Long-term risk for kidney donors with hypertension at donation - a retrospective cohort study

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Abbreviations: BMI: Body Mass Index, CI: Confidence Interval, GFR: Glomerular Filtration Rate, HR: Hazard Ratio, ICD: International Statistical Classification of Diseases and Related Health Problems, PTH: Parathyroid Hormone, SD: Standard Deviation

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Abstract

In the general population, small increases in blood pressure are associated with increased mortality. In kidney donors this association is less certain. We therefore assessed long-term overall and cardiovascular mortality in donors who were hypertensive at the time of donation compared to normotensive donors. Hypertension was defined as blood pressure > 140/90 mmHg or use of antihypertensive drugs. Adequate records available in 2131 donors revealed that 140 were hypertensive and 1991 were normotensive. Multivariable regression analyses were performed for overall and cardiovascular mortality. Hypertensive donors were significantly older (mean 57.7 vs 46.9 years), more were males (44.3% vs 41.5%), had higher body mass index (26.4 vs 24.7) and lower estimated glomerular filtration rate (91.8 vs 101.2 ml/min/1.73m^2). After a median observation time of 20.8 years (interquartile range 11) 71 hypertensive donors had died and 26 of the deaths were cardiovascular. Multivariable analysis did not suggest a generalizable association between hypertension and long-term overall mortality (hazard ratio (HR) 1.1, 95% confidence interval (CI) 0.9-1.5, P=0.34) or cardiovascular mortality (HR 1.1, 95 % CI 0.7-1.8, P=0.55). These data may support the use of older healthy kidney donors with hypertension at donation.

Introduction

The optimal treatment for patients with end-stage renal disease is kidney transplantation from a living donor. However, donating a kidney comes with a cost for the donor. Perioperative mortality has been estimated to 0.03 % [1] and surgical complications to around 5% [2]. In addition there might be long-term risks for end-stage renal disease [3-5] and premature cardiovascular and all-cause mortality [4].

In principle, potential living donors are required to be healthy at time of donation, including a normal blood pressure. However, an increasing number of centers accept living donors with mild hypertension before donation, controlled by one or two antihypertensive drugs [6].

It is well known that hypertension in the general population is associated with cardiovascular morbidity and mortality [7-9] and these risks are even more pronounced in patients with chronic renal disease [10]. Short term studies using surrogate endpoints have indicated that live donors are susceptible to an increase in diverse cardiovascular risk factors after donor nephrectomy [11-13].

The few papers which have addressed the outcome of accepting hypertensive live kidney donors are characteristically short-term [14-16]. In a large, long-term follow-up study on living donors focusing on development of post-donation hypertension, Sanchez et al also showed that 96 donors with hypertension at donation had no increased mortality compared to normotensive donors [17].

There are no previous studies with the primary aim of evaluating long-term mortality or cardiovascular mortality in kidney donors with established hypertension at the time of donation.

We hypothesized that donors with elevated blood pressure at time of donation would be susceptible to increased long-term mortality risks compared to normotensive donors at transplantation.

Materials and Methods

All kidney transplants in Norway are performed at Oslo University Hospital. Potential donors are investigated at their local hospital. For a final accept each case is evaluated at the national transplant center by a medical team consisting of nephrologists, immunologists and transplant surgeons.

The living kidney donor transplant program in Norway began in the sixties, establishing nationwide registries and systems for life-long donor follow-up. These registries allow the evaluation of long term follow up data. Donation criteria have changed over time and the limits for what has been considered “normal” blood pressure have also changed. Also, some donors have been allowed to donate despite mild hypertension or use of one or two antihypertensive drugs.

In this retrospective cohort study 2131 caucasian donors in the period 1963-2007 were included. Hypertension was defined as blood pressure above 140 systolic, above 90 diastolic (although the donor may have been deemed normotensive at the time of evaluation

according to the contemporary definition of hypertension), or use of antihypertensive medication at the time of donation.

Manual office blood pressure was recorded at several different time points during the donor work-up. Blood pressure recordings were read of the donor charts, not specified if single or average recordings. For most donors, some weeks had passed between the evaluation and the time of admission for nephrectomy when blood pressure once again was measured preoperatively. For obvious reasons, this value could have been affected by preoperative anxiety, and not necessarily be representative. Routinely, when both measurements were recorded and available, the lowest value was chosen and included in the study. All donors were followed from date of donation to death, or end of study.

Baseline data were obtained from the national registry and patient hospital files.

No donor was lost to follow-up. Information on mortality and cause of death was acquired from Statistics Norway through use of a personal identification number unique to all Norwegian citizens. Causes of death were based on International Statistical Classification of Diseases and Related Health Problems (ICD). In Norway, when patients die in a hospital setting the doctor on call is responsible for filling out a death certificate and a death report form. The most probable cause of death is registered using the ICD system. When death occurs at home, the patient family doctor is notified who in turn fills out the report. Based on this information records are kept on causes of death in the Norwegian population. Cardiovascular death was defined as ICD-10 codes between I00 and I99. Sudden death (ICD 10 code R99) was included as cardiovascular death. Statistical analyses were performed using IBM Statistical Package for the Social Sciences version 23. Survival analyses were performed as multivariable cox regression adjusted for age at donation, gender, estimated

glomerular filtration rate, donation year, first degree relative of recipient, smoking status and body mass index (BMI). Due to missing data for smoking (23 %) and BMI (12,3%), 35% of donors were omitted from adjusted model 1. Multiple imputation was performed by fully conditional specification method, ten imputations were performed, and the outcome variable was included in the model. Multivariable survival analyses were repeated after replacing missing data using multiple imputation [18], shown as "adjusted 2" in tables 2a and 2b. This is the main analysis.

Results

During the study period, 2131 kidney donors had available data on blood pressure and use of blood pressure medication at time of donation. Of these, 140 had hypertension. At baseline, mean blood pressure was 147/89 mmHg in donors with hypertension and 124/78 mmHg in those without. Baseline data for hypertensive donors and normotensive donors are shown in table 1. Eight hypertensive donors had a well controlled blood pressure on antihypertensive treatment. Four of these donors used a diuretic agent, two donors used a calcium blocker, one used an angiotensin 2 receptor antagonist and one used a betablocker. The remaining 132 donors classified in the hypertensive group were not receiving any antihypertensive treatment at the time of donation. Hypertensive donors had a mean age of 57.7 years, 44.3 % were male. The median observation time for hypertensive donors was 20.8 years, and 18.6 years for normotensive donors. During the study period, there were 71 deaths among donors with hypertension, 26 of which were due to cardiovascular disease.

Among 1991 normotensive donors there were 369 deaths, 115 of which were due to cardiovascular disease. In the entire pool of donors, some of the most prevalent cardiovascular causes of death were myocardial infarction, stroke and heart failure. Other frequent registered causes were cancer (breast, gastrointestinal and lung malignancy being the most prevalent), chronic obstructive pulmonary disease, different types of trauma and unspecified dementia. In multivariable analysis of all 2131 donors, there were no significant associations between hypertension at the time of donation and overall mortality (hazard ratio (HR) 1.1, 95% confidence interval (CI) 0.9-1.5, p=0.34) (table 2a). Correspondingly, there was no significant increase in cardiovascular mortality (HR 1.1, 95 % CI 0.7-1.8, p=0.55) (table 2b).

Discussion

In the present study we showed that kidney donors with hypertension at donation did not have a significant increase in long-term overall mortality or cardiovascular mortality compared with the normotensive donors. Only two previous studies have evaluated the associations between hypertension at the time of donation and mortality. Segev et al. found that pre-donation hypertension in living donors was associated with increased surgical mortality [1]. In a long-term follow-up study Sanchez et al evaluated the potential consequences of having hypertension before donation [17]. Although the primary objective

was not to study outcomes for hypertensive donors at donation they reported that all-cause mortality or incidence of cardiovascular disease was similar in donors with or without pre-donation hypertension. However, these patients were younger and had lower blood pressures and lower mortality rates than in the present study.

The lack of a significant association between hypertension and long-term mortality may be surprising for several reasons. First of all there is epidemiological evidence that even slightly elevated levels of blood pressure associate with mortality [7-9]. Accordingly the mean blood pressure differences between the hypertensive and normotensive donors in the present study would indicate more than a two-fold increase in long-term mortality as shown in studies on hypertension in the general population [19]. However, the present study on kidney donors may be different due to careful selection and screening for comorbidities and thus the donors may have lower risk for cardiovascular or all-cause mortality. An additional point is that our donors are scheduled for life-long regular medical follow-up free of charge which may result in early intervention for risk factors and disease.

Kidney donation inevitably leads to a reduction in glomerular filtration rate (GFR) which itself may associate with increased long-term mortality [20]. Previously we have shown a slight increase in long-term cardiovascular and all-cause mortality in non-hypertensive donors compared with healthy controls [4]. A Canadian study group did not find higher risk of cardiovascular events in their donor cohort compared to healthy controls, but these studies were limited by short follow up time and relatively few events [21,22].

Three different studies have addressed different surrogate markers for cardiovascular disease after kidney donation [11-13]. In these studies the donors were normotensive at the time of nephrectomy. Moody et al [11] showed that donor nephrectomy increased left ventricular mass, and elevated serum markers such as troponin, parathyroid hormone (PTH)

and uric acid. Altmann et al [13] also showed increased left ventricular mass after 1 year while Kasiske et al [12] demonstrated that uric acid and PTH was increased 3 years after nephrectomy. A range of smaller studies in kidney donors with hypertension at donation have shown adverse effects on diverse outcomes such as GFR, albuminuria, diabetes and blood pressure, but the long-term effects remain uncertain [14,15, 23-30].

Our study has some limitations. We included retrospectively a large number of donors over a long time-span with changes in medical care and with increasing restriction of acceptable blood pressure limits. It is also likely that a hypertensive potential donor would undergo repeated blood pressure measurements. Only eight donors were on blood pressure medication, and hypertension was analysed as a binary variable as opposed to a continous arterial blood pressure variable. Our results may not extrapolate to non-caucasians. In Norway, health care is equally accessible to all citizens. Also, Norway offer donors life long free follow-up of donors, making results less generalizeable to other health care systems. A major strength of this study is the complete follow-up of all donors with verified causes of death and the long follow-up time. We also had available data concerning important cardiovascular risk factors, such as smoking and body mass index.

In conclusion, kidney donors with hypertension did not have a significant increase in long-term overall or cardiovascular mortality compared to normotensive donors. These findings may support the practice of using older living donors with hypertension.

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Table 1 Baseline data

	Hypertensive donors		Normotensive donors	
Variable	n	Means (SD), frequencies (%)	n	Means (SD), frequencies (%)
Age	140	57.7 (11.2)	1991	46.9 (12.4)
Male gender	140	62 (44.3)	1991	827 (41.5)
Observation time, yrs	140	20.8 (11)[a]	1991	18.6 (12.6)[a]
Smoker	96	32 (33)	1545	628 (40.6)
BMI	113	26.4 (3.7)	1755	24.7 (3.3)
Systolic BP	140	147 (9.9)	1991	123.8 (10)
Diastolic BP	140	88.9 (7.3)	1990	77.7 (7.3)
eGFR CKD-EPI	139	91.8 (18.3)	1980	101.2 (19.2)
First degree relative	140	117 (83.6)	1991	1579 (79.3)
Deaths	140	71 (50.7)	1991	369 (18.5)
Cardiovascular deaths	140	26 (18.5)	1991	115 (5.8)

Yrs, years

[a] Median (interquartile range)

Table 2a **Hazard ratios for long term death by any cause in 2131 living donors**

	Unadjusted n= 440/2131	Adjusted 1[a] n=226/1476	Adjusted 2[b] n=440/2131
Donation year	1.0 (1.0-1.0, P=0.001)	1.0 (1.0-1.0, P=0.12)	1.0 (1.0-1.0, P=0.01)
Age	1.1 (1.1-1.1, P<0.001)	1.1 (1.1-1.1, P<0.001)	1.1 (1.1-1.1, P<0.001)
Male	1.2 (1.0-1.4, P=0.11)	1.7 (1.3-2.2, P<0.001)	1.4 (1.1-1.7, P=0.001)
Smoking	1.0 (0.8-1.3, P=0.99)	1.8 (1.4-2.4, P<0.001)	1.4 (1.1-1.9, P=0.005)
BMI	1.1 (1.0-1.1, P<0.001)	1.0 (1.0-1.0, P=0.48)	1.0 (1.0-1.0, P=0.41)
Hypertension	2.6 (2.0-3.4, P<0.001)	1.2 (0.8-1.7, P=0.47)	1.1 (0.9-1.5, P=0.34)
First degree relative	1.4 (1.0-1.8, P=0.045)	1.2 (0.8-1.8, P=0.28)	1.2 (0.9-1.6, P=0.23)
eGFR CKD-EPI	1.0 (1.0-1.0, P<0.001)	1.0 (1.0-1.0, P=0.07)	1.0 (1.0-1.0, P=0.23)

1[a] Adjusted for donation year, age, gender, smoking, BMI, first degree relative of recipient and GFR

2[b] After multiple imputation

Table 2b **Hazard ratios for long term cardiovascular death in 2131 living donors**

	Unadjusted n=137/2131	Adjusted 1[a] n=66/1472	Adjusted 2[b] n=137/2131
Donation year	0.9 (0.9-1.0, P<0.001)	0.9 (0.9-1.0, P=0.003)	0.9 (0.9-1.0, P<0.001)
Age	1.1 (1.1-1.2, P<0.001)	1.1 (1.1-1.2, P<0.001)	1.2 (1.1-1.2, P<0.001)
Male	1.1 (0.8-1.5, P=0.65)	1.7 (1.0-2.8, P=0.05)	1.4 (1.0-2.0, P=0.04)
Smoking	0.7 (0.5-1.1, P=0.14)	1.8 (1.0-3.0, P=0.03)	1.2 (0.7-2.0, P=0.42)
BMI	1.1 (1.0-1.1, P=0.01)	1.0 (1.0-1.1, P=0.35)	1.0 (1.0-1.1, P=0.63)
Hypertension	3.1 (2.0-4.7, P<0.001)	0.7 (0.4-1.6, P=0.42)	1.1 (0.7-1.8, P=0.55)
First degree relative	2.2 (1.2-4.3, P=0.02)	2.3 (0.8-6.5, P=0.11)	1.5 (0.8-3.0, P=0.20)
eGFR CKD-EPI	1.0 (1.0-1.0, P<0.001)	1.0 (1.0-1.0, P=0.53)	1.0 (1.0-1.0, P=0.99)

1[a] Adjusted for donation year, age, gender, smoking, BMI, first degree relative of recipient and GFR

2[b] After multiple imputation