

Editorial Review

Potential risks of living kidney donation—a review

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Keywords: hyperfiltration; hypertension; kidney transplantation; living donors; proteinuria; renal function

In the present review the evidence for potential risks associated with living kidney donation is summarized below and is based on PubMed/Medline literature available since the 30 April 2007.

Introduction

In recent decades, increasing interest has been shown in the concept of renal donation and its potential related consequences, particularly following original studies on the hyperfiltration damage due to renal ablation. Specifically, in humans, hyperfiltration damage following surgical kidney ablation has been observed only as a consequence of partial nephrectomy in subjects with single kidney and, in particular, in those in whom more than 75% of the kidney has been removed [1]. Current literature suggests that risks associated with living kidney donation may be acceptably low, with excellent outcomes in terms of morbidity and mortality for the donor. Moreover, renal deterioration is similar to siblings in the same family. Indeed, a number of studies, prospectively evaluating renal function and blood pressure control after nephrectomy in living donors over a period of 10–20 years, found no evidence of development of progressive renal damage [2–5]. Some other studies, characterized by a longer follow-up period (20 years or more) [6,7] and an analysis of 19 longitudinal studies (Table 1), have confirmed the safety of living donation. However, one must be cautious in interpreting these findings, as in most of these studies a significant number of donors were lost, or did not regularly attend follow-up visits.

In recent years, there has been a worldwide increase in the number of living kidney donations, which in turn has been paralleled by an increase in the number of donors requiring clinical follow up for long-term complications potentially related to donation (Table 2).

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Perioperative risks

Nephrectomy represents a major surgery intervention and thus may be associated with the development of serious complications, including bleeding (0.98–6.3%), infections (wound infection 0.6–21%; pneumonia 2.5–9.8%; urinary tract infection 6.7–7.8%) and pneumothorax (0.6–8.8%) [8–11] (Table 1). The incidence rate of these complications remains controversial, as most data originate from small studies including subjects of different age and using non-uniform criteria to define complications. Perioperative mortality associated with living kidney donation has been estimated at 0.03% [7]. However, this risk may vary, based on both the selection and preparation of donors and on the surgical technique employed. Specific European and American guidelines have been developed in order to minimize this risk [12,13]. These guidelines emphasize the importance of patient selection, primarily based on the assessment of cardiovascular risk, particularly in developed countries, which are characterized by a high prevalence of cardiovascular disease. However, serious complications may also occur following an optimal selection and preparation of the candidates. Referring to the surgical technique, nephrectomy by laparoscopy appears to result in a reduction of both recovery time and post-operative pain [14,15]. However, the use of laparoscopy may be associated with an increased risk of acute complications and bleeding [8].

Surgical risks and laparoscopy

The main problem of living kidney donation is that a healthy subject undergoes major surgical intervention for organ procurement for transplantation. Therefore, a nephrectomy should be performed in optimal

Table 1. Comparison among 18 long-term studies on subjects who underwent nephrectomy, either for kidney donation (T) or for urological causes (U)

Patients	Patients in long-term follow up	Age at donation (years)	Follow up (years)	Lab tests	Scr (average, mg/dl)	Proteinuria (>150 mg/24 h)	Hypertension (mean values or%)	Author	Journal, year	Years of donation/nephrectomy
180 (T)	70	19–57	20–32	Scr, CrCl, CG, Rolin-Hall formula	1.2 ± 0.3 2 pts CKD	0.23 ± 0.6 g/24 h	136 ± 19/79 ± 9	Goldfarb <i>et al.</i>	<i>J Urol</i> , 2001	1963–75
57 (T)	57	–	23.7	CrCl	1.1 ± 0.01	23%	32%	Najarian <i>et al.</i>	<i>Lancet</i> , 1992	1972–92
62 (U)	28 deceased 28 living	25	45	CrCl	3 pts >1.5 mg/dl	5 pts >250 mg/24h	not increased	Narkun-Burgess <i>et al.</i>	<i>Kidney Int</i> , 1993	World War II
24 (U)	24	–	–	Scr	4 pts FSGS	7 pts >441 mg/24 h	–	Zucchelli <i>et al.</i>	<i>Kidney Int</i> , 1983	–
1800 (T)	387	–	–	–	7 pts CKD	–	–	Hartmann <i>et al.</i>	<i>NDT</i> , 2003	–
459 (T)	53	22–74	>20	Scr, ⁵¹ Cr-EDTA/Iohexol	5 pts >1.5	4 pts <1 g/24 h	36%	Fehrman-Ekholm <i>et al.</i>	<i>Transplantation</i> , 1997	1964–94
13 (U)	13	–	5–30	Scr	<3.0	–	–	Foster MH	<i>Am J Kidney Dis</i> , 1991	–
20 (T)	20	–	>20	Scr, CrCl, urine test	1.01	1 pt >30 mg/dl	25%	Iglesias-Marquez RA	<i>Transplant Proc</i> , 2001	–
402 (T)	348	49 ± 11	>5	Scr, CG	1.2 ± 0.25 1 pt CKD 5 pts CrCl <30 ml/min	9% <1 g/l 3% >1 g/l	38%	Fehrman- Ekholm <i>et al.</i>	<i>Transplantati on</i> , 2001	1964–95
112 (T)	112	group 1 57.4 ± 4.3 group 2 31.4 ± 7.6	1–7	Scr	1.5 ± 0.3 1.4 ± 0.4	–	–	Kumar <i>et al.</i>	<i>J Urol</i> , 2000	1989–98
150 (T)	102	21–65	10.2	Scr, CrCl	0.89 ± 0.23 1 pt Scr 3.6	4 pts >0.1 g/24h	8.8%	Karakayali	<i>Transplat Proc</i> , 1998	1975–96
160 (T)	100	21–77	3.2	Scr, CrCl	30% >1.2	All in normal range	7%	Siebels <i>et al.</i>	<i>NDT</i> , 2003	1994–01
45 (T)	45	–	10	Scr, CrCl	0.89 ± 0.28	5 pts mild 11% microalb	7%	Sobh	<i>Int Urol Nephrol</i> , 1989	1981–89
773 (T)	125	–	20–37	Scr	3 pts CKD, 2 pts Tx	5–11%	36–38%	Ramcharan T	<i>Am J Transplant</i> , 2002	1963–79
29 (T)	29	37–70	11.1 ± 3.8	Scr, CrCl	0.7–1.6	7 pts microalb 1 pt 300 mg/l	29%	Eberhard <i>et al.</i>	<i>Clin Transplant</i> , 1997	1973–90
75 (T)	47	64 ± 9	12–31	⁵¹ Cr-EDTA	–	34% microalb	74.5%	Saran	<i>NDT</i> , 1997	1963–82
78 (T)	30	54.64	8.92	Scr, CrCl	0.8	–	5%	Toronyi E	<i>Transpl Int</i> , 1998	1973–96
102 (T)	53	45.5	7	Scr	M 1.29 F 1.02	22.6% microalb	35.8%	Schostak <i>et al.</i>	<i>Clin Transplant</i> , 2004	1974–04
152 (T)	135	45 ± 11	11 ± 7	Scr, cystatin C, CrCl, MDRD formula	0.97 ± 0.19	56% >150 mg/24h	134 ± 19/81 ± 9	Gossmann J	<i>Am J Transplant</i> , 2005	1973–01

Data are the findings at last follow-up

Scr, serum creatinine; CrCl, blood creatinine clearance; CG, Cockcroft-Gault formula; ⁵¹Cr-EDTA, radioisotopic clearance; CKD, chronic kidney disease; FSGS, focal glomerulosclerosis; Tx, renal transplantation; microalb, microalbuminuria.

Table 2. Risks of kidney living donation

Peri-operative risks
Bleeding
Fever
Infection (wound infection, abscess, urinary tract infection, pneumonia etc.)
Pneumothorax
Death
Surgical risks
Open surgery vs laparoscopy
Long-term morbidity
Proteinuria
Hypertension
Decrease of glomerular filtration rate
Long-term mortality and dialysis
Effects on quality of life
Disability
Anxiety
Depression (rarely suicide)

conditions, in order to minimize the perioperative risks for the donor [16]. Originally, laparoscopic technique in renal surgery was employed by Clayman *et al.* [17,18] at the beginning of the nineties. Subsequently, it was used by Ratner [19,20] in 1996, as an alternative to traditional nephrectomy surgery in living donors. In recent years, laparoscopic technique has evolved, now providing several approaches to kidney procurement: trans-peritoneal, extra-peritoneal, hand-assisted and with low abdominal pressure ('gasless') [21–27]. To date, more than 200 centres in the world routinely perform kidney procurement using this technique.

The use of laparoscopy may provide the advantage of decreased duration of both bed-stays in hospital and recovery time after intervention. Furthermore, this approach appears to result in reduced post-operative pain and improved aesthetic results, without increasing morbidity and mortality in donors [16,21]. On the other hand, laparoscopy may require longer operating times [25] and is potentially associated with the development of complications, including haemorrhage, need for blood transfusions and delayed bowel re-canalization [28]. The conversion to open surgery has been reported in 0–4.7% of cases and has been mainly ascribed to bleeding or technical problems [25]. However, it should be emphasized that the learning curve has a central role in laparoscopic surgery. Indeed, both operating times and rate of complications for donors and recipients are inversely related to the surgeon's expertise [29]. Furthermore, pre-interventional radiological assessment of the kidney donor by magnetic resonance or CT scan is particularly helpful, as it provides three-dimensional reconstruction of the angiographic and excretive phases, to exclude multiple accessory vessels, which would make the technique of laparoscopy quite difficult.

The use of laparoscopic technique is more beneficial for both the donor, who undergoes intervention more willingly, and the recipient, who accepts donation with minor distress, compared with the traditional

technique. Furthermore, it also appears more cost-effective, as it has been estimated to result in an economic saving of ~4000 US dollars per laparoscopic living donor transplantation [30].

In recent years, the need for organs for transplantation has led to the use of less strict admission criteria for living renal donation.

In consequence, obese subjects, who may have been previously discouraged from organ donation, may now be admitted [31]. A number of studies have evaluated short-term outcomes in terms of morbidity and mortality in obese living kidney donors. Jacobs *et al.* [28] compared safety and efficacy of laparoscopic living donor nephrectomy in both markedly obese (BMI >35 kg/m²) and control donors (BMI <30 kg/m²), matched for sex, race, age, renal function, side of donated kidney and experience level of the surgeon. In this study, laparoscopic living donor nephrectomy, although more difficult to perform in the markedly obese, was associated with an equivalent peri- and post-operative donor morbidity and recipient renal outcome. However, obese donors were more prone to develop cardiopulmonary problems [28]. Another study comparing short-term outcomes in obese (BMI >27 kg/m²) and non-obese (BMI <27 kg/m²) living kidney donors, showed, in obese subjects, both a higher rate of minor complications, mainly wound-related and longer operative times, which, however, did not result in longer hospitalization. Rates of non wound-related infections, bleeding, or cardiopulmonary events were not significantly different between the two groups [30]. Similar outcomes in terms of perioperative complications have also been reported in a more recent retrospective analysis of 553 consecutive hand-assisted laparoscopic living kidney donations [32].

Overall, these data on short-term outcomes in obese living kidney donors appear encouraging. However, studies are needed to evaluate long-term outcomes on the remaining kidney in this group of subjects particularly at risk of developing hypertension and diabetes [31].

Long-term morbidity

Hypertension, proteinuria and decrease in glomerular filtration rate (GFR) are potential long-term complications related to kidney donation. Although most of the transplant centres suggest that risks of incurring these complications may be acceptably low, we should not underestimate them. Donors with low pre-donation GFR are at higher risk of developing renal function impairment [33]. In addition, survival of the transplanted kidney is reduced when GFR of the donor is <80 ml/min [33]. Furthermore, relatives of subjects with chronic kidney disease (CKD) may have a genetic susceptibility to developing renal diseases or may develop clinical conditions, such as diabetes mellitus Type 1 and 2, systemic lupus erythematosus or arterial

hypertension, which in turn may cause the progression of a pre-existing renal injury.

Decrease in GFR

Data from a meta-analysis of 48 studies, including 3124 subjects who underwent nephrectomy and 1703 controls, showed a decrease in GFR of 17.1 ml/min on average after unilateral nephrectomy, that tended to improve every 10 years of follow-up [34]. Furthermore, data from a study on 28 veterans of the Second World War, who underwent nephrectomy as a consequence of trauma, indicated a clearance of 75 ml/min, even at 45 years following intervention [35]. Most of the studies evaluating renal function in living donors after nephrectomy found no evidence of a reduction in GFR in a follow-up period of more than 10 years [3,5]. These data have been confirmed from other studies with a follow-up period of more than 20 years [6,7]. Renal functional reserve persists after nephrectomy, but is probably reduced. However, as outlined earlier, these findings must be interpreted cautiously, as in such studies a significant number of donors were lost or did not regularly attend follow-up visits.

Increase in proteinuria

Prevalence of both proteinuria and albuminuria has been estimated at 20% [6,7] and 30–40% [2,5,6], respectively, in long term follow-up studies, with differences related to gender, the prevalence being higher in males than in females. Whether proteinuria occurs as a consequence of hyperfiltration damage, presence of comorbid conditions, such as hypertension or incipient diabetes mellitus, or as a new renal disease, remains to be confirmed by renal biopsy. A retrospective analysis of 24 subjects who underwent nephrectomy as a consequence of urological diseases showed the development of pathological proteinuria in seven subjects, with focal glomerulosclerosis being the underlying cause, as demonstrated by renal biopsy, in four of the seven patients [36]. These data suggest that hyperfiltration damage may occur in nephrectomized subjects. Furthermore, the observation of a high prevalence of focal glomerulosclerosis in subjects affected by unilateral renal agenesis [37] has led to consider that subclinical abnormalities of the contralateral kidney may predispose a minority of subjects to develop progressive damage, even in the absence of other pathological conditions. But the age at which a kidney is lost is important, to evaluate the frequency of evolution of secondary focal glomerulosclerosis.

Proteinuria should be monitored regularly after donation (proteinuria 24 h, urinary protein/creatinine ratio or urinary albumin/creatinine ratio).

Increase in blood pressure values

A number of studies have reported a prevalence of hypertension in living kidney donors, of ~50%.

This percentage is similar to that observed in the general population [5,6,38]. Consistently, in a meta-analysis, which aimed to evaluate the effects of reduction of nephron mass on renal function, nephrectomy did not appear to affect the prevalence of hypertension [34]. Another study showed significant increases in mean arterial pressure, even within the normotensive range, in normal subjects who underwent uninephrectomy and development of hypertension in 4/18 subjects [39]. Although the long-term effects of living kidney donation on development of hypertension remain controversial and require confirmation in large prospectively designed studies, there is evidence emphasising the importance of monitoring blood pressure, particularly ambulatory blood pressure [40], both before and after kidney donation [12,40,41], in order to detect early increases in blood pressure values.

Long-term mortality and risk of CKD

Post-traumatic nephrectomy in healthy subjects does not appear to be associated with increased mortality after 45 years of follow-up [35]. Data on long-term survival in kidney donors have been originally reported in Scandinavian countries since 1997 [8,42]. In a Swedish survey, 85% of the donors were alive after a follow-up period of 20 years, while the expected survival rate in the general population of the same age was 66% [42]. This increased survival may probably be explained by the selection of healthy subjects for kidney donation and the regular clinical follow-up. Furthermore, another Norwegian survey showed a similar relative risk of mortality in kidney donors and healthy controls. Thus, kidney donation does not appear to negatively impact long-term survival in appropriately selected subjects [8]. Conversely, CKD represents a possible complication. In the same Norwegian study, 7 out of 1800 donors (0.4%) developed CRF, mainly as a consequence of a primary kidney disease rather than glomerulosclerosis caused by hypertension or hyperfiltration [8]. Similarly, another recent study reported a risk of developing CKD in kidney donors of 0.2% (1/402) in Sweden and 0.5% (1/200) in Germany [43].

Data from the OPNT (Organ Procurement and Transplantation Network) database show that, in the period 1987–2002, 56 out of 6371 donors, after a follow-up period of 2–32 years from kidney donation, corresponding to a 15 years follow-up on average, have entered the waiting list for kidney transplantation. In these subjects, causes of renal failure have been hypertensive nephrosclerosis (43%), focal glomerulosclerosis (16%) and chronic glomerulonephritis (13%) [44].

Quality of life and psychosocial outcome

Long-term studies on the quality of life of renal donors were originally performed in the nineties. A Norwegian

study evaluated quality of life in 494 donors, with a mean observation time from donation of 6.7 years, by administering a standardized questionnaire including various items related to quality of life and by comparing the results with those obtained in the general population. The donors exhibited higher scores, thus indicating better quality of life.

Less than 3% of subjects at the moment of the study stated that they would not like to repeat the donation experience, and 5% regretted donation in cases where the recipient had died or had lost the kidney. In the same study, the incidence of disability pensions among the donors, who were still alive in 1998, was significantly reduced, particularly in women, compared with the general population [45].

Also in American and Japanese surveys, quality of life has been reported to be better in donors compared with the general population: <5% of donor experienced dissatisfaction and in a small number, depression or anxiety after donation was present, with rare cases of suicides. The seriousness of these rare complications cannot be overlooked [31,46,47].

Conclusion

Living kidney donation is a relatively safe and low-risk procedure. Clinical complications related to kidney donation may be reduced by careful pre-intervention selection and preparation of candidates and by a lifelong follow-up of donors after donation. The institution of dedicated outpatient collaboration with general practitioners may be helpful to meet this aim. Furthermore, national and international registries are needed to monitor healthiness and long-term complications in donors.

Conflict of interest statement. None declared.

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Received for publication: 12.10.06

Accepted in revised form: 25.6.07