**Effect of A Reduction in Glomerular Filtration Rate After Donor Nephrectomy on Arterial Stiffness and Central Haemodynamics: The EARNEST study**

**Running title:** The EARNEST study

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**Significance statement** (120 words, max 120)

After nephrectomy, renal function in kidney donors declines by approximately a third. Whether living kidney donors are subject to the same increased cardiovascular risks as those with chronic kidney disease is unclear. One previous study has indicated that living kidney donors may be at an increased risk of both all cause and in particular cardiovascular mortality.1

This is the largest longitudinal prospective study of blood pressure and haemodynamics in living kidney donors and healthy control participants to date. There is no significant rise in ambulatory blood pressure or pulse wave velocity in living kidney donors compared to healthy controls at 12 months after nephrectomy. These results can offer reassurance about short-term changes in cardiovascular risk to people considering kidney donation.

**Abstract (249)**

**Background**

EARNEST was a multi-centre, nationwide, prospective, controlled study designed to investigate the effects of an isolated reduction in kidney function on arterial haemodynamics.

**Methods**

Living kidney donors and closely matched healthy controls were recruited from centres with expertise in vascular research. Participants underwent office and ambulatory blood pressure, assessment of arterial stiffness and biochemical tests at baseline and 12 months.

**Results**

A total of 469 participants were recruited and 306 were followed up at 12 months. At follow up, eGFR was reduced by a mean of 27 mL/min/1.73m2 in donors.

At 12 months there were no significant differences between donors and controls in office or ambulatory pressures. In donors but not controls there was an increase in office systolic blood pressure compared to baseline (+1.8mmHg vs -1mmHg, p=0.029) but there was no difference in the change from baseline in 24 hour ambulatory systolic or diastolic pressures. Central systolic and diastolic blood pressures and augmentation index were higher in donors than controls at 12 months (115 mmHg vs 109 mmHg, 78 mmHg vs 74 mmHg and 26% vs 22%) and the change in central systolic blood pressure from baseline was significantly greater in donors (+2.1mmHg vs -1.2mmHg, p=0.030). Pulse wave velocity was not significantly different between the two groups.

**Conclusions**

Kidney donation was not associated with significant changes in ambulatory blood pressure or pulse wave velocity at 1 year after nephrectomy. These results offer reassurance, at least in the short-term, about the arterial haemodynamic effects of living kidney donation.

ClinicalTrials.gov identifier (NCT number): NCT01769924 (https://clinicaltrials.gov/ct2/show/NCT01769924).

**Introduction**

Chronic kidney disease (CKD) is a major risk factor for cardiovascular disease; there is a graded association (independent of multiple cardiovascular risk factors) between glomerular filtration rate (GFR) and cardiovascular risk.2 In early stage CKD, mortality from cardiovascular events is more likely than disease progression and the need for renal replacement therapy.3 Hypertension, increased arterial stiffness, chronic inflammation and uremic toxins are thought to be key mediators of the increased cardiovascular risk.4 In patients with end stage kidney disease (ESKD) increased arterial stiffness as measured by pulse wave velocity (PWV) is a strong and independent predictor of mortality.5 Increased arterial stiffness is also highly prevalent in earlier stages of CKD.6 It is not clear whether hypertension and increased arterial stiffness in CKD are a direct consequence of the reduced GFR or are due to the multiple co-morbid conditions that tend to accompany CKD.

Living kidney donors provide an opportunity to examine prospectively the cardiovascular consequences of a reduction in kidney function without the confounding effects of co-morbid disease. In the long term, kidney donors typically lose approximately 30% of their baseline GFR so that over 65% have a GFR consistent with stages 2 and 3 CKD.7, 8 They also have similar biochemical abnormalities to patients with CKD such as increases in uric acid, inflammatory markers including C-reactive protein (CRP) and fibroblast growth factor 23 (FGF-23).9 The risk of ESKD after nephrectomy varies according to ethnicity and sex but is estimated to be over three times higher than predicted risks in those who have not donated.10, 11 To date, however, most studies of kidney donors have not shown an increase in cardiovascular risk or mortality.12 Only one study performed in Norway has shown an increased cardiovascular mortality compared to controls and this occurred late at over 10 years of observation.1 The aim of this study was to determine the effect of the reduction in kidney function that occurs after kidney donation on arterial stiffness and blood pressure with a sample size adequate to detect small effect sizes.

**Methods**

**Study design**

The EARNEST (**E**ffect of **A R**eduction in glomerular filtration rate after **NE**phrectomy on arterial **ST**iffness and central haemodynamics) study was a prospective multicentre UK national study. We initially aimed to recruit 440 controls and 440 donors from seven centres recognised for performing high numbers of living kidney transplants within the UK over a two year period. Recruitment began in April 2012; the last follow up patient was studied in May 2016. Recruitment was terminated in May 2015 on pragmatic and financial grounds.

**Study population**

The inclusion and exclusion criteria were in accord with national guidelines disseminated by the Joint Working Party of the British Transplantation Society and the Renal Association for living kidney donors.13 Both donors and controls had to be deemed fit to donate a kidney. Therefore participants required an appropriate age specific GFR without proteinuria, previous cardiovascular or pulmonary disease, uncontrolled hypertension or diabetes.

Healthy controls were frequently those undergoing workup for donation but who were ultimately unable to donate due to factors such as immunological mismatch and recipient illness. Alternatively, donor-related family members or volunteers donating blood at local blood donation centres were recruited if they met the same criteria. Further details can be found in a detailed methods manuscript.14

**Study protocol**

A full illustrated and detailed protocol has already been published.14 A summary is presented below. All participants were investigated at baseline (within the 6 weeks prior to nephrectomy for prospective living kidney donors) and at 12 months.

1. **Blood pressure measurement:** Office blood pressure was measured from the non-dominant arm after 5 minutes of rest on three occasions using a validated automated device. Blood pressure was taken in both a sitting and supine position. Participants also underwent 24hr ambulatory blood pressure monitoring using the Mobilo-O-Graph NG; IEM (Stolberg, Germany).15Blood pressure recordings were taken every 30 minutes between the hours of 0800-2200, and every 60 minutes between 2201 and 0759.
2. **Pulse wave velocity:** PWV was measured using SphygmoCor (Atcor Medical, Sydney, Australia) after lying supine for 15 minutes. Repeated pressure waveforms were acquired using a high fidelity micromanometer (SPC-301; Millar Instruments, Houston, TX).16 Velocity was deduced using the distance from the sternal notch to the femoral pulse subtracted by the distance between the sternal notch and the carotid pulse as previously described. 17
3. **Pulse wave analysis:** Using the SphygmoCor device; arterial pressure waveforms were obtained from which central waveforms can be calculated. Central blood pressure and augmentation index (AIx) were calculated using transfer functions as previously described.18
4. **Assessment of kidney function:** Kidney function was determined in all participants using standardised creatinine assays and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine 2009 equation.19,20 A subset of living kidney donors underwent isotopic GFR measurement using clearance of 51Cr-EDTA at both baseline and follow up.21,22
5. **Blood and urine:** Biochemistry measurements included serum creatinine, calcium, albumin, phosphate and uric acid and urinary albumin: creatinine ratio.

**Primary end point**

Ambulatory blood pressure and pulse wave velocity were considered co-primary end points for this study.

**Statement of ethics**

Ethical approval for the main study was obtained in February 2013 from the South Cambridge Regional Ethics Committee (Integrated Research Application System Reference: 118797, Research Ethics Committee approval number 13/EE/0015). The EARNEST sub study (CRIB-DONOR) commenced in 2011, ethical approval was obtained from the West Midlands Research Ethics Committee. All participants underwent informed consent in keeping with the principles set out by the Declaration of Helsinki.

**Power calculations and sample size**

Using data from previous studies, the standard deviation of the within-patient changes was assumed to be 10 mmHg for blood pressure and 1.0 m/s in PWV.16, 23 A sample size of 800 participants (400 subjects per group) was planned in order to provide 80% power to detect a difference of 2.2mmHg in systolic pressure or 0.22 m/s in PWV using a 2-sided *t* test at the 2.5% significance level. Values for a sample size of 400 participants (200 subjects per group) have 92% power to detect a difference of 4 mmHg for systolic blood pressure and 0.4 m/s for PWV and allowing for 15% drop out at a significance level of 5%.

**Statistical analysis**

Statistical analysis was performed using StataCorp®.2017 (Stata statistical software: Release 15. College Station, TX: StataCorp LCC).Baseline demographics of controls and donors recruited into the study were compared. Parametric continuous variables at baseline were compared using independent t tests and non-parametric continuous variables were compared using a Mann Whitney U test. Categorical variables were investigated using either a Fisher’s exact test or a Chi squared test.Comparison between living kidney donors and controls at 12 months were analysed using independent t tests for continuous parametric data. The mean change from baseline was also calculated for both donors and controls. A comparison between mean change in donors and controls was also analysed using an independent t test for continuous parametric data. Carotid-femoral pulse wave velocity was adjusted for both average mean arterial pressure and average supine heart rate using unstandardized residuals calculated from a linear regression model.

**Results**

**Follow up and events**

A total of 469 participants were recruited; 20 were excluded as they lacked the minimal data set required for analysis and two were found to be ineligible after the initial visit (see **Figure 1)**. Recruitment was terminated at 3 years despite the lower than planned sample size due to financial constraints. Of the remaining 447 participants there were 201 controls and 246 donors. One hundred and forty one participants were unable to attend follow up leaving 138 controls and 168 donors with paired data for final analysis. The commonest causes of participants unable to complete the study were moving out of the local area or difficulty attending follow-up visits due to long travel distances, work and childcare commitments.

For comparison between patients who were lost to follow up and those who continued in the study, see **Table S1**. There were few significant differences; compared to those who did not return for follow up at 12 months, participants who continued in the study had a marginally lower eGFR and were more likely to be taking anti-hypertensives.

**Patient characteristics**

The demographics of living kidney donors and healthy controls who attended for both baseline and 12 month follow up visits were comparable with the exception of tobacco use, see **Table 1**. Compared to controls, a higher proportion of donors were either current or ex-smokers. Baseline haemodynamic and biochemical characteristics are shown in **Tables 2 and 3**. There were no significant differences in any of the baseline haemodynamic values.Donors had significantly higher serum potassium and corrected calcium concentrations at baseline compared to controls but the differences were small and not clinically significant.

Patient demographics and haemodynamic and biochemical characteristics at baseline for all those recruited (n=447) are shown in supplementary **Tables S2 and S3**. Donors had a higher mean age than controls; 50.9 yrs. vs 47.3 yrs., p=0.03 and were more likely to have a history of previous smoking; 46% vs. 33%, p=0.007.

**Figure 1:** A flow chart demonstrating those recruited into the study and those that were lost to follow up.



**Comparison of biochemistry in living kidney donors and controls**

Results are shown in **Table 3**. At 12 months, eGFR had fallen by a mean of 27mL/min/1.73m2 in donors but was virtually unchanged in controls. Although iGFR measurement was part of the protocol for donation, in practice few subjects consented to a 12 month iGFR due to concerns about the duration of the test and exposure to ionising radiation. Isotope GFR was recorded in only 90 donors at baseline with relatively few subjects willing to undergo repeat iGFR estimation at 12 months so that the results were not meaningful. Compared to controls, both potassium and uric acid were higher in donors than controls at 12 months with corresponding significant differences in mean change from baseline. In contrast, very minor decreases in both serum phosphate and sodium were seen in donors compared to controls at 12 months although only the mean change for phosphate in donors was significantly different to that in controls.

**Comparison of haemodynamic variables in living kidney donors and controls**

Arterial haemodynamic parameters at baseline and 12 months are given in **Table 2**. There were no significant differences between donors and controls in office or ambulatory blood pressures at 12 months. The changes in office systolic blood pressure from baseline in donors and controls were small. The increase in donors (of less than 2 mmHg) was however greater than that in controls, in whom there was a mean fall of approximately 1 mmHg. Mean ambulatory heart rate was not significantly different at baseline but was significantly higher in donors than controls at 12 months with a difference of 3.4 bpm. Compared to baseline, the +1.5 bpm increase in heart rate in donors was significantly different to the small -1.2 bpm fall seen in controls.

With respect to the SphygmoCor measured arterial haemodynamic values, adjusted PWV was not significantly different at baseline or at 12 months and the changes at 12 months from baseline were not different to controls. Central systolic and diastolic blood pressures and augmentation index were however, significantly higher in donors than controls at 12 months. When considering changes from baseline, only central systolic blood pressure changes were significantly greater in donors than controls.

**Discussion**

In this prospective study we found no change in office or ambulatory blood pressure in donors compared to controls at 12 months after nephrectomy. Pulse wave velocity was also not significantly different in donors compared to controls. Central systolic blood pressure increased more in donors than controls and at 12 months was higher in the donor group. The study proved to be difficult to conduct with a large number of both donors and controls who were unable to return for follow up but it is the largest, controlled, longitudinal prospective study of ambulatory blood pressure and arterial haemodynamics in kidney donors.

These data are important for two reasons. Firstly, kidney donors need to be informed about the risks of donation and the possible effects of the procedure on future health. Secondly, there are robust data showing that even mildly reduced kidney function is independently associated with increased cardiovascular risk although the causative mechanisms are uncertain.

This study suggests that the risk of a significant rise in blood pressure at 12 months in kidney donors is small. Previous studies have been heterogeneous in design and results. In a 2006 meta-analysis of 48 studies of office blood pressure in donors, including a total of 5145 patients, only 11 were prospective.24 However, in four controlled prospective studies totalling 157 donors and 128 controls there was an increase in systolic blood pressure of 6 (95% CI 2-11) mmHg after five years of follow-up. Similarly, in five controlled prospective studies (196 donors and 161 controls) there was a 4 (95% CI 1-7) mmHg increase in diastolic pressure in donors.24 More recently Kasiske et al. examined blood pressure in donors and controls over three years from donation using a prospective controlled study design but without baseline ambulatory blood pressure measurments.25 In over 300 subjects, they found no significant difference between donors and controls in office blood pressure at any time. In 135 donors and 126 controls there was no difference in ambulatory blood pressure at 36 months.25 Taken together, our data and the study of Kasiske et al. suggest that the risk of clinically important change in blood pressure in the medium term following kidney donation is very modest. Longer term controlled prospective ambulatory studies are required. We note that current clinical guidelines recommend that prospective living kidney donors are counselled that blood pressure may rise beyond what is expected for normal ageing but we have not seen such an effect by 12 months.26, 27 Our data are also of pathophysiological importance because almost all subjects with CKD are hypertensive.28 This increase in blood pressure does not appear to be an inevitable consequence of a reduced GFR and suggests that other mechanisms are required to generate hypertension in CKD.

Despite the absence of change in peripheral pressure, both central systolic and diastolic pressures were greater in donors at 12 months compared to controls. These changes might be important. Central blood pressure is more closely correlated to left ventricular mass, carotid intimal thickness and cardiovascular events than brachial pressure.29, 30 In contrast, in a previous study of 17 kidney donors a decline of 10mmHg in office systolic pressure and central aortic pressure was observed six months after nephrectomy with unchanged ambulatory 24-hr values.31 We are unable to account for the difference between our findings and this study but note that our sample size was larger. Given that the central blood pressure in both studies was not measured directly but was derived from brachial pressure using a generalised transfer function these data need to be interpreted with caution.31 Ambulatory heart rate in donors was also elevated compared to controls at 12 months raising the possibility of an increase in sympathetic neural activity which might also have influenced central blood pressure. Sympathetic activity is increased in both animals and humans with CKD.32

With respect to other measures of arterial stiffness, the small increase in AIx was not accompanied by any rise in PWV. The greater AIx in kidney donors at 12 months might help to explain the increase in central blood pressure and raises the possibility of an increase in wave reflection perhaps due to changes in peripheral, rather than central, arterial stiffness. There have been several previous uncontrolled studies examining arterial stiffness in kidney donors with conflicting results. De-Seigneux et al. studied 21 patients before and one year after nephrectomy and found no change in AIx or PWV.33 Similarly Fesler et al. found no change in PWV at 12 months post nephrectomy in 45 donors.34 A cross sectional study of 101 living kidney donors found that PWV was 10% higher than control patients but had no data on pre-donation values.35 We were unable to detect any change in PWV, the ‘gold standard’ measurement of arterial stiffness, in donors compared to controls but the study was underpowered to detect a difference of less than 0.4m/s meaning we are unable to completely exclude a small effect of the reduction in GFR on PWV.

With respect to the pathophysiology of CKD, our findings indicate that increased peripheral blood pressure is not an inevitable consequence of a reduced GFR, and that short-term change in arterial physiology is modest with no evidence of a significant effect on central aortic stiffness.

The changes we observed in biochemistry are mirrored in the wider literature. The increase in uric acid after donation is seen consistently in other studies, which presumably reflects reduced clearance of uric acid.25, 36 Urate is associated with cardiovascular risk and has been suggested to play a direct pathophysiological role.37 In contrast we found that phosphate levels were lower in donors. FGF23 has a pivotal role in phosphate homeostasis by inhibiting parathyroid hormone, reducing intestinal absorption and controlling cotransporters in the renal proximal tubule.38 Circulating levels of FGF23 increase with severity of CKD and are elevated in kidney donors and it is possible that activation of such mechanisms after nephrectomy may result in over-compensation.36, 38 The increase in FGF23 is thought to be an adaptive response to phosphate retention in the earliest stages of CKD and has also been associated with left ventricular hypertrophy.39

**Limitations**

Despite a potentially large pool of patients, a substantial proportion of participants did not return for follow-up. Barriers to studies of living kidney donors have been reported by others.40 They are often geographically remote from the transplant centre (in contrast to the recipient) and once they have donated, are usually active and in full time work. However, this limitation does not affect the internal validity of our results and there were only minor differences between participants who did and did not return for follow-up so our results should be generalizable to the wider pool of potential kidney donors. In addition, the large number of parameters measured beyond the pre-specified primary end-points mean that there are issues of multiple testing and some differences may have arisen by random chance.

We present the results of a large, prospective, multi-centre study of both kidney donors and very similar controls measured nationwide across the UK in centres with extensive experience in vascular research. Our study demonstrates that at 12 months there is no significant rise in ambulatory systolic or diastolic blood pressure or clear evidence of an increase in arterial stiffness measured by the ‘gold standard’ of PWV. These results can offer reassurance about short-term changes in cardiovascular risk to people considering kidney donation. The possible rise in central BP is worthy of further investigation but as it is a derived value it should be viewed with caution.

**Author contributions**

JNT, CJF, IAB, JRC, RPS, CRVT and PBM designed the study; WEM, LAT, NCE, MKH, AMP, DB, TC and BS recruited patients and collected data during patient visits; GHBG, LAT and AMP analysed the data; AMP, JNF, CJF, LCP, AR and JPL drafted and revised the paper; all authors approved the final version of the manuscript.

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**Disclosures**

No conflict of interests to declare.

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**Supplemental material-Table of Contents**

Table S1: Baseline characteristics of patients who were lost to follow up compared to those who continued the study.

Table S2: Baseline patient demographics of the whole cohort recruited

Table S3: Baseline biochemical and haemodynamic characteristics of the whole cohort recruited.

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**Table 1: Baseline patient demographics of study participants at baseline and 12 months.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Controls****n=138** | **Donors****n=168** | **P -value †** |
| **Sex (male)** | 57 (41.3) | 78 (46.4) | 0.369 |
| **Age (years)** | 49 ± 1.2 | 51 ± 1.0 | 0.085 |
| **Ethnic group** | Caucasian=127 (92.0)Non-white=8 (5.8)Unknown=3 (2.2) | Caucasian=158 (94.1)Non-white= 9 (5.4)Unknown= 1 (0.6) | 0.840 |
| **History of hypertension** | 9 (6.5) | 17 (10.1) | 0.243 |
| **Anti-hypertensive usage**  | 9 (6.5) | 18 (10.7) | 0.198 |
| **ACE/ARB usage** | 4 (2.9) | 5 (3) | 0.968 |
| **Calcium channel blocker usage** | 4 (2.9) | 6 (3.5) | 0.742 |
| **Current or ex-smoker** | 38 (27.54) | 74 (44.05) | 0.002 |
| **Normalised isotopic GFR (ml/min/1.73m2)\*** | 88.7 ± 12.8 | 88.9 ± 12.2 | 0.990 |

ACE; Angiotensin Converting Enzyme. ARB; Angiotensin receptor blocker. CKD; Chronic Kidney Disease. GFR; Glomerular Filtration Rate.

Data from participants with complete data at baseline and 12 months is shown. \*Isotopic GFR represents n=90 donors and n=22 controls. Isotopic GFR results from controls were part of the CRIB-DONOR sub study. **†** Categorical variables are presented as n (%) and were analysed using either Fishers exacts tests or Chi squared tests if more than two categorical variables. Continuous data are represented as mean ± standard deviation and were analysed using independent samples t-tests.

**Table 2: Haemodynamic and arterial parameters for kidney donors and controls at baseline and 12 months.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Sample size** | **Baseline** **(Mean ±SD)** | **12 months****(Mean ±SD)** | **P-value****(controls vs donors at 12 months) \*** | **Mean change** **(95% CI)** | **P -value****(mean change in controls vs mean change in donors) †** |
| **Weight (kg)** | 168=Donors136=Controls | 75.4 ± 13.574.7 ± 13.9 | 77.1 ± 14.774.9 ± 13.8 | 0.177 | 1.7 (0.4-3.0)0.2 (-0.4-0.8) | 0.070 |
| **Seated office systolic BP (mmHg)** | 168=Donors135=Control | 125.0 ± 14.1125.3 ±16.7 | 126.8 ± 12.4124.4 ± 17.2 | 0.170 | 1.8 (-0.0-3.6)-1.0 (-2.8-0.7) | **0.029** |
| **Seated office diastolic BP (mmHg)** | 168=Donors135=Control | 78.4 ± 9.077.3 ±10.3 | 80.1 ± 8.578.0± 9.1 | 0.050 | 1.7 (0.4-2.9)0.6 (-0.8-1.9) | 0.245 |
| **Ambulatory day systolic BP (mmHg)** | 119=Donors111=Control | 123.7 ± 10.0122.3 ± 10.0 | 123.8 ± 9.8122.9 ± 11.7 | 0.534 | 0.1 (-1.7-1.9)0.6 (-0.8-2.1) | 0.626 |
| **Ambulatory day diastolic BP (mmHg)** | 124=Donors111=Control | 78.7 ± 8.277.0 ± 8.3 | 78.9 ± 8.077.9 ±8.9 | 0.358 | 0.2 (-0.9-1.4)0.9 (0.0-1.8) | 0.399 |
| **Ambulatory day HR (bpm)** | 65=Donors82=Control | 72.9 ± 9.272.2 ±8.6 | 74.4 ± 10.571.0 ± 10.1 | **0.042** | 1.5 (-0.9-3.9)-1.3 (-2.8-0.2) | **0.041** |
| **Ambulatory night systolic BP (mmHg)** | 115=Donors105=Control | 111.0 ± 10.8110.0 ± 10.4 | 112.0 ± 11.1109.4 ± 11.7 | 0.092 | 1.0 (-1.0-3.016)-0.6 (-2.5-1.3) | 0.243 |
| **Ambulatory night diastolic BP (mmHg)** | 115=Donors105=Control | 67.1 ± 8.466.2 ± 7.7 | 68.4 ± 8.566.4 ± 9.3 | 0.103 | 1.3 (-0.2-2.9)0.3 (-1.2-1.7) | 0.307 |
| **Central systolic BP (mmHg)** | 105=Donors108=Control | 113.1 ± 13.5110.5 ± 16.6 | 115.2 ± 13.6109.3 ±17.1 | **0.005** | 2.1 (-0.2-4.4)-1.2 (-3.1- 0.7) | **0.030** |
| **Central diastolic BP (mmHg)** | 105=Donors108=Control | 76.6± 8.674.8 ± 9.8 | 77.9 ± 9.774.5 ± 9.5 | **0.011** | 1.3 (-0.7-3.2)-0.4 (-1.9-1.1) | 0.220 |
| **Augmentation index, corrected for HR (%)** | 104=Donors108=Control | 22.1 ± 12.020.4 ±12.5 | 25.6 ± 12.222.3 ± 12.0 | **0.047** | 3.4 (1.5-5.3)1.8 (-0.0 - 3.6) | 0.230 |
| **Adjusted Carotid-femoral pulse wave velocity (m/s)** | 168=Donors138=Control | 7.0 ± 1.37.0 ±1.40 | 7.3 ± 1.47.2 ±1.4  | 0.343 | 0.3 (0.1-0.4)0.2(-0.0-0.4) | 0.492 |

BPM; Beats per minute. BP; Blood Pressure, CI; Confidence interval, HR: Heart rate, SD: Standard deviation.

306 participants with complete baseline and follow-up data are represented.

\*Independent samples t tests were used to compare variables at 12 months between donors and controls.

† Analysis of the change in each variable [i.e. mean change in weight in donors (1.7kg) vs mean change in weight in controls (0.2kg)] was analysed using an independent samples t test.

**Table 3: Biochemical parameters for living kidney donors and controls at baseline and 12 months.**

|  |  |
| --- | --- |
|  |  |
| **Sample size**  | **Baseline****(Mean ±SD)** | **12 months****(Mean ±SD)** | **P-value‡** **(controls vs donors at 12 months)**  | **Mean change (95% CI)** | **P-value** † **(mean change in controls vs mean change in donors)** |
| **Sodium (mmol/l)** | 167=Donors137=Controls | 140.2 ± 2.1140.5 ± 2.0 | 139.9 ± 2.0140.4 ± 2.0 | 0.047 | -0.3 (-0.7- 0.0)-0.2 (-0.5- 0.2) | 0.593 |
| **Potassium (mmol/L)** | 167=Donors134=Controls | 4.3 ± 0.3\*4.2 ± 0.3 | 4.4 ± 0.44.2 ± 0.3 | <0.001 | 0.1 (0.0-0.2)-0.0 (-0.1-0.1) | 0.015 |
| **Urea (mmol/L)** | 167=Donors136=Controls | 5.1 ± 1.35.0 ± 1.3 | 6.4 ± 1.75.2 ± 1.4 | <0.001 | 1.4 (1.2-1.6)0.2 (0.0-0.4) | <0.001 |
| **Creatinine (µmol/L)** | 168=Donors136=Controls | 74.8 ± 13.572.5 ± 14.8 | 104.0 ± 20.571.3 ± 14.8 | <0.001 | 29.2 (27.0 -31.4)-1.2 (-3.3-0.8) | <0.001 |
| **eGFR****(mL/min/1.73m2)** | 168=Donors136=Controls | 91.4 ± 15.194.2 ± 15.6 | 64.0 ± 14.396 ± 17.1 | <0.001 | -27.5 (-29.2- -25.7)1.7 (-0.4-3.8) | <0.001 |
| **Albumin (g/L)** | 145=Donors135=Controls | 42.7 ± 3.941.6 ± 4.4 | 42.2 ± 4.341.9 ± 4.8 | 0.533 | -0.4 (-1.0 -0.1)0.3 (-0.1-0.8) | 0.042 |
| **Corrected calcium (mmol/L)** | 148=Donors136=Controls | 2.3 ± 0.1\*2.3 ± 0.1 | 2.3 ± 0.1 2.3 ± 0.1 | 0.295 | 0.0 (-0.0-0.0)0.0 (-0.0-0.0) | 0.281 |
| **Phosphate,****(pmol/L)** | 130=Donors121=Controls | 1.1 ± 0.21.1 ± 0.2 | 1.0 ± 0.21.1 ± 0.2 | <0.001 | -0.1 (-0.1- -0.1)0.0 (-0.0-0.1) | <0.001 |
| **Magnesium,****(mmol/L)** | 77=Donors85=Controls | 0.9 ± 0.70.9 ± 0.7 | 0.9 ± 0. 10.9 ± 0.1 | 0.349 | 0.0 (-0.0- 0.0)0.0 (-0.0- 0.0) | 0.944 |
| **Uric acid (µmol/L)** | 93=Donors95=Controls | 298.8 ± 73.0 285.4 ± 66.0 | 349.2 ± 76.2 284.1 ± 67.0 | <0.001 | 50.5 (41.2-59.8)-1.3 (-9.3-6.8) | <0.001 |
| **Urine albumin: creatinine ratio (mg/mmol)** | 66=Donors69=Controls | 2.78 ± 4.66 2.27 ± 3.69 | 2.61 ± 4.50 1.93 ± 3.61 | 0.338 | -0.2(-1.1-0.8)-0.3 (-1.3-0.6) | 0.807 |

CI; Confidence interval, eGFR; estimated glomerular filtration rate, SD: Standard deviation.

306 participants with complete baseline and follow-up data are represented.

\*Represents significant differences between controls and donors at baseline with p= <0.05

**‡** Independent samples t tests were used to compare variables at 12 months between donors and controls.

† Analysis of the change in each variable [i.e. mean change in weight in donors (1.7kg) vs mean change in weight in controls (0.2kg)] was analysed using an independent samples t test.

**Supplemental data**

**Supplemental material-Table of Contents**

Table S1: Baseline characteristics of patients who were lost to follow up compared to those who continued the study.

Table S2: Baseline patient demographics of the whole cohort recruited

Table S3: Baseline biochemical and haemodynamic characteristics of the whole cohort recruited.

**Table S1: Baseline characteristics of patients who were lost to follow up compared to those who continued the study.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Baseline characteristics** | **Attended follow up n=306 (68.5%)** | **Lost to follow up n=141 (31.5%)** | **P-value\*** |
| **Living kidney donor** | 168 (54.9) | 78 (55.3) | 0.934 |
| **Sex (male)** | 135 (44) | 50 (35) | 0.400 |
| **Age (years)** | 50.1 ± 13.0 | 47.4 ± 12.6 | 0.052 |
| **Ethnic group** | Caucasian=285 (93.1)Non-white=17 (5.6)Unknown=4 (1.3) | Caucasian=108 (77)Non-white=17 (12)Unknown=16 (11) | 0.040 |
| **Weight (kg)** | 75.1 ± 13.6 | 76.4 ± 13.6 | 0.380 |
| **eGFR (ml/min/1.732)** | 92.7 ± 15.3 | 97.2 ± 14.8 | 0.008 |
| **History of hypertension** | 26 (8.5) | 9 (6.4) | 0.080 |
| **Anti-hypertensive usage**  | 27 (19.1) | 8 (5.7) | 0.039 |
| **Current or ex-smoker** | 112 (36.6) | 68 (48.2) | 0.006 |
| **ACE/ARB usage** | 8 (2.6) | 2 (1.4) | 0.295 |
| **Calcium channel blocker usage** | 10 (3.3) | 4 (2.8) | 0.628 |

ACE; Angiotensin Converting Enzyme. ARB; Angiotensin receptor blocker. eGFR; estimated glomerular filtration rate.

\*Categorical variables are presented as n (valid %) and were analysed using either Fishers exacts tests if binary or Chi squared tests for more than two categorical variables. Continuous data are represented as mean ± standard deviation if normally distributed and were analysed using independent samples t tests.

**Table S2: Baseline patient demographics of the whole cohort recruited.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Controls** | **Donors** | ***P* value †** |
| **Male sex** | 79 (39) | 106 (43) | 0.400 |
| **Age, years** | 47.3 ± 13.6 | 50.9 ± 12.1 | 0.003 |
| **Ethnic group** | Caucasian=171 (85)Non-white=21 (10)Unknown= 9 (5) | Caucasian=222 (90)Non-white=13 (5)Unknown=11 (5) | 0.040 |
| **Previous history of hypertension** | 11 (6) | 24 (10) | 0.080 |
| **Anti-hypertensive usage**  | 11 (7) | 24 (14) | 0.039 |
| **ACE/ARB usage** | 5 (2) | 7 (3) | 0.679 |
| **Calcium channel blocker usage** | 5 (2) | 9 (4) | 0.628 |
| **eGFR (ml/min/1.732) ‡** | 95.6 ± 15.2 | 92.6 ±15.3 | 0.048 |
| **Weight, kg** | 74.8 ± 13.8 | 76 ± 13.5 | 0.383 |
| **Current or ex-smoker** | 67 (33) | 113 (46) | 0.007 |
| **Normalised isotopic GFR (ml/min/1.73m2)** | 88.8 ± 13.2 | 89.2 ± 12.0 | 0.884 |

ACE; Angiotensin Converting Enzyme. ARB; Angiotensin receptor blocker. CKD; Chronic Kidney Disease. eGFR; Estimated Glomerular Filtration Rate.

447 participants recruited into the study with valid data sets are represented.

† Categorical variables are presented as n (valid %) and were analysed using either Fishers exacts tests if binary or Chi squared tests for more than two categorical variables. Continuous data are represented as mean ± standard deviation if normally distributed and were analysed using independent samples t tests.

**‡** eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2009).

**Table S3: Baseline biochemical and haemodynamic characteristics of the whole cohort recruited.\***

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Controls****(Mean ±SD)** | **Donors****(Mean ±SD)** | ***P* value †** |
| **Sodium (mmol/l)** | 140.5 ± 1.8 | 140.2 ± 2.2 | 0.159 |
| **Potassium (mmol/L)** | 4.2 ± 0.3 | 4.3 ± 0.3 | 0.041 |
| **Urea (mmol/L)** | 5.1 ± 1.4 | 5.0 ± 1.3 | 0.666 |
| **Creatinine (µmol/L)** | 72.1 ± 14.8 | 73.6 ± 14.0 | 0.290 |
| **Albumin (g/L)** | 41.6 ± 4.5 | 42.8 ± 4.1 | 0.006 |
| **Corrected calcium (mmol/L)** | 2.3 ± 0.1 | 2.3 ± 0.1 | 0.241 |
| **Phosphate (pmol/L)** | 1.1 ± 0.2 | 1.1 ± 0.2 | 0.156 |
| **Magnesium (mmol/L)** | 0.9 ± 0.1 | 0.9 ± 0.1 | 0.643 |
| **Uric acid (µmol/L)** | 287.1 ± 66.3 | 298.8 ± 70.4 | 0.180 |
| **Urine albumin: creatinine ratio (mg/mmol)** | 3.0 ± 6.4 | 2.8 ± 5.3 | 0.787 |
| **Seated office systolic BP (mmHg)** | 124.8 ± 16.3 | 125.5 ± 13.7 | 0.640 |
| **Seated office diastolic BP (mmHg)** | 77.2 ± 9.9 | 78.3 ± 8.9 | 0.196 |
| **Ambulatory day systolic BP (mmHg)** | 123.2 ± 10.4 | 123.8 ± 10.2 | 0.562 |
| **Ambulatory day diastolic BP (mmHg)** | 77.6 ± 8.6 | 78.5 ± 8.2 | 0.355 |
| **Ambulatory day heart rate****(bpm)** | 73.0 ± 9.1 | 73.7 ± 10.6 | 0.566 |
| **Ambulatory night systolic BP (mmHg)** | 111.3 ± 11.5 | 111.5 ± 11.0 | 0.870 |
| **Ambulatory night diastolic BP (mmHg)** | 66.8 ± 8.4 | 67.3 ± 8.5 | 0.588 |
| **Central systolic BP (mmHg)** | 109.7 ± 16.2 | 113.3 ± 13.4 | 0.040 |
| **Central diastolic BP****(mmHg)** | 74.7 ± 9.5 | 76.6 ± 8.4 | 0.064 |
| **Augmentation index, corrected for heart rate (%)** | 20.1 ± 12.5 | 22.7 ± 15.0 | 0.103 |
| **Adjusted carotid-femoral pulse wave velocity (m/s)** | 6.9 ± 1.3 | 7.0 ± 1.4 | 0.667 |

BPM; Beats per minute. BP; Blood Pressure, CI; Confidence interval.

447 participants recruited into the study with valid data sets are represented.

† Independent samples t tests (controls vs donors) were used to compare variables at baseline between donors and controls.