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Short-, medium-, and long-term follow-up of living donors

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ABSTRACT

Live-donor kidney transplants have been performed for more than fifty years. In recent years, live donations have increased notably, given the limited availability of organs from deceased donors, and made easier by laparoscopic nephrectomy.

Although a systematic review of the literature shows that the donor has a low short- and long-term risk of morbidity and mortality, increased incidence of high blood pressure and mild proteinuria have been reported. However, no detrimental effect on renal failure is observed and the incidence of long-term chronic renal failure is lower in the donors than in the general population.

In any case, donors should be followed-up on a regular basis so that risk factors and/or intercurrent medical conditions that pose a risk to the patient can be prevented or detected early, especially those that could affect kidney function, i.e. high blood pressure, diabetes, proteinuria and obesity.

A nation-wide scientific registry would also have to be established, as well as a prospective regular data collection. This will allow for a better assessment of the long-term risk of uninephrectomy and an early detection of new medical data that would contribute to redefine the risk of kidney donation or establish new requirements in donor evaluation protocols.

Seguimiento del donante vivo a corto, medio y largo plazo

RESUMEN

Hace más de 50 años que se vienen practicando trasplantes renales de donante vivo, pero en años recientes el incremento de la demanda y la introducción de la nefrectomía por vía laparoscópica se han traducido en un significativo aumento de este tipo de trasplantes.

Aunque la experiencia publicada demuestra que la morbilidad y mortalidad del donante, a corto y a largo plazo, es razonablemente baja, existen evidencias de que algunos donantes pueden presentar un ligero incremento de presión arterial o proteinuria, sin afectar a la función renal remanente. A largo plazo, la incidencia de insuficiencia renal en los donantes renales es inferior a la observada en la población general.

Es aconsejable hacer un seguimiento clínico periódico de los donantes para prevenir o tratar los factores de riesgo y/o de complicaciones clínicas intercurrentes que pudieran comprometer su salud en general y en especial la función renal: hipertensión arterial, diabetes, proteinuria y obesidad.

También es preciso disponer de un registro científico prospectivo nacional de todos los donantes, con el fin de analizar el impacto a largo plazo de la uninefrectomía y detectar, en su caso, las posibles señales de alarma que ayudarán a modificar los criterios actuales de valoración y aceptación de los candidatos a donación y/o el cuidado clínico de nuestros donantes.

INTRODUCTION

Living-donor kidney transplantation is a treatment for chronic renal failure with excellent survival rates for the recipient and has traditionally represented a low risk to the donor.[1] The recent introduction of laparoscopic nephrectomy has dramatically improved donor recovery and reduced the physical effects of surgery. This situation, coupled with the growing demand for organs, has led to a steady increase in living donations worldwide. As a result, every year thousands of healthy individuals are becoming uninephric. This has caused great interest and some concern in the medical community and a desire to learn more about the real risk of morbidity and mortality and the long-term consequences of nephrectomy.[2-4]

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PERIOPERATIVE MORTALITY AND MORBIDITY

It has been commonly assumed that donor's risk of mortality is reasonably low, but it is quite possible that there are unpublished cases of death and that its incidence is higher than current estimates. In 1992, there were 17 reports of perioperative death in the U.S. and Canada, a figure that represents an incidence of 0.03%.[5] A few years later, the first rigorous analysis of surgery-related mortality risk was conducted by Kasiske, who also estimated 3 deaths for every 10 000 nephrectomies (0.03%).[6] More recently, a published review of 171 transplant centres in the U.S. reported the death of two donors among 10 828 cases.[7] One of deaths occurred five days after surgery due to a pulmonary condition and the second patient died of unknown causes. A third donor remained in a vegetative state after suffering an intraoperative haemorrhage with arterial hypotension. The incidence of operative mortality would once again stand at 0.03%. Even more recently, the UNOS presented data on a broader series of donors, which also counted the two donor deaths mentioned in the Matas study,[7] but in this case with a total of 15 162 nephrectomies. With no new deaths accounted for, the incidence of operative mortality dropped to 0.013%.[8] In 2006, a review of 69 studies was published comparing the impact of laparoscopy and classic laparotomy.[9] In addition to reporting on an additional previously unreported eight donor deaths due to complications from laparoscopic surgery, the review came to the conclusion that complications were related to the learning curve. In order to prevent these deaths, they suggest limiting practice to centres of excellence.

Different perioperative morbidity rates have been reported and it is partly related to the surgical technique employed (open laparotomy or the various modalities of laparoscopic nephrectomy). In general, no specific complications are referred to, with an incidence higher than 10% and the importance of each complication differs significantly within the series. The most frequent complications were pneumothorax (8%-10%),[10,11] injury to the peritoneum or intestinal tract (0.14%-6.4%),[7,10] bleeding with or without the need for transfusions (0.5%-1.5%),[8,11] infections of the urinary tract, lungs and wound (2%-17%),[5-7] pulmonary embolism (0.1%-0.5%),[8,11] reoperation for bleeding, drainage, hernias, etc. (0.5%-1%)[7,11] and a long list of possible complications that appear less frequently.

Surgical complications may be related to the type of technique used. Classic nephrectomy through open surgery is associated with a non-negligible mortality and a long convalescence. The use of laparoscopy offers faster recovery and fewer physical sequelae. The overall incidence of complications is very similar although they differ by type. Pulmonary and vascular complications are more common in open surgery (atelectasis, pneumothorax, thrombophlebitis, deep vein thrombosis), while mechanical injuries are very characteristic of laparoscopy (injuries to the splenic capsule or intestinal tract).[12] Reoperation rates are somewhat higher when using classic laparoscopy (0.84%) or hand-assisted laparoscopy (0.87%) than with open surgery (0.4%).[13] The rate of hospital readmissions is also somewhat higher, although this may be due in part to the increasing trend towards shortening hospital stays when using this technique.[13,14] The renal graft may also suffer the consequences of using this type of surgical technique. Recovery of serum creatinine in the recipient is somewhat slower when the extraction is performed laparoscopically. The time to creatinine nadir is longer. Long-term renal function in the recipient is similar regardless of the surgical technique used. A new method of laparoscopic nephrectomy (retroperitoneoscopic and hand-assisted) improves warm ischaemia times compared to the transperitoneal one and shows excellent renal function recovery, both in the donor and the recipient.[15] The Sokeir et al review, in addition to concluding that laparoscopy offers similar safety levels, also reported that it improves the use of analgesics, shortens hospital stay and speeds the return to working life.[9] They also noted the need for creating a living donor registry in order to better monitor all possible complications.[9]

Donor age influences graft function but does not seem to affect the proper functional recovery of the donor's remaining kidney. The degree of compensatory hypertrophy is not significantly different in older donors when compared to younger ones.[16,17] Furthermore, there are not enough rigorous studies that analyse the impact of age on donor renal function in the longer term, as reported in a recently published comprehensive review.[18]

LONG-TERM COMPLICATIONS

The causes of long-term mortality in kidney donors are similar to those observed in the general population: cardiovascular complications, cancer and traffic accidents being the most frequent.[19,20] The incidence of mortality is actually lower than expected in relation to the general population when adjusted for age and sex.[19,21]

Therefore, unilateral nephrectomy performed on a healthy individual with excellent renal function and no additional risk factors (AHT, obesity, diabetes, etc.) does not pose a long-term risk of nephropathy. Subsequent reviews of broad series with long-term monitoring confirm this statement.[19,22] Advanced age at the time of donation may influence long-term renal function deterioration but in a manner similar to that observed in the general population.

Arterial hypertension (AHT)

The incidence of AHT in long-term controlled donor series is similar to that observed in the general population and is detected more frequently, as expected, in older donors.

A careful study published recently showed that in the short term (one year after nephrectomy), donor's blood pressure remained within normal limits.[23] However, a long-term impact may exist, albeit in a clinically insignificant manner. A study[24] published more than ten years ago analysed blood pressure, albuminuria and renal function and found a certain increase in blood pressure and albuminuria compared to their previous readings, although it had no impact on renal function. A comprehensive review by a group in Minnesota[7] showed a 37% incidence of hypertension in donors with more than 20 years evolution since the nephrectomy. The same incidence (38%) was observed in a review in Sweden on 402 donors with an average of 12 years evolution since the donation.[25] Hypertension was significantly more frequent in men and lower than that observed in the general population, adjusted for age and sex. A meta-analysis published in 2006 included more than 5000 donors of which only 196 were studied prospectively. It concluded that donors had an increase in blood pressure of 5mm Hg between 5 and 10 years after the nephrectomy over what they should have at their age when compared to a control group of 161 patients[26] (Tables 1 and 2).

It is recommended that donors have periodic blood pressure checks since early detection allows for appropriate treatment and prevents the development of more serious complications.

Post-donation gestational hypertension

Two recent publications have studied the possible relationship between kidney donation and the onset of gestational problems. Reisaeter et al reviewed the experience of Norwegian donors and reported that the incidence of preeclampsia was more frequent in donors after the donation than before and was also more frequent in donors than in the non-donor control group.[27] Ibrahim et al published the experience of the Mayo Clinic and concluded that their donors also showed a higher incidence of preeclampsia, gestational hypertension and gestational diabetes after donation than before.[28] Both cases were retrospective studies that raise this issue and encourage more careful analysis should it become important when informing potential donors.

Proteinuria

Reduction of renal mass as a result of nephrectomy minimally increases protein excretion in urine. A meta-analysis by Kasiske in 1995 on a series of 1230 subjects who underwent nephrectomy for various reasons noted a slight increase of 76mg/day/decade.[29] However, the long-term incidence of proteinuria in kidney donors was quite variable depending on the series published. A comprehensive review of Swedish donors revealed a mild incidence of proteinuria (<1g/l) in 9% and a more severe incidence (>1g/l) in 10 donors (3%).[25] In this latter group, the time since donation was 20 years for all except one patient. In general, proteinuria was associated with hypertension and a lower glomerular filtration. Similar results (19% proteinuria >150mg/24h and 7% proteinuria >800mg/24h) have been reported by a group in Cleveland who analysed 70 donors with more than 25 years of evolution.[30] Using a series of 113 donors with more than 20 years of evolution, the Minnesota group reported that 10% of subjects had proteinuria.[7] In more than half of these (6%), the degree of proteinuria was insignificant. In the same study, 58 donors were studied after more than 30 years since nephrectomy. Proteinuria was significant in only 5% of the proteinuric donors. A meta-analysis that included more than 5000 donors concluded that donors show a slight increase in proteinuria compared to the control group[31] (147mg/day and 83mg/day respectively) (Table 3).

We must once again emphasise the importance of early detection of proteinuria since early administration of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor antagonists (ARA) may be particularly useful.

Renal failure

The renal function of the remaining kidney sufficiently compensates for the decrease in renal mass. Normally, serum creatinine and glomerular filtration reach 70%-80% of pre-nephrectomy levels and remain stable over the years. Older donors or those whose filtration rate is at the lower normal limit may see serum creatinine levels significantly affected. Short-term renal function recovery is worse the older the donor is and the higher the BMI is at the time of donation. Furthermore, it will also be worse the lower the glomerular filtration.[32] Black donors also have a worse recovery of baseline glomerular filtration.[33] In a review of 97 donors in our centre with an average evolution of 17 years, only six had serum creatinine levels above 1.3mg/dl. Five out of these six donors were older than 70 years at the follow-up.[21]

Table 1. Meta-analysis of controlled studies on systolic blood pressure in donors with a minimum follow-up of 5 years

Donors after donation				Controls			
Years after donation, mean (range)	No.	SBP, mean (SD) mm Hg	Use of anti-hypertension drugs %	No.	DBP, mean (SD), mm Hg	Use of anti-hypertension drugs %	SBP mean difference (95% CI), mm Hg
8 (1-19)	57	134 (15)	32	50	130 (21)	44	4 (-3.1 to 11.1)
11 (1-21)	30	125 (18)	NA	30	118 (13)	NA	7 (-0.9 to 15.2)
11 (10-12)	32	140 (23)	10	32	132 (29)	NA	8 (-4.8 to 20.8)
13 (10-18)	38	136 (25)	NA	16	129 (16)	NA	7 (-3.7 to 18.5)

Modification of Boudville et al[26]

SBP: Systolic blood pressure, NA: Not available.

Cases have been reported of donors who have developed chronic renal failure and required replacement therapy. A comprehensive review published by the American UNOS registry in 2002 reported 56 patients on transplant waiting lists that had previously been donors.[34] The predominant cause for the nephropathy was nephroangiosclerosis (36%), with 16% suffering from focal glomerulosclerosis. It is important to mention that the donor and recipient were siblings in 86% of the cases. The average time between donation and inclusion in the waiting list was 15 years.

Recently, a broader and more lengthy analysis of donors from a single centre (University of Minnesota) was published that, among other issues, also analysed renal function evolution. The conclusion of this study was that the incidence of renal failure among donors was similar to the general population.[35] In Japan, the long-term incidence of renal failure in a single centre study was 0.7% and there were no differences in the general population, although it should be noted that the statistical analysis was very simple.[36] Lastly, a comprehensive meta-analysis by Garg et al concluded that the initial deterioration of renal function some donors experienced was not accompanied by accelerated deterioration at 15 years.[31]

Currently, long-term prospective and systematic monitoring of donors is recommended and those who develop hypertension should be treated promptly. We also need to highlight the importance of an accurate study on baseline renal function during the evaluation of a donor as candidate. In addition to the serum creatinine values, it is essential to correctly determine glomerular filtration. Potential donors with low glomerular filtration must be ruled out, as they are likely to have poor renal function after nephrectomy. In addition, it is important to remember that low glomerular filtration in the donor also affects the graft. As can be expected as a consequence of the reduced renal mass, a low filtration rate increases the incidence of graft chronic

Table 2. Meta-analysis of controlled studies on diastolic blood pressure in donors with a minimum follow-up of 5 years

Donors after donation				Controls			
Years after donation, mean (range)	No.	SBP, mean (SD), mm Hg	Use of anti-hypertension drugs %	No.	DBP, mean (SD), mm Hg	Use of, anti-hypertension drugs, %	SBP mean difference (95% CI), mm Hg
6 (3-18)	33	83 (10)	3	33	78 (9)	NA	5 (0.4 to 9.7)
8 (1-19)	63	80 (8)	32	50	80 (11)	44	0 (-3.5 to 3.5)
11(1-21)	30	86 (13)	NA	30	79 (9)	NA	7 (1.7 to 12.9)
11 (10-12)	32	90 (10)	10	32	85 (10)	NA	5 (0.1 to 9.9)
13 (10-18)	38	85 (25)	NA	16	82 (16)	NA	4 (-7.6 to 14.5)

Modificado de Boudville et al.[26].

DBP: Dyastolic blood pressure; NA: Not available

Table 3. Meta-analysis of controlled studies of proteinuria in kidney donors

Donors after donation			Controls		
Years after donation, median (range)	No.	UAE 24h, mean (SD), mg/day	No.	UAE 24h, mean (SD), mg/day	Mean difference in UAE 24h (95% CI), mg/day
7 (1-14)	59	19 (21)	58	11 (5)	8 (2 a 14)
11 (10-12)	32	8 (7)	32	5 (6)	3 (0 a 6)
13 (9-18)	22	61 (40)	31	4 (1)	27 (40 a 73)
15 (10-20)	33	66 (66)	14	11 (9)	55 (32-78)

Modification of Garg et al[31]

UAE: urinary albumin excretion

nephropathy, accelerating post-transplant renal failure and shortening graft survival. Furthermore, it increases the incidence of hypertension and proteinuria and, as a result, increases the risk of cardiovascular complications.

CONCLUSION

Living-donor kidney transplants have been performed for more than fifty years and the published experience reports that donor morbidity and mortality in the short and long term are reasonably low. Furthermore, there is evidence that donors may show a slight increase in blood pressure and proteinuria, although remaining renal function is not significantly affected.

Regular clinical follow-up of donors is recommended to prevent or treat risk factors and/or intercurrent clinical complications that may pose a risk to the donor's health or renal function.

A scientific registry should be established, as well as a prospective regular data collection. This will allow for a better assessment of the long-term risk of uninephrectomy and an early detection of new medical data that would contribute to redefine current criteria for kidney donation and establish new requirements in donor evaluation protocols.

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