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Very long-term follow-up of living kidney donors

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Summary

Knowledge of the very long-term consequences of kidney donors has not been previously reported extensively. The 398 persons who had donated a kidney between 1952 and 2008 at Necker hospital were contacted. Among the 310 donors who were located, the survival probabilities for this population were similar to those of the general population and end stage renal disease incidence was 581 per million population per year. All located donors still alive were asked to complete a medico-psychosocial questionnaire and give samples for serum creatinine and urinary albumin assays. Among the 204 donors who responded to the questionnaire, mean eGFR was 64.4 ± 14.6 ml/min per 1.73 m^2 and mean microalbuminuria was 27.0 ± 83 mg/g. Most donors never regretted the donation and consider that it has no impact on their professional or social lives. Among the 59 donors who gave a kidney more than 30 years ago (mean 40.2 years, range 30–48 years) had a mean eGFR of 67.5 ± 17.4 μmol/l, a mean microalbuminuria level of 44.8 ± 123.2 mg/g and none was dialyzed. In conclusion, living kidney donation does not impact survival, kidney function, medical condition or psychological or social status over the very long-term.

Introduction

The first renal transplantation from a living donor was performed during Christmas night 1952 at Necker hospital [1]. This ethical and medical revolution generated passionate debates. The birth of transplant immunology and knowledge of the concept of immunosuppression prompted the initiation of the living donation program at this hospital. Since then, progress in surgical techniques resulted in kidney donation becoming a universally recognized method of transplantation, which yields superior results than cadaveric donation [2]. Currently, living kidney donation programs constitute the most promising means of compensating for organ shortage and is promoted by many organizations [3].

Because of the stringency of the donor selection process in terms of medical conditions, most kidney donors were relatively young [4]. Consequently, such donors will spend most of their lives with one kidney, but will remain exposed to the same classical kidney disease risk factors as their age-matched peers. Although it is widely accepted that kidney donation is safe in terms of kidney function and patient survival, these data are based on studies both limited by the length of the follow-up period and number of subjects studied [5–7]. A very long-term follow-up of large cohorts of patents is therefore helpful to better reflect the consequences of kidney donation in terms of kidney function and survival. Furthermore, the long-term consequences of kidney donation have been evaluated in terms of global health change and quality of life, but

specific psychological and social impacts remain to be established. The particularly long time that elapsed since the earliest living kidney donation at our institution offered the opportunity to report on living kidney donors for a longer follow-up than previously published.

The study presented here analyzed survival, kidney function, and incidence of end stage renal disease (ESRD), as well as the medical, social, and psychological status of a cohort of persons who have donated their kidney between 1952 and 2008 and compared them to the general population. We also focused on the 59 donors who have donated a kidney more than 30 years ago, the oldest donors population analyzed to date.

Patients and methods

Study population

From December 1952 to January 2008, 398 kidney transplantations with a living donor were performed in the Transplant Unit at Necker hospital in Paris (Supplemental table 1). In January 2008, we attempted to contact all persons who had donated a kidney at Necker Hospital since 1952. We consulted telephone directories and asked recipients for their specific donor's contact information. ESRD and vital status were ascertained for all located donors through reports from the subjects themselves or from their families. We also asked for them to complete a medico-psychosocial questionnaire and to report results, if available, of urinalysis and serum creatinine testing. Eighty-eight subjects, most of them were living abroad, could not be located. Overall, 310 donors or their families were located. Of these, 44 were dead and 266 were still alive as of January 2008. Of the 266 living donors, 255 agreed to complete a medical and psychosocial questionnaire (Tables 1 and 2), and 204 donors did return the questionnaire (Fig. 1).

Table 1. Characteristics of the 204 subjects who responded to the questionnaire. Continuous variables are expressed as means ± SD, categorical variables are expressed as *n* (%).

Donors characteristics	*n* = 204
Male gender	85 (42%)
Age at donation (years)	41.4 (13.0)
Family ties	
Sibling	120 (58.9%)
Ancestor	60 (29.4%)
Spouse	20 (9.8%)
Other	4 (2%)
Follow-up time (years)	16.8 ± 16.1
Pregnancy	19 (16.0%)
Diabetes	9 (4.4%)
Dyslipidemia	40 (19.6%)
Cardiovascular diseases	13 (6.4%)
Hypertension	37 (18.1%)
Pain	23 (11.3%)
Dialysis	0
Weight (kg)	71.4 ± 14.2
Systolic blood pressure (mmHg)	128.1 ± 12.1
Diastolic blood pressure (mmHg)	76.1 ± 10.8
Serum creatinine (μmol/l)	99.6 ± 21.7
eGFR (MDRD)	64.4 ± 14.6
Proteinuria (g/g creatinine)	0.1 ± 0.3
Microalbuminuria (mg/g creatinine)	27.0 ± 83.4

Table 2. Answers to the psychosocial questionnaire in 204 donors.

Donors characteristics	*n* = 204
1. Did the donation drive you to change your job? (yes)	6 (3%)
2. Did you change your habits because of the donation? (yes)	29 (14%)
3. How do you characterize your health status?	
Very good	69 (34%)
Good	82 (40%)
Rather good	43 (21%)
Pretty bad	8 (4%)
No answer	2 (1%)
4. Did you ever think that your current health status was partly the consequence of your donation?	
Never	161 (79%)
Sometimes	30 (15%)
Quite often	3 (1.5%)
Often	1 (0.5%)
No answer	9 (4%)
5. Did the recipient present with medical problems since transplantation?	
No problem	60 (29%)
Some problems	59 (29%)
Several problems	20 (10%)
Many problems	24 (12%)
The recipient is dead	33 (16%)
No answer	8 (4%)
6. Did the recipient present with psychosocial difficulties since transplantation?	
No problem	123 (60%)
Some problems	23 (11%)
Several problems	10 (5%)
Many problems	4 (2%)
The recipient is dead	31 (17%)
No answer	13 (6%)
7. Did you ever regret your donation?	
Never	197 (96.5%)
Sometimes	4 (2%)
Quite often	2 (1%)
No answer	1 (0.5%)
8. Did the donation exert a beneficial impact on your personal and social life?	
This kidney donation changed my life	32 (16%)
Much impact	38 (19%)
Average impact	27 (13%)
Low impact	20 (10%)
No impact	78 (38%)
No answer	9 (4%)

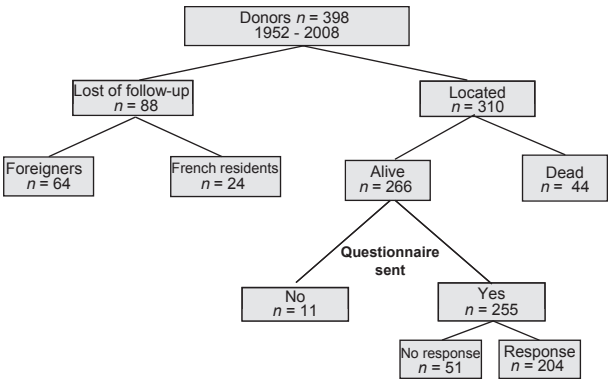

Figure 1 Flow chart of 398 kidney donors.

Instead of using a validated health-related quality of life questionnaire as SF-12 and SF-36 [8,9], which would have brought only generic data, we chose to evaluate how donors perceive the consequences of this experience over the time. Because no validated questionnaire exists on this theme, a psychosocial questionnaire has been created for this study by an expert psychologist in the field of the psychosocial evaluation of living donors and their recipients (http://www.agence-biomedecine.fr/professionnels/donneur-vivant.html). This questionnaire (Table 2) included eight items (questions with 'yes' or 'no' answers for items 1 and 2 and 'open' questions with graduate answers for items 3, 4, 5, 6, 7, and 8).

Age, gender, family ties with the recipient, pregnancy, diabetes, dyslipidemia, cardiovascular disease, hypertension, renal disease, dialysis, and weight were recorded in the medical part of the questionnaire. Estimated Glomerular Filtration Rate (eGFR) was estimated using the Modification of Diet in Renal Disease (MDRD) study equation [10]. Urinary albumin excretion rate was calculated according to the albumin to creatinine ratio in an early-morning urine sample.

Statistical analysis

Categorical variables are presented as percentages and continuous variables as mean ± SD. Survival probabilities for kidney donors were compared with those of the general population using life tables (http://www.mortality.org). These tables provided the yearly probability of dying according to each year of age, each year of follow-up and by gender. The survival of the general population was calculated using the Ederer II method using the 1952–2008 follow-up period [11]. According to this method, the expected survival was estimated until the end of follow-up. For a given subject, we thus provided his/her expected mortality by year of follow-up for a given year. The rate of ESRD in the French population was obtained from the 2009 annual data report REIN (www.soc-nephrologie.org/REIN/index.htm) and in the US population from the 2010 annual data report of the United States Renal Data System [2]. The R statistics packages were used for all analyses (http://www.r-project.org).

Results

Survival and ESRD incidence in located kidney donors

As of January 1, 2008, a total of 266 (67%) donors were alive and 44 (11%) were documented as having died. The mean age of donors at the time of death was 69.9 ± 15 years with a M/F ratio of 24/20. Death occurred 29.6 ± 12.7 years after donation. The cause of death remain unknown for 17 donors; among the remaining 27, cardiovascular disease accounted for 16% of all deaths, cancer for 14% and dementia for 14%. Other causes were accidents (12%) and infections (7%). Donor survival was not different from the survival of the general population (Fig. 2). The ESRD occurred in three donors: two dialyzed donors died and one is still alive, but did not respond to the medico-psychosocial questionnaire. The estimated incidence of ESRD in these donors was 567 per million population per year, compared with an incidence adjusted for age and region of 450 per million population per year in France (www.soc-nephrologie.org/REIN/index.htm).

Kidney function and psychological assessment in the 204 patients who responded to the psychosocial questionnaire

The characteristics of the 204 donors who responded to the medico-psychosocial questionnaire are detailed in Table 1. Most of the donors are Caucasian in this center.

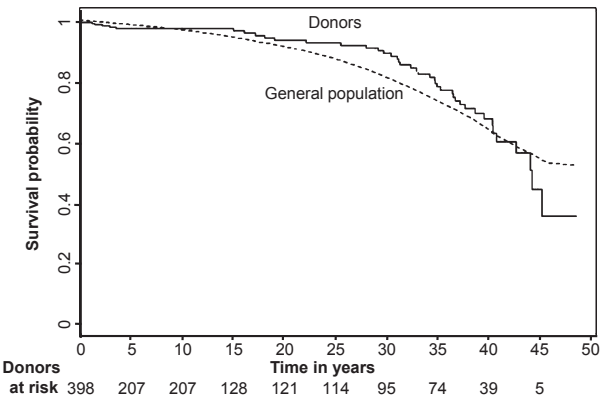

Figure 2 Survival of kidney donors compared with controls from the general population. The survival of the general population was calculated using Ederer II method using the 1952–2008 follow-up period [11], and survival probabilities for kidney donors were compared with those of the general population using life tables (http://www.mortality.org).

Of note, donors who responded to the questionnaire were older than those who did not (mean age ± SD: 57.5 ± 13 vs. 50.1 ± 15, $P = 0.001$). Otherwise, the groups were similar. From the time of donation, an average of 16.8 ± 16.1 years has elapsed. Biological data were available for 93% of the 204 patients who responded to the questionnaire. Mean serum creatinine level at the time of the study was 99.6 ± 21.7 μmol/l, and eGFR was 64.4 ± 14.6 ml/min per 1.73 m^2. Proteinuria was 0.1 ± 0.3 g/g of creatinine and microalbuminuria was 27.0 ± 83.4 mg/g of creatinine. At the time of the study, 37 patients (18%) had hypertension, and 9 patients (4.4%) were diabetic.

The assessment of the long-term psychosocial consequences of kidney donation showed that most of the subjects felt that the donation did not impact their habits, jobs or quality of life (Table 2). Indeed, only 3% changed their job, 14% their habits, and 4% of them perceive their current health status as 'pretty bad'. The great majority (79%) of the donors considered that donation had no direct consequences on their current health status. Most of kidney donors who completed the questionnaire (97%) never regretted the donation and many of them perceived a beneficial impact of this experience (16% 'changed my life'; 19% 'much impact'; 13% 'average').

Kidney function more than 30 years after donation

Among the 68 subjects who donated their kidney more than 30 years ago, 59 responded to the questionnaire. The mean follow-up duration was 40.2 ± 3.9 years, mean age of donors was 71 ± 9 years at the time of eGFR measurement, and 50.7% of them were female (Table 3). The mean serum creatinine level was 93.2 ± 22.5 μmol/l and the eGFR was 67.5 ± 17.4 ml/min per 1.73 m^2. Mean albuminuria was 44.8 ± 123.2 mg/l. No patient had an eGFR that was less than 30 ml/min per 1.73 m^2 and ESRD did not occur. Twenty-one (36%) were hypertensive and 4 (7%) were diabetic, less than observed in the general population [12, see also www.who.int/diabetes/facts/en/diabcare0504.pdf]. Fifty-four (91%) donors considered that donation had no direct consequences on their current health status, 56 (97%) never regretted the donation and 46 (77%) of them perceived a beneficial impact of this experience. These results suggest in the oldest donors population ever described that kidney function and medical status remain satisfactory.

Table 3. Kidney function of the 59 subjects 30 years after donation.

Donors characteristics	*n* = 59
Male gender	29 (49.3%)
Age (years)	71 ± 9
Follow-up time (years)	0.2 ± 3.9
Hypertension	21 (36%)
Diabetes	4 (7%)
Serum creatinine (μmol/l)	93.2 ± 22.5
eGFR MDRD (ml/min/1.73 m^2)	67.5 ± 17.4
Proteinuria (g/g creatinine)	0.1 ± 0.3
Microalbuminuria (mg/g creatinine)	44.8 ± 123.2

Discussion

The results presented here show that long-term medical and psychological costs of kidney donation are limited. Donors' survival was similar to that of the general population, and their kidney function remained excellent. In addition, the psychosocial impacts of kidney donation were limited. We also characterized the renal function of kidney donors who had donated more than 30 years ago. This constitutes the oldest donor population described to date.

We found that relatively few donors had moderate decrease in eGFR and no one had severe decrease of eGFR. Our results support the notion that kidney donation does not negatively impact medical condition, even in the very long-term. These good results could be explained, at least in part, by the fact that kidney donors constitute a highly selected population at baseline not representative of the age-matched general population. Moreover, kidney donation may influence habits and may make donors more attentive to the management of their risk factors, even if most of them answered that donation has no impact on their habits in this study. Conversely, the comparison of kidney donors with the general population may have some caveats as these two populations have not been selected with the same criteria. Criteria for retaining living kidney donors might have changed over time as illustrated by a 2007 survey of U.S. transplantation centers [13]. It reported that, compared with data from 1995, centers were accepting an increased number of potential donors who were older or presented with hypertension. However, in our cohort the survival was not impacted by such a phenomenon.

Overall, our findings confirm recently published data indicating that kidney donors can expect a normal life span and health status without excessive risk of ESRD [14, 15]. Regarding eGFR, our results are close to those of Ibrahim *et al.*, who found that the mean eGFR in 255 kidney donors was 63.7 ± 11.3 ml/min per 1.73 m^2 compared with 64.4 ± 14.6 ml/min per 1.73 m^2 in our population of donors [14]. Moreover, eGFR of kidney donors was 65 ± 17.6 ml/min per 1.73 m^2 more than 30 years after donation, suggesting that eGFR remains stable, even over the very long-term. These results are similar to the estimated age-matched GFRs of the National Health and Nutrition Examination Surveys (NHANES) III

(www.cdc.gov/nchs/nhanes/nh3data.htm). Of note, donors eGFR decline paralleled normal, age-related, mGFR decline (51Cr-EDTA measured GFR) in a French cohort (Dr Marc Froissard, personal communication, and http://www.rein-eform.org/data/FlashConfs/2009/97/Media/index.htm). GFR were estimated using the MDRD study equation, which could constitute a potential caveat, as measuring tracer clearance is a more accurate method than creatinine-based equations [16]. However, the respective performances of eGFR and mGFR in the kidney donor population, especially when the individual's GFR is >60 ml/min per 1.73 m^2, remains to be established. Therefore, the use of the MDRD study equation remains the best method to estimate the GFR based on serum creatinine levels [17]. Interestingly, the results reported by Ibrahim *et al.* suggest that estimating kidney donor GFR with the MDRD formula could underestimate the GFR when compared with the mGFR measured via iohexol® clearance [14]. Taken together, these data suggest that eGFR using the MDRD study equation is an acceptable method for estimating GFR in healthy subjects who donated a kidney. Importantly, creatinine was measured in a centralized lab.

In addition, kidney donation had a very limited impact on the professional and social life of the donors, and most of them had beneficial consequences and never regretted their donation. These data are of importance because information regarding very long-term psychological and social consequences of kidney donation is lacking [18]. Although both physical health and mental health summary scores have been shown to be excellent in a large population of kidney donors [14], they only indirectly reflect the social and psychological impact of kidney donation over the long-term. Validated scores, such as the SF-12 and SF-36 scores, are useful methods for comparing the quality of life regarding physical and mental health status between various medical conditions, including kidney donation [19], but do not specifically address questions related to living kidney donation [8,9]. Even though the questionnaire used in our study is not validated, it integrates univocal and critical questions regarding the psychological and social consequences of kidney donation, which relate closely to each donor. A small proportion of the donors did not respond to the questionnaire and the reasons why remain unknown. We cannot exclude that donors did not respond to the questionnaire for psychological reasons, as they are not doing well, that could slightly influence our conclusions. The findings that donors never regretted their donation and that donation did not impact their social or psychological well-being is an extremely important information that should be conveyed to the potential donors to promote organ donation.

The principal limitation of our study is the response bias that is inherent to its nature. Sixty-five percent (204 of 310) of the located donors responded to the questionnaire. Although this is an acceptable proportion of nonresponse, the reasons for this were not analyzed and we cannot exclude medical or psychological reasons related to the donation. Overall, taking into account loss of follow-up and nonresponse to the questionnaire, we analyzed 51% of all of the subjects who had donated a kidney at our institution since 1952, which is an important proportion with regard to other retrospective studies [14] and representative of the initial population of kidney donors. Another limitation is related to the ethnicity of the population we studied, which is predominantly of Caucasian origin. Therefore, our results may not be applicable to all ethnic groups including African-Americans.

In conclusion, we surveyed the largest and oldest population of living kidney donors to date and found that their life span and kidney function is similar to that of the general population. Very long-term psychosocial consequences of donation appeared limited, and the great majority of donors did not regret their donation.

Author contribution

CF: collected data. NP: wrote the article. ZC and PL: performed statistical analyses. SP: performed psychosocial assessment. HK, AM, MOT and CL: involved in living kidney donation management. CL: designed the study.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. All donors characteristics. Continuous variables are expressed as means ± sd, categorical variables are expressed as n-(%).

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References

1. Legendre C, Kreis H. A tribute to Jean Hamburger's contribution to organ transplantation. *Am J Transplant* 2010; **10**: 2392.
2. USRDS 2010 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States. In: National Institutes of Health ed. *System USRD*. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases, 2010.
3. Abecasis M, Adams M, Adams P, *et al.* Consensus statement on the live organ donor. *JAMA* 2000; **284**: 2919.
4. Delmonico F. A report of the Amsterdam forum on the care of the live kidney donor: data and medical guidelines. *Transplantation* 2005; **79**: S53.
5. Fehrman-Ekholm I, Norden G, Lennerling A, *et al.* Incidence of end-stage renal disease among live kidney donors. *Transplantation* 2006; **82**: 1646.
6. Najarian J, Chavers B, McHugh L, Matas A. 20 Years or more of follow-up of living kidney donors. *Lancet* 1992; **340**: 807.
7. Ramcharan T, Matas A. Long term (20–37 years) follow-up of living kidney donors. *Am J Transplant* 2002; **2**: 959.
8. Ware J, Kosinski M, Keller S. SF-36 Physical and Mental Health Summary Scales: a user's manual. Boston: Health Assessment Lab, 1994.
9. Ware J, Kosinski M, Turner-Bowker D, Gandek B. *How to score version 2 of the SF-12 Health Survey?* Lincoln, RI: QualityMetric, 2002.
10. Klahr S, Levey AS, Beck GJ, *et al.* The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med* 1994; **330**: 877.
11. Ederer F, Heise H. Instructions to IBM 650 programmers in processing survival computations. Methodological note No. 10, End Results Evaluation Section. Bethesda, MD: National Cancer Institute, 1959.
12. Hajjar I, Kotchen JM, Kotchen TA. Hypertension: trends in prevalence, incidence, and control. *Annu Rev Public Health* 2006; **27**: 465.
13. Mandelbrot DA, Pavlakis M, Danovitch GM, *et al.* The medical evaluation of living kidney donors: a survey of US transplant centers. *Am J Transplant* 2007; **7**: 2333.
14. Ibrahim H, Foley R, Tan L, *et al.* Long-term consequences of kidney donation. *N Engl J Med* 2009; **360**: 459.
15. Segev DL, Muzaale AD, Caffo BS, *et al.* Perioperative mortality and long-term survival following live kidney donation. *JAMA* 2010; **303**: 959.
16. Stevens L, Coresh J, Feldman I, *et al.* Evaluation of the modification of diet in renal disease study equation in a large diverse population. *J Am Soc Nephrol* 2007; **18**: 2749.
17. White C, Huang D, Akbari A, Garland J, Knoll G. Performance of creatinine-based estimates of GFR in kidney transplant recipients: a systematic review. *Am J Kidney Dis* 2008; **51**: 1005.
18. Clemens K, Thiessen-Philbrook H, Parikh C, Yang R, Karley M, Boudville N. Psychosocial health of living kidney donors: a systematic review. *Am J Transplant* 2006; **6**: 2965.
19. Clemens K, Boudville N, Dew MA, *et al.* The long-term quality of life of living kidney donors: a multicenter cohort study. *Am J Transplant* 2011; **11**: 463.