Clinical Kidney Journal, 2022, vol. 15, no. 4, 644–656

https://doi.org/10.1093/ckj/sfab271
Advance Access Publication Date: 13 December 2021
CKJ Review

CKJ REVIEW

Risk for subsequent hypertension and cardiovascular disease after living kidney donation: is it clinically relevant?

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ABSTRACT

The first successful live donor kidney transplant was performed in 1954. Receiving a kidney transplant from a live kidney donor remains the best option for increasing both life expectancy and quality of life in patients with end-stage kidney disease. However, ever since 1954, there have been multiple questions raised on the ethics of live kidney donation in terms of negative impacts on donor life expectancy. Given the close relationship between reduced kidney function in patients with chronic kidney disease (CKD) and hypertension, cardiovascular disease and cardiovascular mortality, information on the impact of kidney donation on these is particularly relevant. In this article, we review the existing evidence, focusing on the more recent studies on the impact of kidney donation on all-cause mortality, cardiovascular mortality, cardiovascular disease and hypertension, as well as markers of cardiovascular damage including arterial stiffness and uraemic cardiomyopathy. We also discuss the similarities and differences between the pathological reduction in renal function that occurs in CKD, and the reduction in renal function that occurs because of a donor nephrectomy. Kidney donors perform an altruistic act that benefits individual patients as well as the wider society. They deserve to have high-quality evidence on which to make informed decisions.

Keywords: all-cause mortality, arterial stiffness, blood pressure, cardiovascular disease, cardiovascular mortality, chronic kidney disease, hypertension, kidney donation, transplant, uraemic cardiomyopathy

INTRODUCTION

In 1954, at the age of 23, Ronald Herrick donated a kidney to his twin brother Richard [1, 2]. This was the first successful solid organ transplant in humans. However, Ronald went on to develop end-stage kidney disease (ESKD) requiring dialysis, suffered a stroke, required coronary artery angioplasty and eventually died from cardiovascular disease at the age of 79 [2]. This, and subsequent donations, raised ethical questions regarding the safety of donating a kidney, especially regarding the risks of developing cardiovascular disease [3–6]. Sixty-seven years on from Ronald Herrick's donation, can we now resolve these uncertainties? In this article, we will examine the current available evidence focusing on the risks of hypertension and cardiovascular disease associated with kidney donation to answer these questions.

Received: 1.12.2021; Editorial decision: 1.12.2021

MORTALITY AND CARDIOVASCULAR EVENTS

All-cause mortality

The phrase 'kidney donors live longer' started appearing in the medical literature following a Swedish study published in 1997 [7]. This study followed up 430 donors for up to 31 years and compared their survival with national mortality rates. Perhaps not surprisingly, given that they have been extensively screened for illness and excluded from the donation process if found to have any significant abnormality, donors had a better survival rate. This has been a consistent feature of research into donor survival. Findings from multiple studies, with up to 40 years of follow-up, have shown no evidence of reduced survival compared with the general population [8–12], and indeed many have reported better life expectancy [7, 13–19]. Several studies have sought to overcome this by using selected 'control' populations, attempting to exclude individuals with conditions that would have precluded kidney donation, such as uncontrolled hypertension, diabetes mellitus and cancer (Tables 1 and 2). Thus, these reports often describe health event rates in kidney donors and control subjects far lower than the general population. These studies are also mostly of relatively short duration, with a median follow-up of <10 years. The highly selected nature of kidney donors means that it should not be surprising that adverse events are rare, at least in the medium to short term.

Concerns relating to possible long-term adverse effects of donation arose in 2014 in an article examining 15-year outcomes in 1901 Norwegian donors and 32 621 control patients who were potentially eligible for donation [20]. The hazard ratios (HRs) for all-cause mortality {HR 1.30 [95% confidence interval (CI) 1.11–1.52)]} were significantly increased in donors with curves diverging after about 10 years. Limitations of this study included exclusion of marginal donors, an older donor group (8 years) than controls and longer follow-up of donors compared with controls. In addition, the rural area of Norway used to conduct the study has an unusually high life expectancy [21]. Nevertheless, these data are at least cause for concern and at the very least, certainly warn against complacency. A Markov medical decision analysis found that donors had a reduced life expectancy of 0.5 to 1 year as a direct consequence of donation [22]. However, this was largely based on donors having chronic kidney disease (CKD) and, as will be discussed later, this is not necessarily correct. Nevertheless, for now, most of the available evidence does not seem to indicate that kidney donation is associated with a significant increase in all-cause mortality. Indeed, a recent meta-analysis of four studies [12, 13, 18, 20], including the Norwegian study, published between 2010 and 2016 with 84 495 donors and 62 484 controls did not find any evidence of an increase in all-cause mortality in donors [pooled adjusted relative risk (RR) 0.60 (95% CI 0.31–1.10)] [23]. However, it should be noted that two of these studies contributing 97% of donors only had a median follow-up of 6.3 and 6.5 years [12, 13]. More intensive, longer-term follow-up of donor populations with suitable control groups are required. These studies are needed to counsel younger potential donors about the risks involved and any potential reduction in life expectancy. They will by their nature be difficult to fund, administrate and maintain.

Cardiovascular disease and cardiovascular events

The main observational studies exploring the relationship between kidney donation and cardiovascular mortality and events are shown in Table 1. In general, studies have shown either a decrease or no increase in cardiovascular mortality [10, 11, 15]. Similarly, studies have not shown an increase in cardiovascular events or risk of developing cardiovascular disease [12, 14, 17, 19]. A recent meta-analysis of four studies [9, 12, 20, 24] published between 2009 and 2016 with a total of 4274 donors and 53 246 controls, and an average follow-up time ranging from 6 to 15 years, found no evidence of an increase in cardiovascular risk in donors [pooled-adjusted RR 1.11 (95% CI 0.64–1.70)] [23].

These findings are perhaps surprising in the context of the strong relationship between CKD and cardiovascular disease. However, most of these studies are of relatively short duration, meaning that increased long-term cardiovascular risk cannot be excluded. To date, most studies have median follow-up periods of 6–8 years, which may be too much short to detect the adverse cardiovascular effects of donation on disease processes that may take decades to develop. Furthermore, all the same limitations that apply to studies that examine all-cause mortality apply to the studies examining cardiovascular events, especially those that relate to donor selection and control group comparisons, as well as duration of follow-up. There are also other potential explanations that relate to the degree and nature of the reduction in kidney function observed in donors. These are explored below.

Relationship between renal function and all-cause mortality and cardiovascular events

The relationship between CKD and increased all-cause and cardiovascular mortality and events is now well established, with several large observational studies showing an increased risk at estimated glomerular filtration rates (eGFRs) <60 mL/min/1.73 m^2 [25–28]. However, the really large increases in cardiovascular disease start to occur at an eGFR <45 mL/min/1.73 m^2. For example, in a study of over 1 million patients followed up for a median of 2.84 years, the age-standardized all-cause mortality per 100 person-years was 0.76, 1.08, 4.76 and 11.36 for the eGFR ranges of >60, 45–59, 30–44 and 15–29 mL/min/1.73 m^2, respectively [25]. Similarly, the age-standardized rates of cardiovascular events per 100 person-years was 2.11, 3.65, 11.29 and 21.80 for the eGFR ranges of >60, 45–59, 30–44 and 15–29 mL/min/1.73 m^2, respectively [25]. Furthermore, it should also be noted that patients with only mildly reduced eGFR without proteinuria or an elevated cystatin C have a much attenuated cardiovascular risk [29, 30].

A donor nephrectomy represents the sudden loss of approximately 50% of the nephron mass with a concomitant and proportional initial decrease in GFR. However, the remaining kidney can compensate for a significant percentage, usually somewhere between 20% and 40% of the lost function [31–35]. As a consequence of this 'adaptive hyperfiltration' studies have shown that only a minority of donors have a measured GFR consistent with stage 3 CKD. For example, a study using iohexol clearance to measure GFR in 255 donors at a mean time of 12.2 years post-donation found that only 15% of donors had a measured GFR <60 mL/min/1.73 m^2 and none had a measured GFR <30 mL/min/1.73 m^2 [9]. Furthermore, only 11% had microalbuminuria and only 1% had macroalbuminuria [9]. No donor had an eGFR <45 mL/min/1.73 m^2 and albuminuria [9]. In a prospective study of 68 donors measuring GFR isotopically, one-third had a measured GFR <60 mL/min/1.73 m^2, whereas half had an eGFR <60 mL/min/1.73 m^2 1 year post-donation [36]. Only 7% of this cohort developed microalbuminuria. The cardiovascular risk of

Table 1. Key studies examining the all-cause mortality, cardiovascular mortality and cardiovascular events associated with kidney donation

Study/year/country	Donors	Control group	Median follow-up	All-cause mortality	Cardiovascular mortality	CV events	Comments
Munch *et al.* 2021 Denmark [19]	1325	General population 11 030 Blood donors 260 494	10 years	HR 0.57 (95% CI 0.40–0.80) SIR 1.10 (95% CI 0.75–1.61)		HR 0.68 (95% CI 052–0.89) SIR 1.17 (95% CI 0.88–1.55)	Coded Registry Data
Chaudry *et al.* 2020 Denmark [17]	1262	12 620 from general population	7 years	Mortality lower in donors (2.4% versus 3.4%; P < 0.001)		CV disease 6.5% donors, 7.1% controls (P = 0.37)	Coded Registry data
De La Mata *et al.* 2020 Australia and New Zealand [16]	3253	National Population Data	6.2 years	SMR 0.33 (95% CI 0.24–0.47) CRS			Registry data linked to national death registry
Janki *et al.* 2020 Netherlands [15]	761	1522 propensity score matched from general population studies	8 years	Mortality lower in donors [OR 0.06 (95% CI 0.05–0.08)]	No difference [OR 0.13 (95% CI 0.01–1.24)]	No difference [OR 1.06 (95% CI 0.64–1.74)]	
Kim *et al.* 2020 South Korea [11]	1292	33 805 with no evidence of contraindication to kidney donation at voluntary health examination	Mean 11.4 years	No difference [HR 1.01 (95% CI 0.71–1.44)]	Donor 0.36 and control 0.36 CV deaths per 1000 patient years (P = 0.9)		Coded registry data
Krishnan *et al.* 2020 UK [14]	9750	19 071 from Primary Care Database with no contraindication to kidney donation	8 years	Mortality higher in controls [HR 3.45 (95% CI 2.40–4.96)]		CV disease higher in controls [HR 2.43 (95% CI 1.39–4.26)]	
Kiberd *et al.* 2017 USA [22]				Live kidney donation reduced remaining life expectancy by 0.5–0.9 years			Assumes reduced GFR developed as a consequence of donation the same as CKD
Reese *et al.* 2014 USA [10]	3368	3368 matched from general population cohort study with comorbidity and diagnosis exclusions	7.84 years	No difference [HR 0.90 (95% CI 0.71–1.15)]	No difference (from alternative dataset of Medicare claims)	HR 1.02 (95% CI 0.87–1.20)	Older donors, >55 years
Mjoen 2014 Norway [20]	1901	32 621 general population with age, and comorbidity exclusions	15.1 years	Donors increased mortality [HR 1.30 (95% CI 1.11–1.52)]	Donors increased CV mortality 1.40 (95% CI 1.03–1.91)		
Garg *et al.* 2012 Canada [12]	2028	20 280 matched from the healthiest segment of the general population	6.5 years	No difference in mortality between donors and controls (0.8% versus 1.8%; P > 0.05)	Death and major cardiovascular event lower in donors [HR 0.66 (95% CI 0.48–0.90)] Major CV event censored for death lower in donors [HR 0.85 (95% CI 0.57–1.27)]		

Table 1. Continued.

Study/year/country	Donors	Control group	Median follow up	All-cause mortality	Cardiovascular mortality	CV events	Comments
Berger *et al.* 2011 USA [18]	219 aged >70	219 matched from general population cohort study with no contraindication to donation.	Not given	Donors versus controls [HR 0.39 (95% CI 0.21–0.65); P < 0.001]			
Segev *et al.* 2010 USA [13]	80 347	80 347 comorbidity matched from general population cohort study	6.3 years	Mortality lower for donors (1.5%) than controls (2.9%) (log rank < 0.001)			
Ibrahim *et al.* 2009 USA [9]	3698	3698 from NHANES matched for age, sex, race and BMI.	Mean 12.2 years	No difference			
Garg *et al.* 2008 Canada [8]	1278	6359 matched randomly selected healthy residents (1:5)	Mean 6.2 years	Composite endpoint of death or CV events not different			
Fehrman-Ekholm *et al.* 1997 Sweden [7]	430	Expected survival calculated from mortality data in the general Swedish population	Data censored at 20 years	33 deaths compared with an expected 46 (P = 0.04)			

CRS, cumulative relative survival; CV, cardiovascular; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

Table 2. Key studies since 2019 examining the incidence of hypertension and change in blood pressure associated with kidney donation

Reference/year/country	Donors	Controls	Follow-up	Main results	Comments
Munch *et al.* 2021 Denmark [19]	1103	11 030 general population (coded diagnoses excluded)	Median 10 years	HR 1.11 (95% CI 0.93–1.32) for being diagnosed hypertension	Hypertension defined as redemption of prescriptions for at least two different antihypertensive drug classes
	1007	260 494 blood donors (coded diagnoses excluded)	Median 10 years	SIR 1.40 (95% CI 1.17–1.66) for starting antihypertensive medication	
Price *et al.* 2021 UK [37]	50	45 screened as per live donor protocol except for investigations requiring radiation.	5 years	No difference in 24-h ambulatory BP. Mean difference +1.91 (95% CI −2.72 to 6.54)	Prospectively collected data with 24-h ambulatory BPs
Krishnan *et al.* 2020 UK [14]	9750	19 071 from Primary Care Database with no contraindication to kidney donation	Live donors median 8.4 years Controls median 5.5 years	Controls had a lower risk of developing hypertension at 5 years but not at 10 years [OR 0.66 (95% CI 0.61–0.73) at 5 years] [OR 0.86 (95% CI 0.73–1.00) at 10 years]	Clinically assigned or BP >140/90 mmHg
Chaudry *et al.* 2020 Denmark [17]	1262	12 620 From National Registries (coded diagnoses excluded)	Median 7 years	Donors have a higher 10-year absolute risk of hypertension than controls [1.64 (95% CI 1.44–1.88)]	Hypertension defined as being on two antihypertensive medicines 7% of donors already hypertensive pre-donation on one agent
Janki *et al.* 2020 Netherlands [15]	761	1522 propensity score matched from population cohort studies	Median 8 years	New onset of hypertension lower in donors [OR 0.45 (95% CI 0.33–0.62)]	Incidence of hypertension defined as use of antihypertensive medication, systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg),
Price *at al.* 2020 UK [38]	168	138 prospectively recruited with same criteria as potential donors	1 year	Compared with baseline, at 1 year the mean within-group difference in ambulatory systolic BP in donors was 0.1 mmHg (95% CI −1.7 to 1.9) and 0.6 mmHg (95% CI −0.7 to 2.0) in controls. The between-group difference was −0.5 mmHg (95% CI −2.8 to 1.7)	Multicentre, prospectively collected data with 24-h ambulatory BP
Haugen *et al.* 2020 Norway [39]	1029	16 084 from general population studies	Mean 11.3 years	New onset of hypertension higher in donors [OR 1.25 (95% CI 1.12–1.39)]	Hypertension defined as BP >140 mmHg systolic and/or 90 mmHg diastolic, use of antihypertensive medication or clinical diagnosis
Kasiske *et al.* 2020 USA [40]	203	205 matched for age and sex evaluated as if potential kidney donors.	9 years	No difference in clinic or ambulatory BP or in incidence of hypertension. Proportion of nocturnal dipping not different	Multicentre prospective study using 24-h BP monitoring
Holscher *et al.* 2019 USA [41]	1295	8233 propensity score matched from cohort non-donor studies	6 years	Higher risk of developing hypertension in donors [adjusted HR 1.19 (95% CI 1.01–1.41)]	Self-reported incidence of hypertension

BP, blood pressure; OR, odds ratio; SIR, standardized incidence ratios.

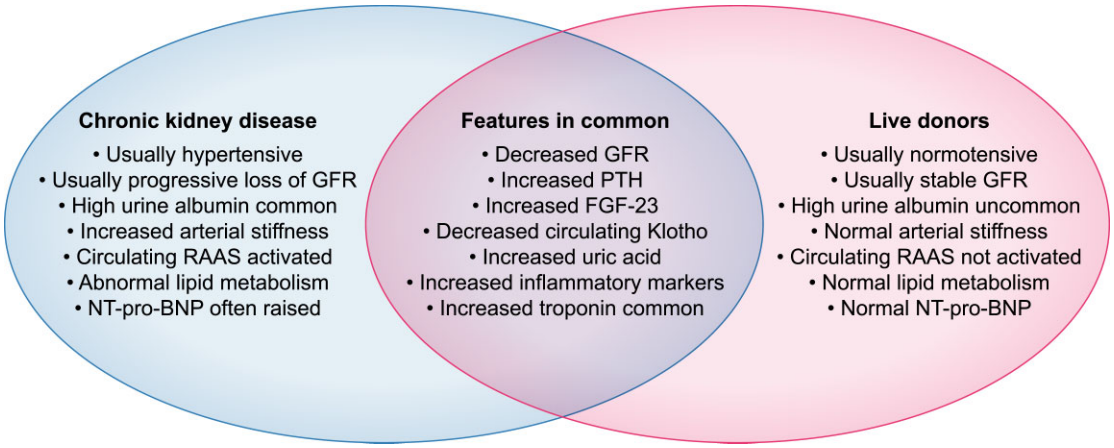

FIGURE 1: Similarities and differences between patients with chronic kidney disease and live kidney donors. Live kidney donors share some similarities with patients with chronic kidney disease. There are also some potentially important differences. FGF-23, fibroblast growth factor-23; GFR, glomerular filtration rate; NT-pro-BNP, N-terminal pro-B type natriuretic peptide; PTH, parathyroid hormone; RAAS, renin–angiotensin–aldosterone system.

the large proportion of donors who have an eGFR in the range of CKD stage 2 remains uncertain and again requires further long-term study, particularly in view of data suggesting abnormalities in cardiac function at this level of eGFR [42, 43].

In the general population, decreases in eGFR over time are also associated with an increase in cardiovascular risk [44, 45]. Also of note is that patients with stable eGFR on repeated measurements also have a markedly attenuated cardiovascular risk [46–48]. In kidney donors, however, the usual decline over time in GFR does not appear to happen [37, 40, 41, 49]. For example, in a prospective study of 203 donors and 205 carefully selected controls, donors did not experience any further decline in iohexol-measured GFR from 6 months to 9 years post-donation, whereas the GFR in controls declined by an average of 1.26 mL/min/1.73 m^2 per year [40]. Albuminuria did not increase in donors over this 9-year period either [40]. Similar findings were also observed in a 5-year prospective study of kidney donors using isotopic GFR to measure renal function. In 48 donors studied 5 years post-donation, there had been no further decline in either eGFR or isotopically measured eGFR in donors, whereas the 45 healthy controls had an annual mean reduction in eGFR of 1 ± 2 mL/min/1.73 m^2 [37].

Although there are many similarities between kidney donors and patients with CKD, there are also important differences (Figure 1). While most will have a sub-normal eGFR and a structural abnormality, it is a subject of contention as to whether kidney donors should or should not be classified, as having CKD with all the implied attendant increases risks to health. The mechanisms underlying the 'adaptive hyperfiltration' that occur in the remaining kidney are complex and influenced by several factors including age, sex, race and body size [32, 50]. Furthermore, although there is a decrease in GFR associated with ageing, if and when this process switches from being a physiological one to a pathological one also remains unclear [51–54]. Similarly, it is unclear whether the microalbuminuria observed in a minority of donors has any clinical relevance and should be used to classify donors as having CKD, irrespective of GFR [50]. Essentially, donors develop a reduced GFR and microalbuminuria through a process that does not involve the remaining kidney. The prognostic relevance of these changes, as opposed to patients with CKD acquired through different disease processes, remains to be determined.

HYPERTENSION

In the general population, every 10 mmHg increase in systolic and 5 mmHg increase in diastolic blood pressure is associated with a 1.5-fold increase in death from ischaemic heart disease and stroke [55]. It is well established that blood pressure increases with age [56] and that >80% of patients with CKD have hypertension [57]. Kidney donation could therefore potentially increase the risk of hypertension over time possibly through changes in physiology such as kidney hyperfiltration, changes in vascular tone and activation of the renin–angiotensin–aldosterone system [58]. The data on blood pressure and the development of hypertension in kidney donors are still surprisingly unclear and are subject to profound 'surveillance' bias as a result of more contacts with medical services post-donation and more frequent blood pressure measurements [8, 58].

Multiple studies have been published examining the incidence and prevalence of hypertension post-kidney donation. Most are generally small and vary greatly in methodologial rigour, blood pressure measurements, duration of follow-up, selection of control group, information presented on pre-donation characteristics and the conclusions they present on whether donation increases blood pressure and future risk of developing hypertension. A meta-analysis and systematic review published in 2006 found 48 studies from 28 countries with a total of 5145 donors followed up for an average of 7 years post-donation [59]. On average, 31% of surviving donors were lost to follow-up, potentially biasing results in either direction. Ten of these studies had healthy volunteers as control subjects. In nine of these studies, the control group appeared to be assembled at the time of donor follow-up evaluation, with only one study following up control participants prospectively. Studies with >5 years of follow-up (range 6–13 years) were reviewed to determine whether increases in blood pressure post-donation were above what could be attributable to normal ageing. For systolic blood pressure, there were four [60–63] studies (157 donors, 128 controls) and for diastolic blood pressure there were five [60–64] studies (196 donors, 161 controls). At approximately 10 years after donation, donors had a 6 mmHg (95% CI 2–11 mmHg) and 4 mmHg (95% CI 1–7 mmHg) increase in systolic and diastolic blood pressure, respectively, compared with controls. Six studies [61, 62, 65–68] examined the risk of developing hypertension

with an average follow-up period ranging from 2 to 13 years in 249 donors and 161 controls. Only one study [66] reported an increased risk of hypertension. There was marked statistical heterogeneity between the studies, so they were not pooled. However, these kinds of studies led to the widespread adoption of the 'fact' that kidney donation was associated with higher blood pressures and potentially higher rates of hypertension.

However, a subsequent meta-analysis and systematic review published in 2018 [23] examined observational studies of live kidney donors with a minimum of 1-year follow-up post-donation that provided a comparison group of control subjects that had not donated a kidney. Six studies, published between 2007 and 2016, were included in the meta-analysis for systolic and diastolic blood pressure [9, 36, 69–72] with a total of 712 donors and 830 controls. There was no difference in systolic blood pressure between donors and controls, with a standardized mean difference of 0.14 (95% CI −0.10 to 0.40) mmHg. Donors have a slightly higher diastolic blood pressure, with a standardized mean difference of 0.17 (95% CI 0.03–0.34) mmHg. Four studies examined the incidence of hypertension with a total of 1726 donors and 6949 controls and a follow-up period of 6 to 10 years [8, 9, 24, 71]. There was no increased risk observed for donors developing hypertension with a pooled adjusted relative risk of 1.08 (95% CI 0.46–2.34). The authors of this meta-analysis suggested that the different result they reported compared with the earlier systematic review [59] could be explained by better selection and matching of donor and control groups in these more recent and better quality studies [23].

Several further studies have been published since the publication of this second meta-analysis in 2018. Key studies published after 2018 are summarized in Table 2 and report varying results. Some have reported a higher incidence of hypertension compared with controls [17, 39, 41]. Munch *et al.* [19] reported no difference in the incidence of hypertension between donors selected from the general population but a higher incidence when compared with a control group selected from blood donors, once again highlighting the importance of donor group selection in these type of studies. Krishan *et al.* [14] reported that donors had a higher risk of developing hypertension than controls at 5 years but not at 10 years. Janki *et al.* [15] in a study from the Netherlands on 761 donors and 1522 propensity score-matched controls from general population cohort studies and a median follow-up period of 8 years found a lower incidence of hypertension in donors. Three studies are perhaps worthy of special mention [37, 38, 40]. All three of these studies recruited controls that had passed the selection criteria for donation except for those that required exposure to radiation. They also performed 24-h ambulatory blood pressure measurements providing a gold standard for the measurement of blood pressure and the diagnosis of hypertension. After 1 [38], 5 [37] and 9 [40] years of follow-up, none of these studies found any difference in 24-h systolic or diastolic blood pressure, nor in the incidence of hypertension.

Given the close interrelationship between CKD and blood pressure, it is perhaps surprising that a reduction in GFR post-nephrectomy is not more clearly observed in donors. However, as already discussed earlier, it is still not clear that a reduction in GFR that occurs through a non-pathological process is in fact really CKD. Blood pressure rises in CKD are thought to be caused by a number of processes including sympathetic nervous system overactivity, increased intracellular calcium, sodium retention, reversal of hypoxia-driven vasodilatation and activation of the renin–angiotensin–aldosterone system [73]. It is not established whether these processes occur as a consequence of kidney donation though at least one study showed no evidence of renin–angiotensin system activation in donors [36]. Interestingly, patients with renal cancer treated by partial nephrectomy have higher blood pressures, an increased risk of cardiovascular disease and no evidence of increased survival compared with those treated by radical nephrectomy in some, but not all, observational studies, and in the only randomized controlled trial to date [74–78]. This was despite patients treated with partial nephrectomy having higher GFR postoperatively, suggesting that the presence of damaged renal parenchyma may be driving the hypertension rather than the reduction in GFR *per se*.

For now, the available evidence suggests that any potential increase in blood pressure after kidney donation is likely to be small. High-quality, prospective long-term studies of blood pressure in kidney donors are expensive and difficult to perform. There are significant obstacles with respect to finding appropriate controls and the requirement for periods of observation of decades. Furthermore, live donor transplants are often carried out in large hospital centres involving long travelling times. In Korea, for example, just 11% of patients were followed up despite over 80% of kidney transplantation in that country involving live donors [79]. Nevertheless, these barriers need to be overcome so that potential donors have the information they require.

ARTERIAL STIFFNESS

A highly distensible aorta and arterial system buffer the oscillatory changes in blood pressure that result from intermittent ventricular ejection, ensuring that most tissues receive near steady flow with no exposure to peak systolic pressures [80, 81]. Aortic and large arterial stiffness increases with age and exposure to risk factors including high blood pressure, diabetes and CKD [80–84]. While multiple studies have shown an association between decreasing renal function, even within the normal range, and increased arterial stiffness [82–85], there still remains some controversy about whether arterial stiffness is increased in CKD independently of blood pressure and other comorbidities [86, 87].

The speed at which the pressure wave travels down an artery is inversely related to its distensibility, that is, the stiffer the vessel the faster the pulse wave velocity (PWV) [80, 81]. Carotid-femoral or aortic PWV is currently considered the 'gold-standard' measurement of arterial stiffness [88, 89]. Increased aortic PWV has been shown to be associated with all-cause and cardiovascular mortality in the general population and elderly, diabetic and hypertensive patients, as well as in patients with CKD, including those on dialysis and kidney transplant recipients [90–100].

In a cross-sectional study, aortic PWV was increased in 101 donors (12.0 ± 2.0 m/s) compared with 134 healthy volunteers (8.5 ± 1.5 m/s; $P < 0.001$) [101]. In an uncontrolled study of 45 donors, there was no difference in aortic PWV 12 months after donation (7.2 ± 1.3 m/s versus 6.8 ± 1.1 m/s; $P = 0.74$) [102]. Similar results were observed in another uncontrolled study of 21 donors at 12 months [103]. In a prospective controlled study, aortic distensibility, measured using magnetic resonance imaging, was slightly reduced in 45 donors compared with 40 controls [difference in change between groups −0.57 (95% CI −1.09 to -0.06×10^{-3} $mmHg^{-1}$); $P = 0.03$] at 12 months post-nephrectomy [36]. However, in a subgroup of this cohort with 42 donors and 42 controls that reattended 5 years after kidney donation, aortic PWV had increased in both groups over time, but there were no detectable differences between groups at 5 years [−0.24 (95% CI −0.69 to 0.21 m/s)] [37]. These 5-year results are consistent with the findings of an American study of 205 donors and 203 controls followed up for 9 years. In a subset of 100 donors and 113

controls, there was no difference in PWV between groups over this period [PWV at 9 years: donors 7.69 (95% CI 7.28–8.10 m/s); controls 7.90 (95% CI 7.44–8.36 m/s)] [40].

It has been estimated that the required sample size to adequately power a study to determine a 0.4 m/s change in PWV is >350 patients per group [104]. There are no studies of this size. It is therefore perhaps not unsurprising that the literature is inconsistent. However, recent work has provided some information. The EARNEST (Effect of A Reduction in glomerular filtration rate after NEphrectomy on arterial STiffness and central hemodynamics) study had a prospective, UK, multicentre, controlled, longitudinal design [38, 104]. It had the ambitious aim of recruiting 400 donors and controls, but was eventually terminated with 469 subject recruited and 306 (168 donors and 138 controls) followed up at 12 months. Overall, the study provided no evidence of prognostically important changes in arterial stiffness at 12 months after kidney donation but did suggest a need for further longer term detailed studies. These are expensive and difficult to perform so that further data on arterial stiffness in kidney donors may be slow to accumulate [105, 106].

In summary, the effects of kidney donation on arterial function are still uncertain and at an early stage of investigation. The few data available are limited in size and/or duration of follow up but have shown no clear signal of major adverse effects of kidney donation on arterial stiffness although larger and longer-term studies are required.

URAEMIC CARDIOMYOPATHY

The term uraemic cardiomyopathy was coined in the 1980s with reports of frequent abnormalities in cardiac function and structure in patients with CKD/ESKD: namely increased left ventricular (LV) mass and left ventricular hypertrophy (LVH); diastolic and systolic dysfunction; together with, often extreme myocardial fibrosis on histology [107–114]. However, LV hypertrophy had been noted in conjunction with kidney disease as early as 1827 by Richard Bright at Guys Hospital in London [115]. The aetiology of uraemic cardiomyopathy is likely to be multifactorial and include pressure and volume overload, anaemia, increased oxidative stress and activation of the renin–angiotensin–aldosterone system, as well as elevated concentrations of cardiotonic steroids, uric acid, parathyroid hormone, fibroblast growth factor-23 (FGF-23) and other uraemic toxins [112, 113, 116, 117]. Many of these factors including uric acid, parathyroid hormone and FGF-23 increase post-kidney donation [36, 37, 40, 118]. The severity of uremic cardiomyopathy as measured by LV mass is a powerful predictor of cardiovascular mortality [119–131]. Uraemic cardiomyopathy probably not only is present in almost all patients with ESKD on dialysis, but also appears to present to a lesser degree in patients with milder forms of CKD [109–111]. Studies of subjects with stage 2 and 3 CKD have reported a high frequency of cardiac abnormalities consistent with uraemic cardiomyopathy [43, 111, 116].

As uraemic cardiomyopathy appears to begin early in patients with CKD, it might be expected that some features might be present in kidney donors, particularly those with lower post-donation renal function. Until recently, data were restricted to a few small, cross-sectional or uncontrolled studies that reported conflicting results after kidney donation. A small cross-sectional echocardiographic and cardiac magnetic resonance imaging (CMR) study of 15 Italian donors compared with age- and sex-matched healthy controls from the USA at a median of 8.4 years (minimum of 5 years) from donation found that most measures of LV geometry and function were not different in donors and controls, but donors did exhibit abnormalities of LV apical rotation and torsion [132]. In an uncontrolled study of 23 kidney donors using CMR, LV mass increased at 12 months without change in office blood pressure [133]. By contrast, a two-dimensional speckle tracking echocardiographic study of 30 kidney donors at baseline and 12 months after donation found no significant differences in left or right ventricular function [134].

A UK prospective, controlled study of myocardial structure and function in kidney donors has provided 1- and 5-year data. In 68 donors and 56 equally healthy controls (many of whom were worked up for donation but did not donate), with a blinded endpoint analysis at 12 months, there was an increase in LV mass measured by CMR in donors but not controls [36]. Global circumferential strain was also decreased, indicating early changes in systolic dysfunction. There was no change in blood pressure measured by 24-h ambulatory monitoring and no association between change in LV mass and changes in blood pressure. However, at 5 years post-donation, 50 donors and 45 controls from the original cohort were restudied using CMR imaging [37]. In this subgroup, the increase in LV mass at 1-year post-donation was still observed. However, the change in LV mass in kidney donors at 5 years was not different from healthy controls [0.40 (95% CI 4.68–5.49 g)]. There were no significant differences in the changes in LV or left atrial volumes, LV geometry, global longitudinal strain or global circumferential strain at 5 years [37]. Furthermore, at 5 years, there were no differences between donors and controls in surrogate CMR markers of LV fibrosis (T1 mapping and late gadolinium enhancement) [37]. There was an increase in high-sensitivity C-reactive protein, high-sensitivity troponin T and vitamin D over time in both donors and controls. At 12 months, the prevalence of detectable troponin T was greater in donors than controls; at 5 years, the prevalence had increased in both groups, reducing the between-group difference [37].

There are several potential explanations for the different findings at 1 year and 5 years in kidney donors compared with controls. Effects due to random chance given the relatively low numbers of participants is certainly one possibility. Another possibility is the narrowing in the difference in renal function between donors and controls 1–5 years post-donation. Whereas in donors the mean GFR increased by 2 mL/min/1.73 m^2 over this period, the GFR in controls declined by 1 mL/min/1.73 m^2 per year. Given the strong association between GFR and LV mass in observational studies [125, 131, 135], a reduced difference in GFR between donors and controls would be expected to be associated with a reduced difference in LV mass. Furthermore, other factors associated with increased LV mass such as anaemia, increased erythropoietin and C-reactive protein levels are seldom present after 12 months in donors [136].

Coronary microvascular dysfunction, as measured by coronary flow reserve velocity, is highly prevalent in patients with CKD and is associated with an adverse prognosis [137]. It is also thought to be a contributor to the development of uraemic cardiomyopathy [137]. In a small cross-sectional study of 23 donors with a median of 30 months post-donation and 25 closely matched controls, donors were found to have significantly lower coronary flow reserve velocity than controls [138]. These findings need to be replicated in larger, prospective, longitudinal studies.

In summary, there are few studies investigating cardiac structural and functional change after kidney donation. The studies that do exist have small sample sizes and have provided conflicting results. Current evidence suggests that although kidney donation may result in small changes in cardiac structure and function within 1 year, these do not appear to be sustained

in the longer term. Well-controlled and much longer follow-up studies with serial cardiac investigations are required.

CONCLUSION

Ronald never had any regrets about donating a kidney to his brother. Then, as now, live donor kidney donation offers patients with ESKD the best chance of long-term, dialysis-free survival [58, 139]. Donors get no direct reward for their efforts. However, well before donation, potential donors need, and indeed deserve, to have good quality information on the future risks to their overall health, quality of life and potential impact on life expectancy. Given the close relationship between cardiovascular disease and CKD, information on future risks of cardiovascular disease and hypertension are particularly relevant. This is especially true given the ongoing relaxation of selection criteria, as a direct consequence of the increasing demand for kidney transplants, to include donors with metabolic syndrome, diabetes and hypertension [140–143]. As this review highlights, the evidence required is still sadly lacking. It is therefore perhaps not surprising that there is a large variation in how often (from always to never) different long-term risks are discussed with potential donors [144].

Long-term (at the very least 20 years) prospective studies and registries, with appropriate healthy control groups, with adequate representation of different racial groups and comorbidities, are required so that donation-attributable risks can be calculated as required [140]. It is perhaps a comforting thought that there is increasing evidence that altruism and volunteering is associated with longer life expectancy and reduced health-care use [145–147]. However, given that their actions benefit not only the recipient but also the much wider society as a whole, live donors deserve much more than just wishful thinking. Considering the current uncertainty over the risks involved with kidney donation, transplanting centres should develop a long-term relationship with donors allowing close follow-up of all factors related to cardiovascular risk. For the moment, it seems reasonable to provide counselling, monitoring and treatment of modifiable cardiovascular risk factors, and reassurance that although the evidence base is imperfect, no study has provided robust evidence of increased risk of cardiovascular death or disease.

CONFLICT OF INTEREST STATEMENT

None declared.

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