

# Importance of Comprehensive Cardiovascular Screening in Patients Scheduled for Kidney Donation

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## Abstract

**Introduction:** End stage renal disease is on the rise in many parts of the world. Kidney transplant is a common procedure and definitive treatment for end stage renal disease. Along with its various advantages, it presents with an array of complications, associated with the procedure. Hence, an effective screening program to identify eligible donors is of crucial importance. The main aim of this study was to identify the frequency of possible undetected cardiovascular abnormalities in scheduled donors and its association with gender.

**Methods:** A sample size of 402 was selected with an equal number of donor and non-donor participants after age and gender matching. A positive electrocardiogram (ECG) change was defined as cardiac ischemia, occurring during exercise tolerance test (ETT), with 2 mm horizontal or down sloping ST-segment depression occurring 0.08 milliseconds after J-point whereas an exaggerated blood pressure (BP) was defined as high systolic blood pressure (SBP) at rest to maximum effort  $\geq 7.5$  mmHg/MET (metabolic equivalents) and/or SBP at the peak of effort  $\geq 220$  mmHg or subjects with high diastolic blood pressure (DBP) at rest to maximum effort  $\geq 15$  mmHg, from normal levels of blood pressure at rest. Chi square was used as the primary statistical test.

**Results:** Scheduled kidney donors had significantly ( $P=0.007$ ) higher proportion ( $n=19$ , 9.5%) of positive ECG changes and exaggerated BP response ( $n=35$ , 17.4%) ( $P<0.0001$ ) compared with the controls. Also, female donors had significantly ( $P=0.025$ ) higher ( $n=16$ , 13.2%) chances of having a positive ECG change.

**Conclusion:** A significant number of kidney donors have undetected cardiovascular abnormalities which could lead to post-transplant complications. Therefore, effective screening should be made imperative to avoid preventable complications such as hypertension of kidney transplantation.

**Keywords:** kidney donor, renal transplantation, hypertension, ECG

## 1. Introduction

End stage renal disease, also known as the stage 5 of chronic renal disease, is an extremely common problem worldwide. It has been estimated that 2 million people suffer from end stage renal disease worldwide (U.S. Renal Data System, 2015). More than 600,000 patients have end stage renal disease in the United States of America alone. Statistics suggest that the situation is likely to worsen. Previous data also shows that end stage renal disease is increasing worldwide at the rate of five percent per year (U.S. Renal Data System, 2015). The irony is that many patients who have advanced kidney disease do not know they have deteriorating kidneys. It is vital that patients are counseled that early detection and treatment can prevent catastrophic complications.

As the treatment of choice for end stage renal disease, kidney transplantation occurs globally in 27,000 patients per year. It is projected that the rate will rise over the next 10 years due to an increasing number of patients with terminal renal disease (Horvat, Shariff, & Garg, 2009), (The UNOS Scientific Renal Transplant Registry). Already, the waiting list for kidney transplant is in millions making kidney donation an important public health topic (U.S. Department of Health and Human Services: OPTN). For instance in the United States of America there are more than hundred thousand patients on the renal transplant list but annually only less than twenty thousand kidney donors are available. It has also been projected that the need for kidney donors is increasing at a rate of 8 percent annually (U.S. Renal Data System, 2015).

It is widely acknowledged that living donor kidneys have a better graft survival as compared with cadaveric donor kidneys (Koo et al., 1999; Ojo et al., 2001). Due to the recent shortage of deceased kidney donors, there has been an upward trend in kidney transplantations from living kidney donors (LKDs), worldwide, accounting as much as 39% of all kidney transplants. Over the last decade alone, 62% of countries reported at least a 50% increase in living donor transplantations (Horvat, Shariff, & Garg, 2009). However living donor transplants come with their own share of problems. For the transplant to occur, the donor undergoes a major operation with its own associated mortality and complications (Najarian, Chavers, McHugh, & Matas, 1992; Johnson et al., 1997). The long term risks for kidney donors are also of some concern. Long term follow up has shown that mild, non-progressive proteinuria develops in 33% of donors while a substantial number of donors experience a decrease in their glomerular filtration rates (Kasiske, Ma, Louis, & Swan, 1995; Bay & Hebert, 1987). Moreover, a significant number of living kidney donors have a 5 mmHg increase in blood pressure within 5 to 10 years of donation over that anticipated with normal aging (Boudville et al., 2006; von Zur-Mühlen, Berglund, Yamamoto, & Wadström, 2014). This is concerning because research suggests that In the general population, every 10 mmHg increase in systolic blood pressure and 5-mm Hg increase in diastolic blood pressure is associated with a 1.5-fold increase in death from ischemic heart disease and stroke (Lewington et al., 2001).

As donors do not benefit directly from their surgery and medical ethical principles dictate to 'do no harm' (Barri, Parker, Kaplan, & Glassock, 2009) it is imperative that the risk of negative medical and psychological consequences is minimized after donation. Hence, screening of donors is vital to ensure the well-being of both the donor and recipient in the short and long term. However, even proper screening has been unable to prevent the above problems from occurring (Sachdeva et al., 2011). Especially, with illegal organ selling commonly found in many uneducated areas of our region, awareness regarding thorough screening before donation must be preached.

We suggest that post-transplant high blood pressure in donors could be due to pre-existing, yet hidden cardiovascular problems. Keeping this in mind, the main objective of this study was to determine the frequency of hidden cardiovascular problems in donors and its association with gender.

## 2. Material and Methods

This study was conducted in the cardiology and nephrology departments of a tertiary care hospital from January 2011 to January 2014 after approval from Dow University of Health Sciences. Using the difference in long term systolic BP among donors and controls as reported by Undurraga A et al. (1998), and taking 99% confidence interval with 95% power of the test, the minimum sample size calculated was 360 (180 donors and 180 controls). Anticipating a high possible drop-out rate, we decided to include 210 donors initially of whom 7 were not able to complete the study and 2 refused to give consent for participation in the study. To equilibrate the data, 201 age and gender matched controls were retrospectively queried from the healthcare data warehouse and patient medical records, who had visited our hospital during the same time frame to give us an overall sample size of 402.

The inclusion criteria were set to only include patients between the ages of 18 and 65 years, who had no known co-morbid such as diabetes, cancer or kidney disease as these can rule out a person from donating. Subjects were excluded from the study if they had murmurs, arrhythmias or any sort of previous heart surgery or took anti-hypertensives or any other drug (e.g. Beta blockers, Amiodarone etc.) that could interfere with blood pressure measurement during exercise tolerance test. No imputation models were used and only subjects with complete data were included. Informed consent was taken from all the participants for inclusion in our study. Demographic variables were recorded, after which they were subjected to exercise tolerance test (ETT) while their blood pressure and electrocardiogram (ECG) was continuously monitored during the duration of the test. For donors, this test was conducted 4 weeks prior to donation.

A positive electro cardiogram change was defined as cardiac ischemia, occurring during exercise tolerance test-indicated by typical chest pain with 2mm horizontal or down sloping ST-Segment depression occurring 0.08

milliseconds after J-point (Rywik et al., 2002). An exaggerated BP response was defined as high systolic blood pressure (SBP) at rest to maximum effort  $\geq 7.5$  mmHg/MET (metabolic equivalents) and/or systolic blood pressure at the peak of effort  $\geq 220$  mmHg or subjects with high diastolic blood pressure (DBP) at rest to maximum effort  $\geq 15$  mmHg, from normal levels of blood pressure at rest (Lima et al., 2013).

The collected data were entered and analyzed on Statistical Package for Social Sciences (SPSS) software version 20. Descriptive measures were presented in terms of frequency and percentages. To compare blood pressure response and electro cardiogram changes between donors and non-donors, chi-square test was used. P value less than 0.05 was considered to portray significant effect.

### 3. Results

Among the 402 participants, 160 (39.8%) were males and 242 (60.2%) were females with equal gender distribution in the donor and control groups. There was also no statistical difference between the two groups in terms of obesity ( $P=0.829$ ), smoking ( $P=0.770$ ) and socio-economic status ( $P=0.135$ ). Both groups also had similar mean glomerular filtration rates and serum creatinine values.

The proportion of positive electro cardiogram changes among donors ( $n=19$ , 9.5%) was significantly higher than non-donors ( $n=6$ , 3%) ( $P=0.007$ ). Similarly, the exaggerated blood pressure response among donors ( $n=35$ , 17.4%) was also significantly more compared with non-donors ( $n=7$ , 3.5%) ( $P<0.001$ ). These results are displayed in Table 1.

Table 1. Characteristics of donors versus non-donors

		Donors	Non-donors	P Value
Mean Age (years)		42.4	42.4	0.999
Females		121 (60.2%)	121 (60.2%)	0.999
Smokers		27 (13.4%)	29 (14.4%)	0.770
Obese (Body mass index $\geq 30$ )		12 (5.97%)	11 (5.47%)	0.829
Low socioeconomic status		110 (54.7%)	95 (47.3%)	0.135
Glomerular Filtration rate (ml/min/1.73m <sup>2</sup> )		119 $\pm$ 6	118 $\pm$ 8	0.157
Serum Creatinine (mg/dl)		0.93 $\pm$ 0.2	0.89 $\pm$ 0.27	0.092
ECG changes	Positive	19 (9.5%)	6 (3%)	0.007
	Negative	182 (90.5%)	195 (97%)	
BP response	Appropriate	166 (82.6%)	194 (96.5%)	<0.001
	Exaggerated	35 (17.4%)	7 (3.5%)	

We found that positive electro cardiogram changes occurred more frequently in female donors ( $n=16$ , 13.2%) compared with male donors ( $n=3$ , 3.8%). This difference was found to be statistically significant ( $P=0.025$ ). Higher number of female donors ( $n=25$ , 20.7%) had an exaggerated blood pressure response than male donors ( $n=10$ , 12.5%). These findings are consistent with earlier studies suggesting that women who have donated a kidney have a higher risk of gestational hypertension and preeclampsia than matched non donors with similar indicators of baseline health (Garg et al., 2015). However, this was not found to be statistically significant ( $P=0.135$ ). Table 2 depicts these findings.

Table 2. Proportion of positive ECG changes and exaggerated BP response in male and female donors

		Male	Female	P Value
ECG changes	Positive	3 (3.8%)	16 (13.2%)	0.025
	Negative	77 (96.3%)	105 (86.8%)	
BP response	Appropriate	70 (87.5%)	96 (79.3%)	0.135
	Exaggerated	10 (12.5%)	25 (20.7%)	

#### 4. Discussion

With the increasing incidence of end-stage kidney disease, living donor kidney transplantation is on the rise. Research suggests that of studied kidney transplantations done between 1976 to 2002, as low as 3.5% of the total living donor pool had a truly normal blood pressure at one year post transplantation, without the use of antihypertensive medications (Kasiske et al., 2004). These results are not surprising. Hypertension and pre-existing heart disease have long been considered contraindications to kidney donation with the former being a considered a relative contraindication as opposed to the latter. (Nephrology-Donors at risk: Hypertension (Guidelines)), (Karpinski et al., 2006). Therefore most screening programs for kidney transplantation reject donors who have any antecedent cardiovascular problems. (Living Donors Online!: Contraindications to Living Donation), (University of Maryland Medical center: Living Donor Kidney Evaluation Process). Yet, even with these uncompromising screening programs, a significant majority of donors still develop hypertension-post donation possibly due to undetected cardiovascular problems (Boudville et al., 2006; von Zur-Mühlen, Berglund, Yamamoto, & Wadström, 2014).

Our results indicate that a significant number of donors have undetected cardiovascular problems that only manifest on exercise tolerance tests. More donors had a positive electro cardiogram change as compared to non donors. This is dangerous because these individuals are 2.7 times more likely than the general population to develop cardiac abnormalities (Rywik et al., 2002). Donors also had a greater number of people with exaggerated blood pressure responses. According to Matthews CE et al. (1998) exaggerated blood pressure response on exercise tolerance test is an independent risk factor for development of hypertension. Miyai N et al. (2002) stated that the risk to develop hypertension within 5 years of the test was approximately 4 times greater in those with exaggerated blood pressure responses as compared to those who had normal blood pressure response on exercise tolerance testing.

Females were more susceptible to these inconspicuous problems as compared to males with electro cardiogram changes on exercise tolerance testing being more prevalent in the female gender. These results prove that donors, compared to non-donors are more at risk of developing new onset hypertension and adverse cardiovascular events. It can further be argued that the prevalence of hidden cardiovascular abnormalities in kidney donors could possibly be a reason for the development of post-transplant hypertension in said group. However this is a casual argument, at best, as our research only reveals the presence of obscure cardiovascular abnormalities in a considerable number of donors without following them up to determine establishment of post-transplant hypertension. Also, considering the possible selection bias in our study, we recommend larger clinical studies should be undertaken to confirm the validity and clinical applicability of our findings.

Regardless of the limitations, we believe our study reinforces the vitality of proper effective screening of donors. By confirming that donors harbor anomalies that are not picked up by regular screening programs, this study not only encourages the use of regimented screening but also prompts us to re-evaluate our screening strategies, to minimize any problems.

#### 5. Conclusion

In summary it can be stated that a significant number of kidney donors have undetected cardiovascular abnormalities that could possibly lead to the development of post-transplant complications such as hypertension. Although, the impact of these complications needs further in-depth studying and widespread research, and with present studies being inconclusive to the effect of these complications, it is of pertinent importance that cardiovascular screening be made an essential tool to avoid these preventable consequences of kidney donation and to be able to study them further.

#### Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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