Live Donor Study – Implications of Kidney Donation on Cardiovascular Risk with a Focus on Lipid Parameters including Lipoprotein a

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Carmel Hawley has no conflicts to declare.

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Abstract

In this prospective observational cohort study we evaluate the change in cardiovascular risk parameters, with a focus on lipids, in live kidney donors one year post donation. Body mass index (BMI), systolic/diastolic blood pressure, kidney function (51 Cr-EDTA eGFR), and lipid parameters were measured at baseline and one year. Data on 87 live kidney donors was collected. BMI increased from 26.5 ± 2.7 pre to 27.4 ± 3.0 kg/m^2 post donation ($p<0.0001$). 51 Cr-EDTA eGFR decreased from 111.8 ± 20.0 pre to 72.1 ± 13.1 ml/min/1.73m^2 post donation ($p<0.0001$). Serum triglyceride levels increased from 0.8 (IQR 0.6-1.3) pre to 1.0 mmol/l (IQR 0.7–1.6) post donation ($p=0.0004$). Statin use increased from 11.5% pre to 21% post donation ($p<0.005$). LDL remained stable and other lipids (HDL, Apo B, Lp(a)) did not change post donation.

KEYWORDS

Living donor transplantation; Transplantation; Lipids; Lp(a); Cardiovascular risk

Introduction

Living kidney donors take on immediate and long term risks for the benefits that are gained by the grafts' recipients. Recent studies suggest that live kidney donors are at a small but increased risk of progression to end stage kidney disease (ESKD) and cardiovascular events when compared to healthy matched donors (1, 2). Other studies have shown increased uraemic toxin levels and small but significant increases in blood pressure and proteinuria in live donors (3-5). These newly appreciated risks call for further investigation into kidney donor cardiovascular risk.

Chronic kidney disease (CKD) is associated with cardiovascular disease risk that increases as kidney function declines (6). Lipoprotein metabolism and function is altered in patients with CKD as the renal dyslipidaemic lipid profile demonstrates increased total cholesterol, triglycerides and Lp(a) with decreased high-density lipoprotein (HDL) levels (7). The aim of this prospective observational cohort study is to examine cardiovascular risk parameters, with a focus on lipid profiles, in living kidney donors pre and post donation.

Materials and Methods

Participants and study design

This study was conducted at a tertiary Australian hospital. Prospective donors were deemed eligible according to the Queensland Renal Transplant Service protocol (8). Enrolment began in September 2007. Participants provided informed consent and ethics approval was obtained through the institution's Human Research Ethics Committee (HREC/2007/078).

Laboratory Assessment and statistical analysis

Serum samples were collected from fasting participants before and one year after nephrectomy. Serum total cholesterol, triglycerides, HDL, LDL, and creatinine were measured with standard laboratory methods. The Sebia Hydrasys LC was used to measure Lp(a). Apo A-1 and Apo B were measured with the Siemens BN2 Nephelometer. Kidney function was measured with chromium-51 ethylenediaminetetraacetic acid (EDTA). Wedderburn SK-VET scales correct to 0.1kg were used to measure weight. Height was measured using a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight (Kg)/height $(m)^2$ and classified according to the World Health Organisation classification. Statistical analysis was performed using Stata (version 12;2012;StataCorp, College Station, TX). The null hypothesis was rejected at the 0.05 level.

Results

Baseline Characteristics

Eighty-seven donors were recruited and followed-up at one year post donation. Baseline Characteristics are listed in Table 1. Mean donor age was above 51 years and 66% were female. The mean BMI of the participants was 26.5 ± 2.7 Kg/m^2. Pre-existing cardiovascular disease (1%), anti-hypertensive use (10%), and statin use (11.5%) along with family history of hyperlipidaemia (15%) was self-reported by the donors. 51 Cr-EDTA eGFR reported the mean baseline eGFR of 111.8 ± 20.0 $ml/min/1.73m^2$.

Longitudinal Changes

BMI increased following donation by 0.86 kg/m^2 (0.54, 1.17) ($p<0.0001$) with an average weight gain of 2.43 Kg (1.55, 3.32) ($p<0.0001$). The number of obese (BMI 30-35) donors increased from 8% to 15% (Figure 1). No cardiovascular events were observed. Post donation 51 Cr-EDTA eGFR was 72.1 ± 13.1 $ml/min/1.73m^2$ with a mean decrease of 39.6

(42.23, 36.92) ml/min/1.73m^2 ($p<0.0001$) (Table 2). There was no significant change in systolic or diastolic blood pressure (Table 2). Statin use increased from 11.5% pre to 21% post donation ($p<0.005$). Small but statistically significant increases in triglycerides and Apo A-1 were observed (Table 2).

Discussion

The live donor study is the first prospective study to evaluate cardiovascular risk parameters including extensive lipid profiles of kidney donors before and one year after donation. This study identifies an increase in BMI and triglycerides post donation which may have implications for donor cardiovascular risk. Statin use was increased post donation and in this setting there was no significant change in total cholesterol, LDL, HDL, Apo B, or Lp(a).

BMI

Increased kidney donor BMI of 0.86 kg/m^2 was observed across this study (Table 2). The percentage of obese donors more than doubled from 8% to 15% at follow-up (Figure 1). Previous retrospective studies have identified weight gain and progression to obesity in kidney donors (9,10). This is a concerning finding as obesity is a risk factor for diabetes and hypertension and for the development and progression of kidney disease (11-13). Obesity has been associated with the development and progression of renal failure in non-donation associated nephrectomy (14). The observed increase in donor weight may reflect a regain of weight lost pre-donation, as specified weight targets are often advised according to unit criteria. Better understanding of the risks of such practices is required. Overall, weight gain and progression to obesity may be a contributor to poor long-term donor outcomes and requires further study.

eGFR

Mean one year post donation 51 Cr-EDTA eGFR was 72.1 ml/min/1.73m^2 (Table 2). With the use of radiolabelled chromium, we report a decrease in donor eGFR of 39.6 ml/min/1.73m^2.

Hypertension

No change in systolic or diastolic blood pressure was observed and mean donor blood pressure remained well controlled post donation (table 2). Increased blood pressure of 6 mmHg systolic and 4 mmHg diastolic has been observed within 5 to 10 years post donation (4). This suggests vigilant monitoring for hypertension is required years after donation.

Lipids

Concerning donor lipid profiles, median triglyceride levels increased from 0.8 mmol/L to 1.0 mmol/L (Table 2). There was no change in total cholesterol, HDL, LDL, or Apo B. The observed increase in Apo A-1 of 0.09 g/L is not clinically significant. Aside from the increase in triglycerides, we did not observe changes consistent with the renal dyslipidaemic profile despite the decline in renal function observed. The mechanism of increased triglycerides in donors is not clear, however it may reflect dietary changes post-donation. Triglycerides are a well-established cardiovascular risk factor (15), however with the increase in median triglycerides to 1.0 mmol/L donors remain in the low risk category.

Statin use

Statin use increased from 11% to 21% post donation. Statins act to decrease total cholesterol, decrease triglycerides, decrease LDL, increase HDL, increase Apo A-1 and decrease Apo B (16, 17). No data was collected on the reason for statin commencement, however pre donation demographics predictive of starting a statin included total cholesterol, triglycerides,

LDL, and Apo-B (univariate logistic regression, data not shown). In view of the small number of donors started on statins (n=8), multivariate logistic regression was not appropriate. The increased statin use may have masked changes in other donor lipid parameters.

Lp(a)

This study helps clarify the role of the kidney in Lp(a) kinetics and the impact of kidney donation on Lp(a) related cardiovascular risk. Lp(a) is believed to be influenced by GFR with previous studies reporting increasing Lp(a) levels across all stages of kidney disease (18). The relationship between Lp(a) and GFR has appeared inversely proportional (18). Live kidney donors in this study sustained a substantial decrease in eGFR, however we observed no corresponding increase in serum Lp(a) levels (Table 2). The mechanism of increased Lp(a) levels in individuals with kidney disease remains uncertain but this data suggests that reduced clearance (from 72-111 ml/min/1.73m^2) may be a concomitant instead of causative factor. Furthermore, individuals with serum Lp(a) levels above 30mg/dl have a 1.75 fold risk of myocardial infarction (19). The number of donors with serum Lp(a) levels greater than 30mg/dl (29 donors) did not change after donation. Statins have no Lp(a) lowering effects (20) therefore the increased statin use is unlikely to account for these results.

Limitations

There are limitations to this study. Donors are encouraged to achieve optimal weight before donation and the observed increased donor BMI may reflect a return to individual baseline. No data was collected on weight loss that occurred prior to referral to the transplant unit and this is an important area requiring further study. Increased statin use post donation likely influenced lipid outcomes, however no record of factors considered when initiating statins are available as statins were commenced by patients' General Practitioner. This study presents

one year follow-up data while long-term follow-up would be better identify which donors progress to cardiovascular events and ESKD.

Conclusions

This is the first prospective observational cohort study to examine cardiovascular risk parameters with a focus on lipid parameters in living kidney donors pre and post donation. We found significant increases in BMI and statin use, but overall cardiovascular risk factor profiles remained well controlled. This is somewhat reassuring but warrants further longer term studies to delineate if there is any increase in cardiovascular risk associated with live donor nephrectomy.

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Table 1. Baseline Characteristics

Characteristic	
Age (years)	51.8 ± 10.4
Female Gender (n) %	57 (66%)
BMI (kilograms/meters^2)	26.5 ± 2.7
Weight (kilograms)	75.3 ± 12.1
Cardiovascular Disease (n) %	1 (1%)
Creatinine (micromoles/litre)	68.5 ± 13.8
Kidney Function Cr51 EDTA eGFR (millilitre/minute/1.73metre^2)	111.8 ± 20.0
Anti-hypertensive use (n) %	9 (10%)
Systolic Blood Pressure (mmHg)	124.3 ± 11.7
Diastolic Blood Pressure (mmHg)	76.5 ±8.5
Family History of Hyperlipidaemia (n) %	13 (15%)
Statin use (n) %	10 (11.5%)
Total Cholesterol (millimoles/litre)	5.4 ± 1.1
Triglycerides (millimoles/litre)	0.8 (0.6, 1.3)
HDL (millimoles/litre)	1.4 ± 0.4
LDL (millimoles/litre)	3.5 ± 0.9
Apo A-1 (grams/litre)	1.6 ± 0.2
Apo B (grams/litre)	0.98 ± 0.27
Lp(a) (grams/litre)	0.18 (0.06, 0.46)

Mean +/- standard deviation; Median (Interquartile Range). BMI (Body Mass Index), 51 Cr-EDTA eGFR (Chromium-51 ethylenediaminetetraacetic acid estimated glomerular filtration rate), Lp(a) (lipoprotein a), HDL (High-Density Lipoprotein), LDL (Low-Density Lipoprotein), Apo A-1 (apolipoprotein A-1), Apo B (apolipoprotein B).

Table 2. Change in characteristics at 1 year post kidney donation

Characteristic	Baseline	1 Year	Delta over one year	P- Value
Body Mass Index (kilograms/meters^2)	26.5 ± 2.7	27.4 ± 3.0	0.86 (0.54, 1.17)	P< 0.0001
Weight (Kilograms)	75.3 ± 12.1	77.7 ± 13.0	2.43 (1.55, 3.32)	P< 0.0001
Cardiovascular Disease	1 (1%)	1 (1%)	0%	P=N/S
Kidney Function 51 Cr-EDTA eGFR (ml/min/1.73m^2)	111.8 ± 20.0	72.1 ± 13.1	-39.6 (-42.23, -36.92)	P< 0.0001
Ant-hypertensive use	9 (10%)	10 (11%)	1.1% (-2.2, 4.5)	P= 0.317
Systolic Blood Pressure (mmHg)	124.3 ± 11.7	124.8 ± 13.4	0.33 (-2.70, 3.35)	P=0.830
Diastolic Blood Pressure(mmHg)	76.5 ± 8.5	78.4 ± 7.8	1.84 (-0.01, 3.7)	P=0.0516
Statin Use	10 (11.5%)	18 (21%)	10.3% (2.0, 16.4)	P<0.005
Total Cholesterol (millimoles/litre)	5.4 ± 1.1	5.4 ± 1.0	-0.01(-0.18, 0.16)	P=0.873
Triglycerides (millimoles/litre)	0.8 (0.6, 1.3)	1.0 (0.7, 1.6)		P=0.0004
HDL (millimoles/litre)	1.4 ± 0.4	1.5 ± 0.4	+0.04 (-0.01, 0.09)	P=0.103
LDL (millimoles/litre)	3.5 ± 0.9	3.4 ± 1.0	-0.15 (0.29, 0.002)	P=0.0530
Apo A-1 (grams/litre)	1.6 ± 0.2	1.7 ± 0.3	+0.09 (0.05, 0.13)	P=0.0001
Apo B (grams/litre)	0.98 ± 0.27	0.99 ± 0.24	0.01 (-0.02, 0.05)	P=0.457
Lp(a) (grams/litre)	0.18 (0.06, 0.46)	0.19 (0.06, 0.51)		P=0.072

Mean +/- standard deviation, Median (Interquartile range). BMI (Body Mass Index), 51-Cr EDTA eGFR (chromium-51 ethylenediaminetetraacetic acid estimated glomerular filtration rate), HDL (High-Density Lipoprotein), LDL (Low-Density Lipoprotein), Apo A-1 (apolipoprotein A-1), Lp(a) (lipoprotein a), Apo B (apolipoprotien B).

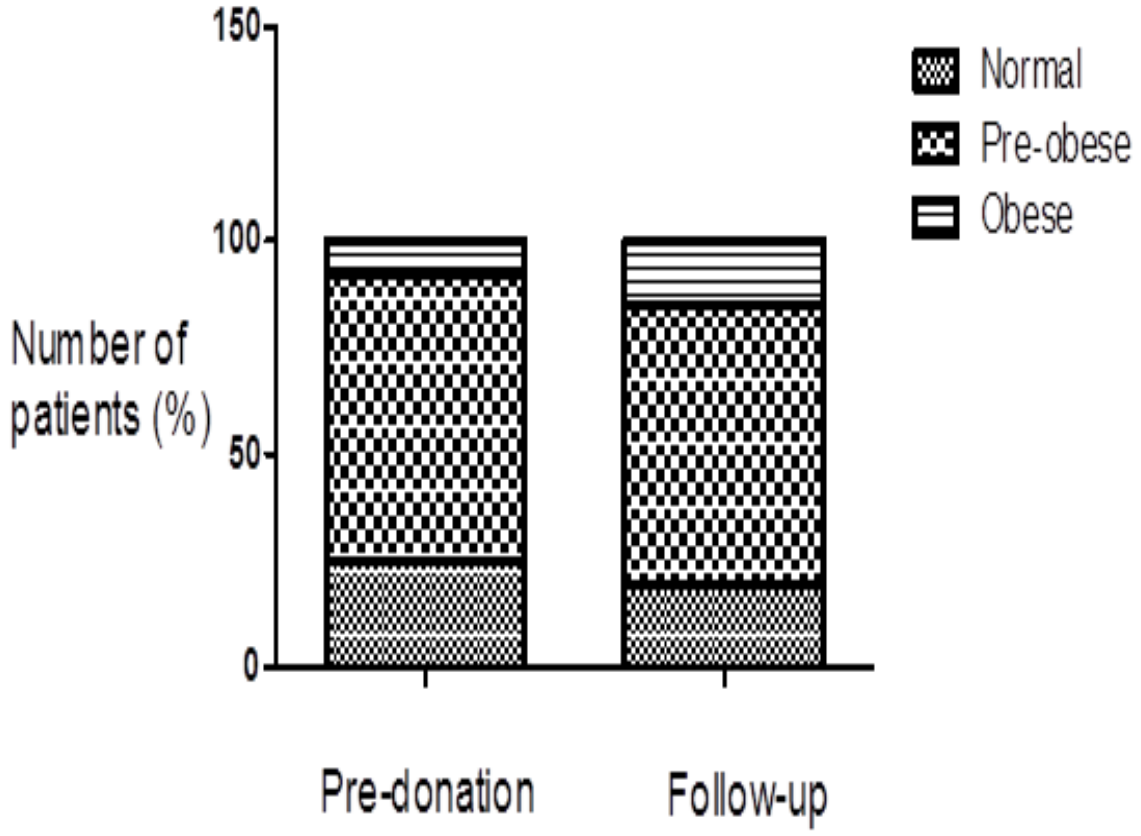

Figure 1. BMI distribution before and after kidney donation; Normal (BMI 18.5-24.9 kg/m2), Pre-obese (BMI 25 to 29.9 kg/m2), Obese (BMI ≥ 30 kg/m2).