an elevated serum creatinine or the presence of urine protein is not recommended. However, living donors are a group who may be at higher risk of renal sequelae, and to prevent future morbidity it remains unclear which renal screening tests should be performed, how long donors should be followed, and which health care providers should be responsible for such follow-up. However, until the prognostic significance of low-grade proteinuria or reduced kidney function in some kidney donors is better understood, consideration should be given to a lifetime of annual serum creatinine and urine protein screening.

- A better understanding of long-term medical risks of becoming a living kidney donor will guide patient selection, consent, prescription cost reimbursements, and the follow-up of donors.

1. Living kidney donation – a complex ethical, moral and medical issue

Kidney transplantation, a 'miracle' of modern medicine, is the preferred treatment option for end-stage renal disease. Compared to dialysis, patients who receive kidneys have a 70% reduction in the risk of death, a dramatically improved quality of life, and reduced health care costs. As a result there are over 3000 Canadians on the waiting list for a kidney. To meet the shortage in cadaveric kidneys, rates of living kidney donation have nearly doubled over the last 10 years and will continue to rise with growing demand.

Yet despite its advantages for the recipient, living kidney donation remains a complex ethical, moral and medical issue. The premise for accepting living donors is that the "minimal" risk of short and long-term medical harm realized by the donor is outweighed by the definite advantages to the recipient and potential psychosocial benefits of altruism to the donor. The short-term medical consequences of living donation are well established. The immediate medical risk of the operative procedure is a mortality rate of 3 per 10 000, a pulmonary embolism rate of less than 2%, and morbidity such as minor wound infections, urinary tract infections, and low-grade fever in less than 10% of patients. Overall, an average hospitalization lasts less than a week and most patients feel fit enough to return to work within a month after the procedure. On the other hand, the long-term implications of living kidney donation are far less appreciated. The main medical concerns of living kidney donation are potential risks of hypertension, proteinuria and reduced kidney function. Estimates of these outcomes remain variable and inconsistent despite numerous studies in the literature. Confidence in the safety of live kidney donation will improve, if the long-term medical risks of living kidney donation are better appreciated.

Commemorative Pin
'Gift of Life' of living kidney donation
(US National Kidney Foundation)

2. Risk communication and informed consent

We recently conducted a survey of 63 health care providers worldwide (predominantly nephrologists and surgeons) who are responsible for informing potential donors of the risks of living kidney donation. Health care providers differ significantly in their beliefs of the long-term medical risks of living kidney donation. Accordingly, in various transplant programs in Canada and across the world, donors are provided different information on the long-term risks of this procedure (Table 1).

Table 1: Differing perceptions of medical risk following kidney donation.

	Proportion of health care providers* who believe the following medical risks are increased, no different, or decreased, compared to if a donor had elected not to have a nephrectomy		
	Increased	**No different**	**Decreased**
Blood pressure			
Higher systolic blood pressure than expected for age	57%	41%	0%
Higher diastolic blood pressure than expected for age	51%	47%	0%
Hypertension	44%	55%	0%
Proteinuria			
Higher 24 hour urine protein than expected for a given age	65%	33%	0%
Higher 24 hour urine albumin than expected for a given age	65%	33%	0%
Microalbuminuria (30 – 300 mg / 24 hours)	71%	29%	0%
Proteinuria (> 300 mg / 24 hours)	59%	40%	0%
Reduced kidney function			
GFR 60 to 80 mL/min *	79%	21%	0%
GFR < 60 mL/min *	53%	43%	2%
Other			
Cardiovascular disease	14%	78%	5%
Death not related to surgery	6%	82%	10%

* GFR – glomerular filtration rate, a measure of the filtering capacity of the kidney.
Healthy young adults have a GFR > 100 mL/min

3. Limitations of existing medical literature on long-term medical risks

There are a number of important limitations with existing medical research on the long-term medical risks of living kidney donation. These concerns include the suitability of controls, informative censoring due to differential losses to follow-up, biases in recall, secular challenges in applying the results to modern day donors, and interpreting the prognostic significance of certain findings in living kidney donors.

Suitability of controls: The medical and general community is mostly interested in knowing what a donor's health would be if they had elected not to donate a kidney. Studies which compared donors with transplant-eligible non-donor controls would best guide such inferences. However, in the majority of studies in the literature, controls were not assembled and followed prospectively alongside donors, and, an absence of relevant co-morbidity was not confirmed at the time the comparable donor had their surgery. While individuals accepted as kidney donors pass a rigorous set of investigations and are expected to have good long-term health, those in the general population may be less fit. Thus, the types of

controls used in the previous studies may have biased towards demonstrating no increased risk of various medical conditions after donation.

Informative Censoring: In the literature, on average 29% of surviving donors were lost to follow-up, and in some studies larger numbers of eligible donors went missing. Estimates of long-term risk may be biased, if donors who participate in follow-up systematically differ from non-participants. For example, if kidney donors who became hypertensive are more likely than others to keep in touch with their transplant physicians, then studies with greater losses to follow-up may report larger increases in blood pressure after donation.

Applying previous results to modern day donors: Many previous studies have used inconsistent definitions of important medical outcomes such as hypertension. For example, studies often relied on higher thresholds for systolic and diastolic blood pressure than used today, complicating the interpretation of these results.

Uncertain prognostic significance of some medical findings in donors: The prognostic significance of any changes in blood pressure, renal function or urinary protein after kidney donation is uncertain. In the general population, every 10 mmHg increase in systolic blood pressure and 5 mmHg increase in diastolic blood pressure is associated with a one and a half fold increase in mortality from both ischemic heart disease and stroke. Similarly, in the general population, reduced kidney function and proteinuria may be signs of systemic atherosclerosis, and both are associated with concurrent metabolic disturbances, future premature mortality, cardiovascular disease, and kidney failure. For this reason some, but not all, consider a GFR of 30 to 59 mL/min as the pathologic state of stage 3 chronic kidney disease. However, kidney donors may develop reduced kidney function or low grade proteinuria through a different mechanism, and their prognostic significance in this segment of the population remains uncertain. Similarly, whether any increase in blood pressure from kidney donation is similarly prognostic requires future consideration, as closer surveillance and early intervention in these otherwise healthy adults could offset any such risk.

4. A comprehensive literature review of long-term medical risks

Recognizing its limitations, we reviewed literature which examined the long-term medical implications of live kidney donation. In brief, we considered all studies where 10 or more healthy normotensive adults donated a kidney, and a medical outcome was assessed at least 1 year later. From screening 2588 citations, 249 full-text articles were retrieved, and 49 studies were reviewed. Non-English articles were translated. Forty-three primary authors were successfully contacted, and 31 kindly provided additional data or confirmed the accuracy of abstracted data. The 49 studies, from 28 countries, were published between 1973 and 2004. In total there were 4614 donors (Table 2).

Table 2. Characteristics of 49 Long-term Medical Outcome Studies of 4614 Live Kidney Donors

Source*	Primary Location	No. of Donors	Years of Donation	Years after donation, mean (range)	Prospective Study	Patient Age, Mean (Range), y †	Women, %	Proportion lost to follow-up, %	Incidence of hypertension, %	GFR mL/min (per 1.73 m2), 30-59%
Mimran et al, 1993	Montpellier, France	18	…	1.2 (...)	Yes	48 (20-62)	56	…	22	…
Yasumura et al, 1988	Kyoto, Japan	124	1970-1986	1.5 (...)	No	52 (21-71)	66	49	2	…
Sobh et al, 1989	Mansoura, Egypt	45	…	1.9 (1,10)	No	26 (22-64)	53	…	7	…
Friedlander et al, 1988	Iowa City, USA	12	1980-1985	2 (1,3)	Yes	36 (19-61)	75	46	45	…
Kostakis et al, 1997	Athens, Greece	255	1986-1996	2 (...)	No	60 (24-82)	74	24	0	…
Beekman et al, 1994	Leiden, Netherlands	47	1981-1988	2 (...)	Yes	36 (20-66)	49	0	0	…
Tondo et al, 1998	Parma, Italy	10	1986-1996	2.1 (0.2,5)	No	46 (...)	30	0	0	…
Hida et al, 1982	Bohseidai, Japan	34	1976-1981	2.8 (0.5,5)	Yes	56 (24-66)	59	0	…	…
Thiel, 1998	Basel, Switzerland	181	1993-1997	3 (...)	Yes	50 (25-72)	…	0	2	…
Abomelha et al, 1993	Riyadh, Saudi Arabia	70	1979-1989	3.1 (1,10)	Yes	32 (18-58)	29	64	3	…
Liu et al, 1992	St. Leonards, Australia	17	…	3.1 (0.1,10)	No	48 (27-61)	76	…	…	…
Edgren et al, 1976	Helsinki, Finland	46	…	3.2 (0.2,6)	No	... (20-74)	70	28	…	…
Siebels et al, 2003	Munich, Germany	122	1994-2001	3.2 (0.1,5)	Yes	52 (21-77)	80	24	2	…
Basseri et al, 1995	Teheran, Iran	87	…	3.2 (1,8)	No	34 (17-58)	43	0	0	…
Enger, 1973	Oslo, Norway	13	1963-1971	3.5 (0.5,8)	Yes	48 (29-65)	69	0	8	15
Ghahramani et al, 1999	Shiraz, Iran	136	1988-1997	3.6 (0.3,9)	Yes	34 (...)	…	21	24	…
Mendoza et al, 1987	Mexico City, Mexico	152	1968-1985	3.7 (0.1,12)	No	28 (...)	57	15	9	0
Rivzi et al, 2002	Karachi, Pakistan	75	1986-1999	3.8 (1,15)	Yes	40 (20-65)	61	0	4	…
Gonzalez et al, 1989	New York, USA	25	1976-1987	4.2 (0.5,12)	No	36 (20-58)	68	43	16	…
Fourcade et al, 2002	Lyon, France	99	1967-1994	4.3 (0.1,19)	No	38 (18-57)	54	0	2	6
Dunn et al, 1986	Nashville, USA	250	1970-1984	4.4 (0.5,15)	Yes	34 (18-67)	44	18	14	…
ter Wee et al, 1994	Groningen, Netherlands	15	1983	4.9 (1.5,13)	No	38 (…)	40	38	0	…
O'Donnell et al, 1986	Johannesburg, South Africa	33	1966-1984	5.8 (3,18)	No	38 (...)	45	62	33	…
Laskow et al, 1991	Birmingham, USA	48	…	5.9 (...)	No	40 (...)	52	…	…	…
Miller et al, 1985	New York, USA	47	1984	6 (2,15)	No	40 (18-60)	68	77	33	…
Rodriguez-Iturbe et al, 1985	Maracaibo, Venezuela	25	…	6 (1,11)	No	…. (20-60)	44	7	16	…
Marekovic et al, 1992	Zagreb, Yugoslavia	50	1973-1990	6.1 (1,15)	No	50 (23-69)	34	…	10	…
Prandini et al, 1987	Bologna, Italy	32	1970-1980	6.2 (5.2,17)	No	42 (22-54)	72	22	0	…
Sato et al, 1994	Sendai, Japan	97	1968-1989	6.3 (2,17)	No	60 (37-77)	…	3	…	…
Chen et al, 1992	Taipei, Taiwan	76	1980-1991	6.4 (...)	No	44 (18-66)	59	0	10	…
D'Almeida et al, 1996	Porto Alegre, Brazil	110	1977-1993	6.6 (1,14)	No	36 (...)	…	67	14	…
Gracida et al, 2003	Mexico City, Mexico	628	1992-2001	6.7 (0.5,10)	Yes	36 (18-64)	49	0	1	…
Schostak et al, 2004	Berlin, Germany	53	1974-2002	6.9 (...)	No	48 (...)	56	48	36	…
Horcickova et al, 2002	Prague, Czech Republic	93	1966-1999	7.1 (0.2,31)	No	50 (26-69)	68	…	27	…
Lumsdaine et al, 2003	Edinburgh, UK	47	1986-2000	7.1 (...)	No	... (…)	…	69	17	…
Wiesel et al, 1997	Hildelberg, Germany	67	1967-1995	8 (...)	No	... (...)	…	43	27	…
Najarian et al, 1992	Minneapolis, USA	472	1963-1980	8.3 (1,19)	No	36 (18-68)	69	25	7	…
Toronyi et al, 1998	Budapest, Hungary	30	1973-1996	8.9 (...)	No	… (...)	83	62	17	…
Haberal et al, 1998	Ankara, Turkey	102	1975-1996	10.2 (0.7,22)	No	42 (21-65)	56	32	9	…
Undurraga et al, 1998	Santiago, Chile	74	…	10.9 (1,21)	No	40 (...)	73	…	49	…
Talseth et al, 1986	Oslo, Norway	70	1969-1974	11 (9.9,12)	No	46 (33-55)	47	5	8	…
Eberhard et al, 1997	Hannover, Germany	29	1973-1990	11.1 (5.3,20)	No	... (...)	76	79	29	28
Fehrman-Ekholm et al, 2001	Stockholm, Sweden	348	1964-1995	12.5 (2,33)	No	50 (22-76)	74	13	36	…
Williams et al, 1986	Philadelphia, USA	38	…	12.6 (10,18)	No	40 (19-59)	68	32	47	8
Watnick et al, 1988	New Haven, USA	29	1969-1978	13 (9,18)	No	... (...)	45	19	62	0
Mathillas et al, 1988	Göteborg, Sweden	46	1965-1973	14.9 (10,20)	No	46 (23-70)	57	13	39	20
Saran et al, 1997	Newcastle, UK	47	1963-1982	19.6 (12.5,31)	No	... (...)	51	21	74	19
Iglesias-Marquez et al, 2001	San Juan, Puerto Rico	20	1977-1980	20 (...)	No	42 (...)	60	…	25	…
Goldfarb et al, 2001	Cleveland, USA	70	1963-1975	25 (20,32)	No	40 (19-57)	59	47	48	…

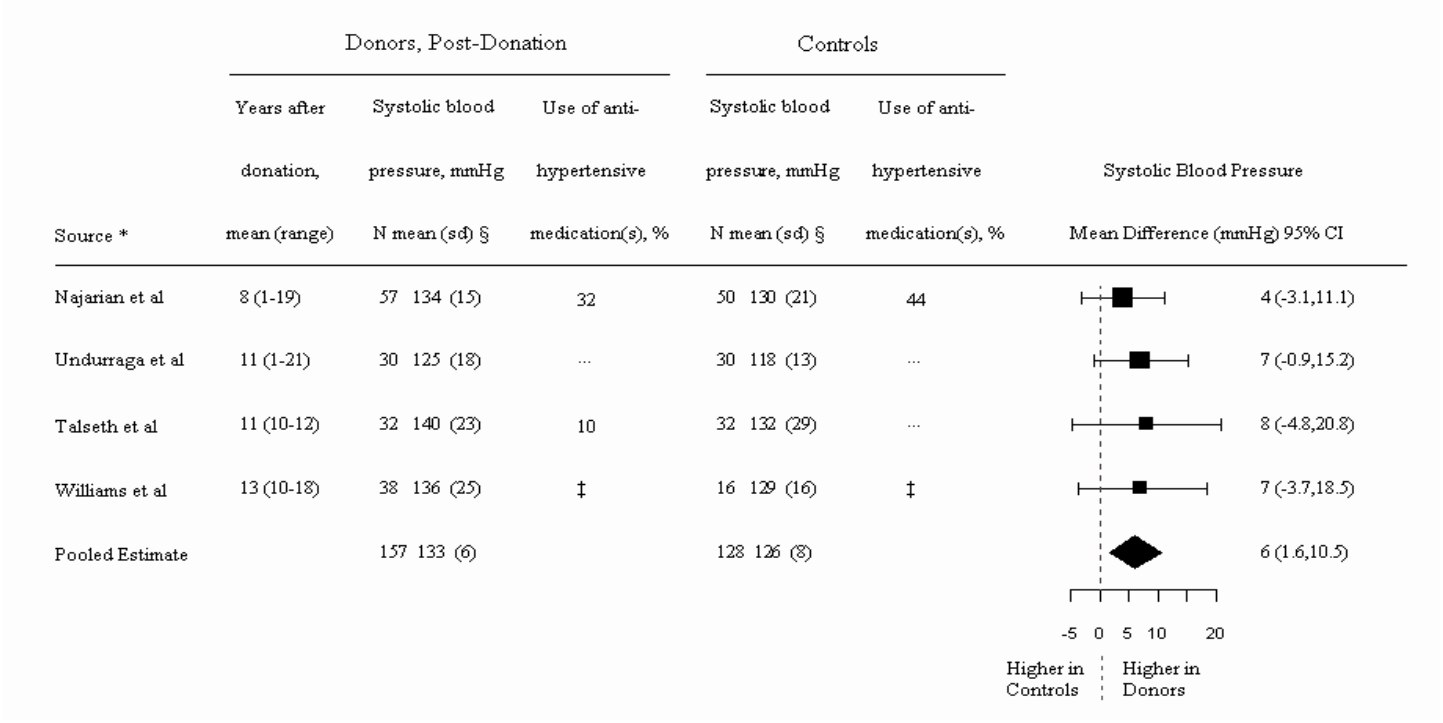
Ellipses (…) indicate not reported. † Age is reported at the time of donation. * Studies are arranged by the average number of years after donation.

Premature cardiovascular disease or death: No study to date, using appropriate controls, has examined whether donating a kidney increases the risk of premature death or cardiovascular disease over the long-term. Individuals accepted as kidney donors pass a rigorous set of investigations, and in one study they were shown to live longer than the general population.

Higher blood pressure than expected for age: It would seem that one's blood pressure increases 5 mmHg after donating a kidney above the natural increase which occurs with normal aging: We mathematically combined the results of studies where donors were compared to non-donor controls to determine whether increases in blood pressure after donation were above that attributable to normal aging. Approximately a decade after transplant surgery, compared to controls, donors demonstrated a 5 mmHg increase in blood

pressure (weighted mean 6 mmHg in systolic blood pressure, 95% confidence interval [CI] 2 to 11; weighted mean 4 mmHg in diastolic blood pressure, 95% CI 1 to 7).

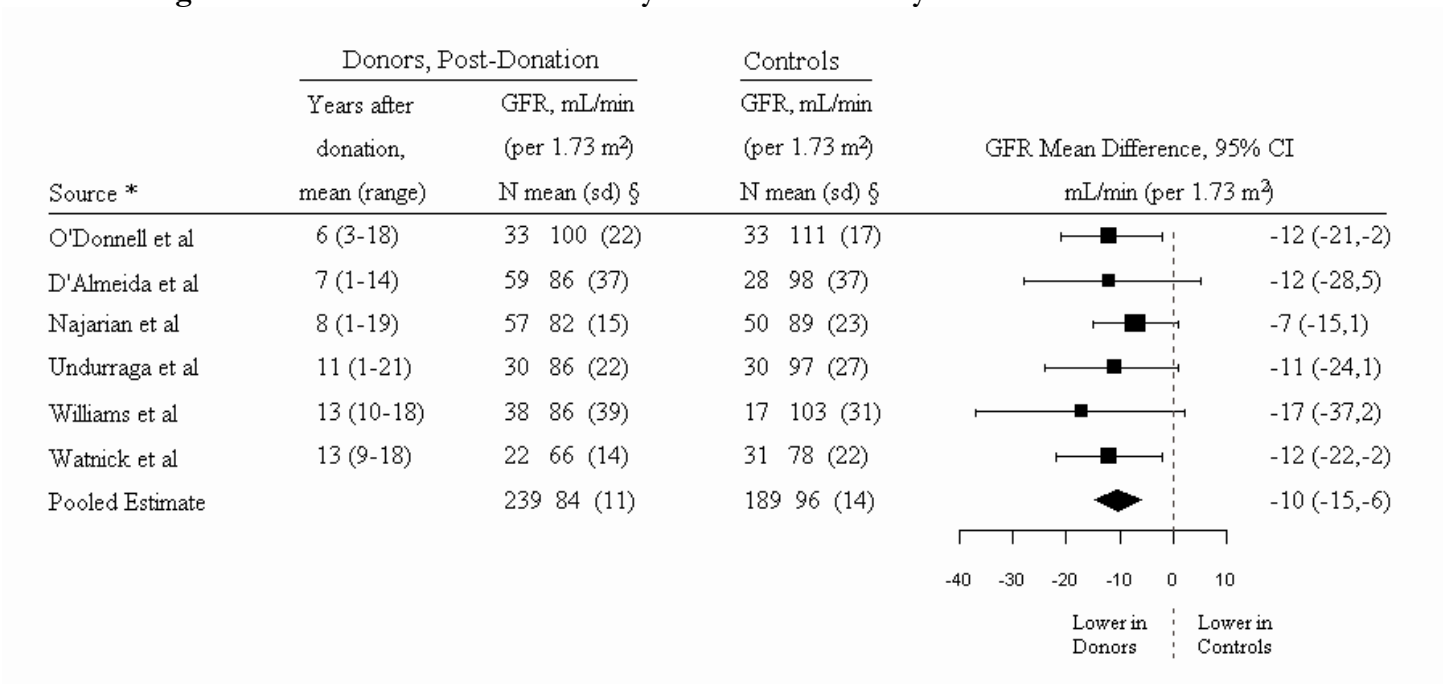
Figure 1. Controlled studies of systolic blood pressure at least 5 years after kidney donation



Hypertension: Six studies with average follow-up times ranging from 2 to 13 years after donation assessed the risk of hypertension in a total of 249 donors compared to 161 controls. A two-fold increased risk of hypertension after donation was observed in one study, but not others.

Kidney function: Kidney function (glomerular filtration rate; GFR) decreases 10 mL/min after donation, and subsequent reductions in kidney function are as anticipated with normal aging. In follow-up, approximately 13% of donors developed a GFR between 30 and 59 mL/min and 0.4% a GFR less than 30 mL/min. There have been rare cases of kidney failure after kidney donation. In cases of reduced kidney function or kidney failure after kidney donation, the extent to which donating a kidney per se was a contributing factor is uncertain. A small proportion of these individuals would have developed these outcomes even if they had not donated a kidney.

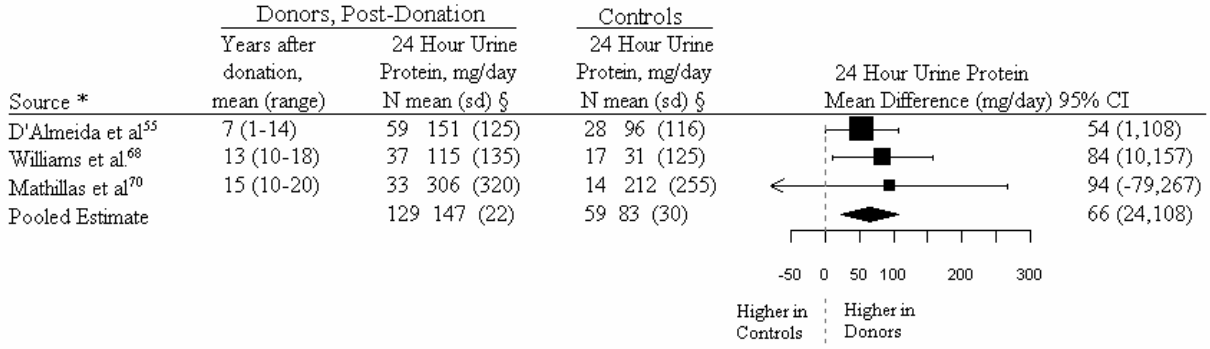
Figure 2. Controlled studies of kidney function at least 5 years after donation.



Urine protein: Kidney donation results in small increases in urine albumin (increase in 66 mg/day of urine protein; in follow-up, the average urine protein was 83 mg/day in controls and 147 mg/day in donors). Higher amounts of protein are seen in donors who are followed for longer periods of time.

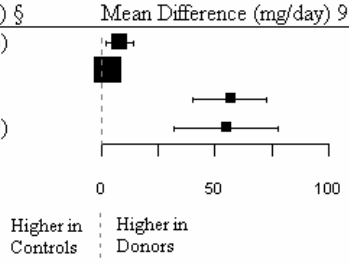
Figure 3. Controlled studies of proteinuria after kidney donation

24 hour urine protein



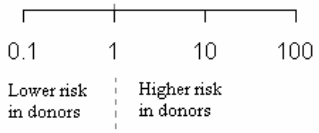
24 hour urine albumin ‡

Source *	Donors, Post-Donation: Years after donation, mean (range)	Donors, Post-Donation: 24 Hour Urine Albumin, mg/day N mean (sd) §	Controls: 24 Hour Urine Albumin, mg/day N mean (sd) §	24 Hour Urine Albumin Mean Difference (mg/day) 95% CI
D'Almeida et al[55]	7 (1-14)	59 19 (21)	28 11 (5)	8 (2,14)
Talseth et al[65]	11 (10-12)	32 8 (7)	32 5 (6)	3 (0,6)
Watnick et al [69]	13 (9-18)	22 61 (40)	31 4 (1)	57 (40,73)
Mathillas et al [70]	15 (10-20)	33 66 (66)	14 11 (9)	55 (32,78)



Microalbuminuria

Source*	Years after donation, mean (range)	Donors n/N	Controls n/N	Relative Risk of Microalbuminuria 95% CI
Sobh et al[28]	2 (1-10)	8/45	2/20	1.8 (0.4,7.6)
Watnick et al[69]	13 (9-18)	6/22	0/31	18.1 (1.1,305.3)
Pooled Estimate		14/67	2/51	3.9 (1.2,12.6)



5. The need to understand better the long-term medical risks

A better understanding of the long-term medical risks of becoming a living kidney donor will guide patient selection, consent, drug cost reimbursement, and the need for long-term surveillance.

Informed consent: Providing better estimates of long-term medical risks will improve the informed consent process for potential donors. Yet, a decision to become a donor comes out of an intense desire to help a recipient, and most would disregard any warnings of these risks. For those select donors who do carefully consider risk-benefit, or those circumstances where the recipient has strong preferences, disclosure of accurate long-term risks might influence the decision to donate. For those who consider accepting kidneys from altruistic strangers, risk-benefit can also be considered.

Donor selection: In the current era, the eligibility criteria for donation are expanding. For example, some centres now accept potential donors with a history of hypertension or other co-morbidities. There is a paucity of existing data on both donor and recipient outcomes to guide the practice of accepting such 'expanded criteria' donors.

Drug cost reimbursement and insurance: Some individuals advocate that donors should be reimbursed for their out-of-pocket expenses related to donation. For example, suppose the risk of hypertension is increased after donation. This would guide the need to reimburse anti-hypertensive prescription costs and associated higher insurance premiums.

Long-term surveillance / screening: Some screening tests, such as those for renal function or urine protein, are not recommended routinely in the general population. A better understanding of long-term medical risks would guide the use of these tests in donor follow-up to maintain good long-term health. Similarly, an understanding of the risks guides the need for health promotion, including adopting a lifestyle which reduces any long-term risks. This includes adhering to a low salt diet and a regular exercise program, early recognition of the symptoms of renal calculi or infection, the need for long-term blood pressure and renal function monitoring through a health care professional, and the avoidance of tobacco, obesity, and potential nephrotoxins. Currently, there is no consensus on best methods to coordinate such care.