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Effect Of Donor Nephrectomy On Clinical, Biochemical Profile And Renal Function Of Live Kidney Donor

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Abstract:
Introduction:
Currently, available data indicates that long-term health risks associated with donor nephrectomy are pretty low. However, since live related donors form a formidable pool of kidney donors in our country & no available study from our country throws light on the incidence of potential complications like hypertension, proteinuria, and metabolic and renal functions post-donation, there is a need for a prospective study of living related kidney donors.
Methodology:
The study is a prospective study as well as a retrospective study involving 50 voluntary donors who are on follow-up in Urology OPD. Live kidney donors ≥ three months post-donation were studied. The investigations done before kidney donation in these subjects were recorded from their outdoor clinic file records. The statistical analysis was performed on SPSS version 17.0.
Result:
So,Currently, available data indicates that long-term health risks associated with donor nephrectomy were relatively low. The mean follow-up period was 12.8 months. The mean age in our study was 44 yrs. Female donors comprised 63.6% of the total donors. The mean systolic BP in our study was 124.1, while diastolic BP was 82.2 mm of Hg. Mean systolic BP increased to 129.8, and diastolic BP was 82.7 mm of Hg. Two hypertensive donors on single hypertensive drugs had an increased requirement of 2 drugs for adequate control. Four donors developed new Hypertension after Kidney donation. Two donors developed proteinuria. DTPA GFR post-donation reduced from an initial mean of 79.0 ml/min to 67.1 ml/min. Mean serum creatinine increased from 0.87 to 0.97 mg/dl. Mean serum homocysteine increased from a mean 5.89 to 8.12 umol/L. Changes in Fractional excretion of Calcium, phosphorous and uric acid were insignificant.A P-value of < 0.05 was considered significant.

Keywords: *Renal transplant; Live donor; End-stage renal disease*

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I. Introduction

Presently, living-related renal transplant is the preferred treatment for most end-stage renal disease (ESRD) patients **[3].** The rising number of patients reaching ESRD intensifies the demand for expanding the living kidney donor pool **[4].** Although the risk-benefit ratio for the recipient is very much favourable, the benefit for the donor is much harder to define. It is probably minimal if pure medical criteria are considered. Nonetheless, non-medical benefits, predominantly psychosocial, may outweigh the small medical risk. Early renal functional adaptation with no long term ill effects has been documented in most Western studies.

The life expectancy of kidney donors appears to be similar to that of non-donors or perhaps even longer, as suggested by one study **[5].** However, at least two reports have described donors in the United States who were subsequently placed on the waiting list for kidney transplantation. **[6,7]** The risk of ESRD among donors does not appear to be increased, and their current health seems similar to that of the general population. Cross-sectional studies have reported no significant elevated serum creatinine levels for up to 30 years after donation **[8-12].** Uninephrectomy is followed by a compensatory increase in the GFR in the remaining kidney to about 70% of prenephrectomy values**[13].** Compensatory hemodynamic changes in some animal models after a reduction of 50% or more in renal mass have been reported to be ultimately deleterious **[14-16].** There has been

a concern that kidney donors (who undergo a 50% reduction in renal mass with donation) might have hyperfiltration damage in addition to the average loss of kidney function with age **[17-18].**

Whether or not hypertension is increased after kidney donation remains unresolved. The observed incidence of hypertension after kidney donation is variable and reflects age, time since nephrectomy, sex, ethnicity, and definitions/methods used to detect hypertension. On the basis of the limited studies conducted to date, living kidney donors may have a 5-mm Hg increase in blood pressure within 5 to 10 years of donation over that anticipated with normal ageing **[19].** Hypertension does, however, remain an issue of concern in kidney donors. Untreated hypertension is a known risk factor for nephrosclerosis and renal failure in this population. This risk may be enhanced in those with a solitary kidney. The renal reserve is reduced even if serum creatinine remains within normal limits **[20].**

There are reports of microalbuminuria and proteinuria developing after kidney donation. Donors develop microalbuminuria at a faster rate than age and cardiovascular risk matched controls **[21,22].** The aetiology of this new-onset proteinuria or albuminuria is presumed to be related to glomerular changes rather than generalized endothelial dysfunction, although this has not been confirmed. Predictors of a post-donation GFR <60 mL/min include older age (47 ± 12 years), hypertension and proteinuria at the time of donation **[23].**

Not only the above parameters but also tubular functions may alter with kidney donation. Two studies described a reduced renal tubular reabsorption of phosphate after uni-nephrectomy. A significant decrease in renal excretion of calcium was noted one year after donation **[24,25]** Few studies also compared donors before and after uninephrectomy for changes in uric acid metabolism **[26,27].**

An increased prevalence of hyperhomocysteinemia has been seen amongst end stage renal disease patients and numerous studies have shown that kidney function is one of the most important determinants of plasma homocysteine levels. In one of the studies, there was a significant rise in total homocysteine levels immediately after surgery and six months after surgery **[28].**

Therefore currently available data indicates that long term health risks associated with donor nephrectomy are pretty low. However, since live related donors form a formidable pool of kidney donors in our country & no available study from our country throws light on the incidence of potential complications like hypertension, proteinuria, metabolic and renal functions post-donation, there is a need for a prospective study of living related kidney donors.

II. Material and method

This study was a prospective as well as a retrospective observational study conducted from May 2015 to December 2016 in the department of Urology, Nuclear medicine, Biochemistry and Surgery at tertiary care teaching hospital. This study including 50 voluntary donors who were on follow up in Urology OPD included live kidney donor who were in between age group18-65 yrs and excluded voluntary donor suffering from HIV, HBsAG anti HCV positive pts after ethical clearance from the institute's ethical committee**.** Live kidney donors ≥ 3 months post-donation were studied. Those subjects who donated prior to this period but came for follow-up from May 2015 to December 2016 were also included in the study. The investigations done prior to kidney donation in these subjects were recorded from their outdoor clinic file records.Subjects were explained about the study as per the participant information sheet. Informed consent was taken . A detailed history and physical examination were carried out for each living kidney donor pre and post-donation who entered the study per a pre-designed preform .Hypertension was defined by at least two clinic readings of either systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg or on an antihypertensive drugs. The mean blood pressures of two clinic readings were recorded for analysis. Those found to be hypertensive were treated and underwent additional evaluation in fundoscopy examination and 2-dimensional echocardiography. Proteinuria was evaluated by 24 - hour urine collection for protein and adequacy assessed by urinary creatinine excretion. Proteinuria was expressed in grams per gram of creatinine. Tc 99m DPTA GFR was taken as the gold standard. Tc 99m DPTA GFR was measured by two sample plasma methods after intravenous administration of 1 milliCurie Tc^{99m} DTPA, with oral hydration at a rate of 10ml/kg/hour, 30 minutes before the study. Blood samples were collected in heparin anti-coagulated blood samples at 60 minutes and 180 minutes after the injection from the opposite forearm.All living kidney donors were evaluated for hypertension, proteinuria, GFR and any other comorbidities prior to their acceptance for kidney donation.These kidney donors have subsequently evaluated at least three months post-donation for the development of hypertension. Renal function tests including blood urea, serum creatinine, GFR estimation and 24-hour urine protein and creatinine analysis were done. These parameters were compared before and after kidney donation. Kidney donors were also evaluated for fractional excretion of calcium (FeCa), phosphate ($FePO_4$) and uric acid (FeUa) in a state of clinical euhydration. 24-hour urine was collected and was analyzed for creatinine, calcium, phosphorus and uric acid. Serum homocysteine levels were done by the chemiluminescence method. Levels between 5 and 15 micromoles per litre (µmol/L) are normal. Abnormal concentrations were classified as moderate (16-30),

intermediate (31-100), and severe (greater than 100 µmol/L) [66].10 ml of blood each pre and post kidney donation were drawn for analysis. The statistical analysis was performed on SPSS version 17.0. All data were calculated as mean ± standard deviation using Descriptive statistics. The Paired Student′s t-test was used to compare the means between pre and post kidney donation groups. P-value of < 0.05 was considered significant.

III. Observation and Results

Fifty kidney donors were studied for various physiological and biochemical parameters. The study population's pre and post-donation baseline characteristics are shown in Tables 1 and 2.

Age:
The mean age of kidney donors was 44.4±9.1 years. It ranged from 24 years to 65 years.
Sex: Females outnumbered males as kidney donors. 36/50 (61.1%) were females.

Blood pressure:
The mean systolic blood pressure was 124.1±7.2 mm Hg, and the mean diastolic blood pressure was 82.2±4.6 mm Hg. Two donors were hypertensive pre-donation with blood pressure control with a single antihypertensive drug. There was no target end-organ damage on electrocardiogram, 2-dimensional echocardiography, fundoscopy and urine protein/microscopy analysis.

Proteinuria:
The mean 24-hour proteinuria was 0.138±0.042 gram/gram of urine creatinine. It ranged from 0.10 to 0.23.

GFR:
DTPA GFR was performed on all donors. The mean GFR was 79.0±8.8 ml/min.

Biochemical parameters:
The mean serum creatinine was 0.87±0.13 mg/dl. Mean serum homocysteine was 5.89±1.38 (µmol/L). However, serum homocysteine levels were available for only 44 kidney donors, as those who donated kidneys prior to the study period did not undergo homocysteine estimation as part of donor workup. The mean fractional excretion of calcium, phosphorus and uric acid were 2.31±0.39%, 10.39±1.18%, and 8.32±0.84%, respectively.
* The data for homocysteine was available for 44(88%) kidney donors (pre-donation)

	Mean± Standard deviation	Range
Age (years)	44.4±9.1	24-65
Male/female	42/66	-
Systolic BP (mmHg)	124.1±7.2	110-138
Diastolic BP (mmHg)	82.2±4.6	70-90
24-hour urine protein(gram)/gram creatinine	0.138±0.042	0.10-0.23
Serum creatinine (mg/dl)	0.87±0.13	0.6-1.1
DTPA GFR (ml/min)	79.0±8.8	70-120
Serum homocysteine *(µmol/L)	5.89±1.38	3-9
Fractional excretion calcium (%)	2.31±0.39	1.3-3.1
Fractional excretion phosphorus (%)	10.39±1.18	7.8-12.9
Fractional excretion uric acid (%)	8.32±0.84	5.8-10.1

Table 1: Baseline characterstics of the kidney donors (50) pre-donation

Table 2: Characteristics of the kidney donors (50) post-donation

	Mean± Standard deviation	Range
Follow-up (months)	12.8±16.3	4-97
Systolic BP (mmHg)	129.8±10.7	110-162
Diastolic BP (mmHg)	82.7±5.8	70-100
24-hour urine protein(gram)/gram creatinine	0.197±0.185	0.10-2.80
Serum creatinine (mg/dl)	0.97±0.18	0.6-2.4
DTPA GFR (ml/min)	67.1±6.6	54-91
Serum homocysteine (µmol/L)	8.12±3.46	3-50
Fractional excretion calcium (%)	2.26±0.43	1.3-3.0
Fractional excretion phosphorus (%)	10.54±1.15	8.5-12.9
Fractional excretionuric acid (%)	8.50±0.74	6.7-10.1

Follow-up:
The mean follow-up period was 12.8±16.3 months. It ranged from 4 months to 97 months.

Blood pressure:

The mean systolic blood pressure was 129.8±10.7 mm Hg, and the mean diastolic blood pressure was 82.7±5.8 mm Hg. Two donors who were hypertensive pre-donation on a single antihypertensive drug had an increase in requirement to 2 drugs for adequate control. Four (8 %) donors developed new hypertension after kidney donation. There was no evidence of any target end-organ damage on electrocardiogram, 2-dimensional echocardiography, fundoscopy and urine protein/microscopy analysis. The mean systolic blood pressure significantly increased from 124.1±7.2 mmHg at pre-donation to 129.8±10.7 mmHg (p-value 0.000), while there was no change in diastolic blood pressure (82.2±4.6 mmHg vs 82.7±5.8 mmHg, p-value 0.529) Figure-1.

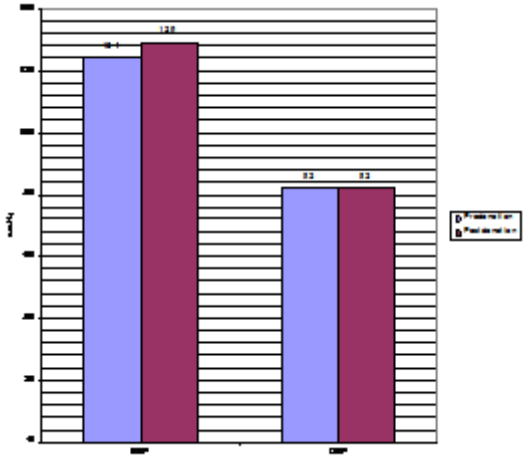

Figure 1:Comparison of Systolic & Diastolic blood pressure Pre and Post kidney donation

Proteinuria:

The mean 24-hour proteinuria was 0.197±0.185 gram/gram of urine creatinine. It ranged from 0.10 to 2.80g/day. Two (12.9%) donors developed proteinuria ranging from 0.30-1.0 g/day—one developed 2.80 g/day of proteinuria with normal renal function tests. A renal biopsy was performed for the same and revealed acute interstitial nephritis. It was implicated to rifampicin use as he also developed pulmonary tuberculosis after kidney donation and was on anti-tubercular drugs. There was a statistically significant increase in 24-hour urine protein from a mean of 0.138±0.042 g to 0.197±0.185g (p-value 0.001) figure-2.

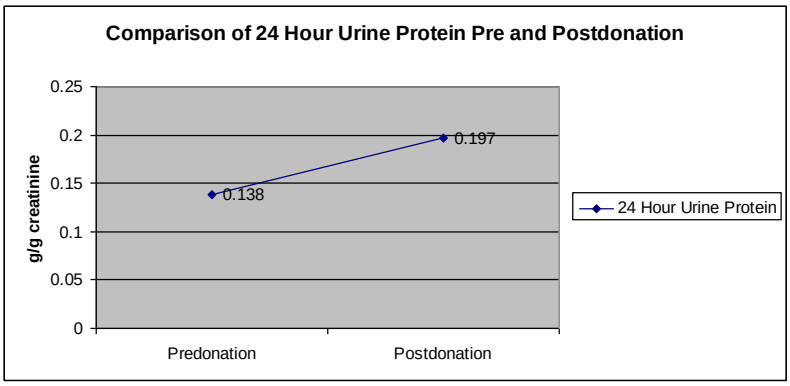

Figure 2:Comparison of 24 Hr Protein Pre and Post kidney donation

GFR:

DTPA GFR was performed in all donors after kidney donation. The mean GFR was 67.1±6.6 ml/min. fall in DTPA GFR from 79.0±8.8 ml/min to 67.1±6.6 ml/min (p value 0.000) after donation figure-3

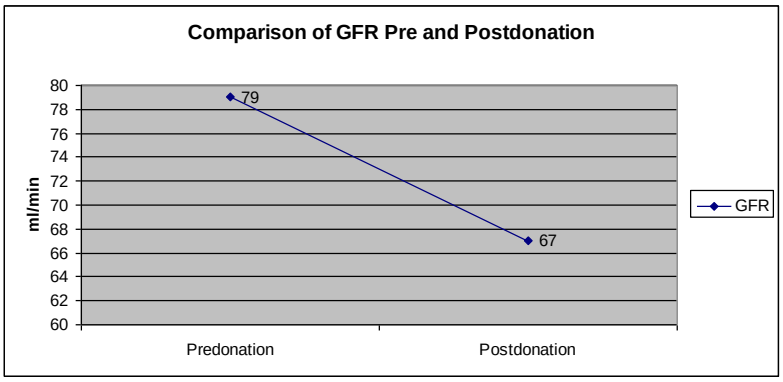

Figure 3: Comparison of GFR Pre and Post kidney donation

Biochemical parameters:

The mean serum creatinine was 0.97±0.18 mg/dl. One donor increased serum creatinine to 2.4 mg/dl without proteinuria. A renal biopsy was done and showed non-proliferative glomerulonephritis. He was put on ramipril, and subsequently, his serum creatinine decreased to 1.6 mg/dl. In renal functions, serum creatinine increased from 0.87±0.13 mg/dl to 0.97±0.18 mg/dl (p-value 0.000).

Mean serum homocysteine was 8.12±3.46 (µmol/L). 5 (4.6%) donors had moderate hyperhomocysteinemia and one (0.9%) had intermediate hyperhomocysteinemia (serum homocysteine 50 µmol/L). Those with moderate hyperhomocysteinemia after kidney donation had normal serum homocysteine levels pre-donation. Isolated donors with intermediate hyperhomocysteinemia did not have pre-donation levels to compare. None of the donors developed severe hyperhomocysteinemia. There was also a significant increase in serum homocysteine after kidney donation (5.89±1.38 µmol/L vs 8.12±3.46 µmol/L, p-value 0.000) figure-4.

The mean fractional excretion of calcium, phosphorus and uric acid were 2.26±0.43%, 10.54±1.15%, and 8.50±0.74%, respectively. No significant changes in fractional excretion of calcium, phosphorus and uric acid were seen after donation as compared to pre-donation respectively (2.31±0.39 % vs 2.26±0.43 % p value 0.304; 10.39±1.18 % vs. 10.54±1.15 % p value 0.272; 8.32±0.84 % vs. 8.50±0.74 % p value 0.062) figure-5.

As there is marked variability amongst the kidney donors, we divided the donors according to age groups (age ≤ 45 and > 45 years. There were 33 donors with age ≤ 45 and 17 of age > 45 years. On analyzing the difference in proteinuria, it was seen that younger donors had a statistically significant change in proteinuria of 0.078±0.213 as compared to an older group of donors, i.e. 0.014±0.091. (p-value 0.03). However, this difference was not seen with respect to change in DTPA GFR (- 10.95±9.3 vs - 12.91±10.6, p-value 0.35). On subgroup analysis, there were 42 male and 66 female kidney donors. On analyzing the difference in proteinuria, it was statistically non-significant amongst males and females (0.021±0.094 vs .079±0.221, p-value 0.06). The change in GFR was also non-significant about sex (- 11.8±10.1 vs - 11.4±9.6, p-value 0.85) table 3,4&5.

Table 3: Comparison of the difference in 24-hour urine protein and difference in GFR of donors pre and post-donation according to age ≤ 45 and > 45 years

	Δ 24 hour proteinuria in gram/g creatinine (pre& post donation) Mean±S.D.	Δ GFR ml/min (pre& post donation) Mean±S.D
Age≤ 45 (n=33)	0.078±0.213	- 10.95±9.3
Age> 45 (n=17)	0.014±0.091	- 12.91±10.6
P value	0.03	0.35

Table 4: Comparison of the difference in 24-hour urine protein and difference in GFR of donors pre and post-donation according to sex

	Δ 24 hour proteinuria in gram/g creatinine (pre& post donation) Mean±S.D.	Δ GFR ml/min (pre& post donation) Mean±S.D
Male (n=19)	0.021±0.094	- 11.8±10.1
Female (n=31)	0.079±0.221	- 11.4±9.6
P value	0.06	0.85

Table 5: Comparison of various biochemical parameters and GFR pre and post-donation

	Pre-donation	Post-donation	P value
Systolic BP (mmHg)	124.1±7.2	129.8±10.7	0.000
Diastolic BP (mmHg)	82.2±4.6	82.7±5.8	0.529
24-hour urine protein(in grams)/gram creatinine	0.138±0.042	0.197±0.185	0.001
Serum creatinine (mg/dl)	0.87±0.13	0.97±0.18	0.000
DTPA GFR (ml/min)	79.0±8.8	67.1±6.6	0.000
Serum homocysteine (µmol/L)	5.89±1.38	8.12±3.46	0.000
Fractional excretion calcium (%)	2.31±0.39	2.26±0.43	0.304
Fractional excretion phosphorus (%)	10.39±1.18	10.54±1.15	0.272
Fractional excretion uric acid (%)	8.32±0.84	8.50±0.74	0.062

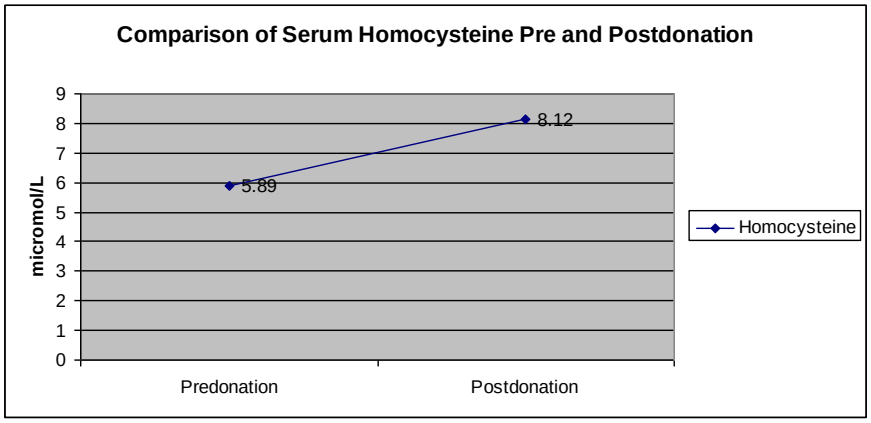

Figure 4: Comparison of serum Homocysteine Pre and Post donation

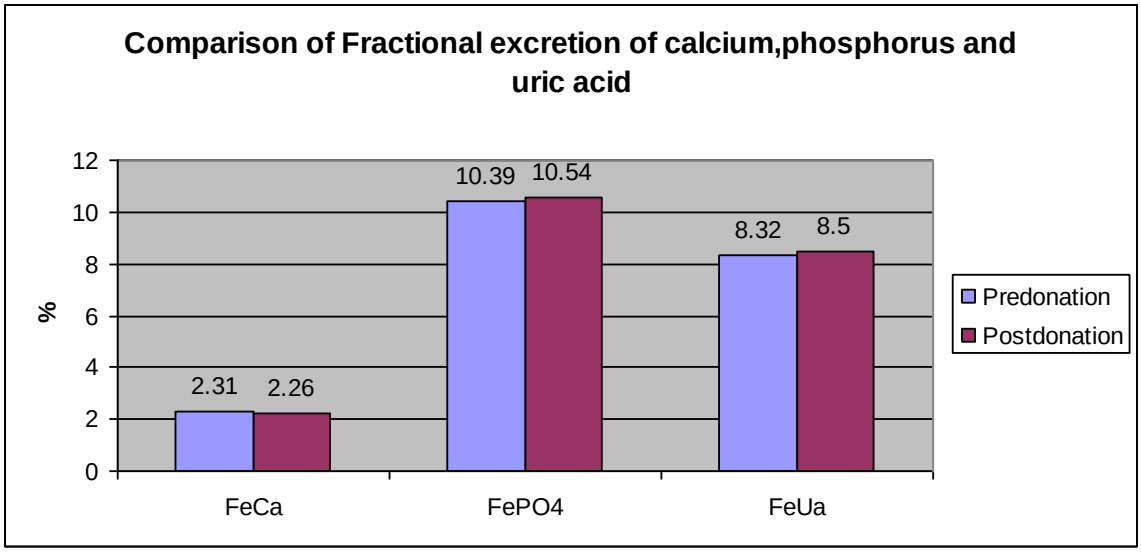

Figure 5:Comparison of Fractional excretion of calcium, phosphorus and uric acid Pre and post kidney donation

IV. Discussion

In recent decades, increasing interest has been shown in the concept of renal donation and its potential related consequences, particularly following original studies on the hyperfiltration damage due to renal ablation. Specifically, in humans, hyperfiltration damage following surgical kidney ablation has been observed only as a consequence of partial nephrectomy in subjects with single kidney and, in particular, in those in whom more than 75% of the kidney has been removed **[67].** Current literature suggests that risks associated with living kidney donation may be acceptably low, with excellent outcomes in terms of morbidity and mortality for the donor. Most live kidney donors are highly selected and by virtue of this process deemed to have no

cardiac risks. Renal donor survival bias has been suggested by some investigators **[68].** Donor follow up studies have reported variable outcomes, in part due to inconsistent end points, assessment and follow up methodologies.

Hypertension, proteinuria and decrease in glomerular filtration rate (GFR) are potential long-term complications related to kidney donation. Although most of the transplant centres suggest that risks of incurring these complications may be acceptably low, we should not underestimate them. Donors with low pre-donation GFR are at higher risk of developing renal function impairment **[69].** In addition, survival of the transplanted kidney is reduced when GFR of the donor is < 80ml/min [**69**]. Furthermore, relatives of subjects with chronic kidney disease (CKD) may have a genetic susceptibility to developing renal diseases or may develop clinical conditions, such as diabetes mellitus Type 1 and 2, systemic lupus erythematosus or arterial hypertension, which in turn may cause the progression of a pre-existing renal injury.

Data from a meta-analysis of 48 studies, including 3124 subjects who underwent nephrectomy and 1703 controls, showed a decrease in GFR of 17.1ml/min on average after unilateral nephrectomy, which tended to improve every 10 years of follow-up. (59) Furthermore, data from a study on 28 veterans of the Second World War, who underwent nephrectomy as a consequence of trauma, indicated a clearance of 75ml/min, even at 45 years following intervention **[70].** Most of the studies evaluating renal function in living donors after nephrectomy found no evidence of a reduction in GFR in a follow-up period of more than 10 years. [**50,71**]. These data have been confirmed from other studies with a follow-up period of more than 20 years [**10,22**]. Renal functional reserve persists after nephrectomy, but is probably reduced. However, as outlined earlier, these findings must be interpreted cautiously, as in such studies a significant number of donors were lost or did not regularly attend follow-up visits.

Prevalence of both proteinuria and albuminuria has been estimated at 20% [**10,22**]. and 30–40% [**22,49,50**], respectively, in long term follow-up studies, with differences related to gender, the prevalence being higher in males than in females. Whether proteinuria occurs as a consequence of hyperfiltration damage, presence of comorbid conditions, such as hypertension or incipient diabetes mellitus, or as a new renal disease, remains to be confirmed by renal biopsy. A retrospective analysis of 24 subjects who underwent nephrectomy as a consequence of urological diseases showed the development of pathological proteinuria in seven subjects, with focal glomerulosclerosis being the underlying cause, as demonstrated by renal biopsy, in four of the seven patients [**57**]. These data suggest that hyperfiltration damage may occur in nephrectomized subjects. Furthermore, the observation of a high prevalence of focal glomerulosclerosis in subjects affected by unilateral renal agenesis [**58**] has led to consider that subclinical abnormalities of the contralateral kidney may predispose a minority of subjects to develop progressive damage, even in the absence of other pathological conditions. But the age at which a kidney is lost is important, to evaluate the frequency of evolution of secondary focal glomerulosclerosis.

A number of studies have reported a prevalence of hypertension in living kidney donors, of ~ 50%. This percentage is similar to that observed in the general population [22,50,72]. Consistently, in a meta-analysis, which aimed to evaluate the effects of reduction of nephron mass on renal function, nephrectomy did not appear to affect the prevalence of hypertension [59]. Another study showed significant increases in mean arterial pressure, even within the normotensive range, in normal subjects who underwent uninephrectomy and development of hypertension in 4/18 subjects [73]. Although the long-term effects of living kidney donation on development of hypertension remain controversial and require confirmation in large prospectively designed studies, there is evidence emphasising the importance of monitoring blood pressure, particularly ambulatory blood pressure [4], both before and after kidney donation [4,74,75], in order to detect early increases in blood pressure values.

Kidney donation does not appear to negatively impact long-term survival in appropriately selected subjects [76]. Conversely, CKD represents a possible complication. In a Norwegian study, 7 out of 1800 donors (0.4%) developed chronic renal failure, mainly as a consequence of a primary kidney disease rather than glomerulosclerosis caused by hypertension or hyperfiltration [76]. Similarly, another recent study reported a risk of developing CKD in kidney donors of 0.2% (1/402) in Sweden and 0.5% (1/200) in Germany [77].

Data from the OPNT (Organ Procurement and Transplantation Network) database show that, in the period 1987–2002, 56 out of 6371 donors, after a follow-up period of 2–32 years from kidney donation, corresponding to a 15 years follow-up on average, have entered the waiting list for kidney transplantation. In these subjects, causes of renal failure have been hypertensive nephrosclerosis (43%), focal glomerulosclerosis (16%) and chronic glomerulonephritis (13%) [6].

Not only the above parameters but also tubular functions may alter with kidney donation. Two studies described a reduced renal tubular resorption of phosphate after uni-nephrectomy. A significant decrease in renal excretion of calcium was noted at one year after donation. [**24,25**] Few studies also compared donors before and after uni- nephrectomy for changes in uric acid metabolism [**26,27**].

An increased prevalence of hyperhomocysteinemia has been seen amongst end stage renal disease patients and numerous studies have shown that kidney function is one of the most important determinants of plasma homocysteine levels. In one of the studies there was a significant rise in total homocysteine levels immediately after surgery and 6 months after surgery [28]

Therefore currently available data indicates that long term health risks associated with donor nephrectomy are quite low. However since live related donors form a formidable pool of kidney donors in our country & no available study from our country throws light on incidence of potential complications like hypertension, proteinuria, metabolic and renal functions post donation, there was a need for a prospective study of living related kidney donors.

With this background the present study was undertaken to look for the presence of hypertension post kidney donation, to compare proteinuria and GFR pre and post kidney donation. The other objective of the study was to evaluate fractional excretion of calcium, phosphate and uric acid, and to look for the presence for hyperhomocysteinemia post kidney donation.

The subjects studied were live kidney donors aleast $\geq$ 3 months post donation. All kidney donations were done at All India Institute of Medical Sciences, Delhi. All living kidney donors were evaluated for hypertension, proteinuria, and DTPA GFR pre and post donation. Kidney donors were also evaluated for fractional excretion of calcium (FeCa), phosphate ($FePO_4$) and uric acid (FeUa) and serum homocysteine.

The principal findings of the present study are discussed below:

Renal functions

Our study showed that there was a statistically significant increase in serum creatinine from 0.87±0.13 mg/dl to 0.97±0.18 mg/dl over mean follow up of 12.8 months. This corresponded to a significant fall in DTPA GFR from 79.0±8.8 ml/min to 67.1±6.6 ml/min. This roughly amounts to 15% fall in GFR. However, there was no end stage renal disease in our series. An important meta- analysis concluded that nephrectomy in healthy individuals results in an immediate 17% overall loss of renal function, with the subsequent yearly rate of loss slightly less than that found in the general population [59].

Despite the loss of renal function that follows nephrectomy, it appears that donors may live longer than the general population [5], probably because they are so well evaluated.

For the donor who is destined to develop ESRD in later life, from our results we can at least say for certain that donation means that approximately 1 out of 7 dialysis-free years will be lost, at a minimum. Moreover, a donor who later develops CKD will unavoidably be almost 15% more uremic at any time point before dialysis is needed because he donated. The metabolic risks associated with decreasing renal function (cardiovascular and bone disease for example) would also be increased proportionately. It is not as obvious whether nephrectomy would accelerate the rate of progression of subsequent chronic renal disease. After compensatory hypertrophy occurred and chronic renal disease subsequently developed, hyperfiltration in the remaining kidney could 1) be controllable with medications, [2] occur at such an early stage in two-kidney individuals that the effects would be very similar to the effects on donors [78], or 3] materially shorten the duration of dialysis-free time [79].

Sahay et al from India reported their data of 50 renal donors. They found that mean serum creatinine increased from 0.97 ± 0.09 to 1.22 ± 0.82 mg/dl and GFR decreased from 102.74 ± 6.9 to 74.54 ± 14.64 ml/min. The rise in serum creatinine was although nonsignificant, but fall in GFR was statistically significant. The postdonation decrement in GFR was 27% as compared to 15 % in ours. The mean age at nephrectomy was 41.26 ± 8.12 years which is similar to ours (44.4±9.1) while the mean follow up duration was 63 months in their study and 12.8 months in our study. The longer duration of follow up as compared to our study could explain the relatively more decrease in GFR postdonation. Age related decline in GFR may well have contributed to this [53]

Bieniasz et al analyzed their data of 46 living donor nephrectomies in Poland. They found that mean creatinine concentration was higher at 3 months after nephrectomy than preoperatively (P <.05). Mean creatinine clearance according to Cockroft–Gault formula and mean creatinine clearance according to abbreviated modification of diet in renal disease equation (aMDRD) decreased after donation by 30% (P <.05). Living kidney donation resulted in a reduced creatinine clearance in the donor [33].

Another study by Rowinski et al from Poland reported their data of 118 donors, followed for 2-8 years. The overall mean serum creatinine had increased from 0.8 to 1.25 mg/dl; however, in 2 subjects it was > 2mg/dl. The calculated creatinine clearance (MDRD for-mula) had significantly decreased from 95 to 65 ml/min (P < .05). This amount to 31% decrease in GFR [80]

In comparison to the above two short term follow up studies where there was a significant fall in GFR of 30%, our data also shows a decrease in GFR though of a lesser magnitude i.e. 15%. The mean age was 39 years in the Bieniasz et al study while it was 44 in ours. However, our study was similar sex ratio to his analyses, women comprising sixty-one percent of the donors.

Several studies indicate that functional adaptation occurs rapidly after uninephrectomy, with GFR remaining stable over many years. Indeed, data from the Swiss Organ Living Donor Health Registry (SOL-DHR) showed stable (or improved) serum creatinine levels in donors followed for up to 10 years after donation [29]. The SOL-DHR registry data indicate a slow improvement for measurement of serum creatinine and creatinine clearance. This finding is in sharp contrast with the expected physiologic decline in GFR associated with the ageing (i.e. approximately 1ml/min/year) [30]. Thus, the effect of nephrectomy in terms of increasing GFR by hyperfiltration outweighs the effect of normal renal ageing, at least during the first decade. The as yet unanswered questions are whether this trend will continue beyond the first decade after nephrectomy and whether it, may, over time, result in adverse changes (e.g. glomerulosclerosis, interstitial fibrosis) within the remnant kidney.

We looked whether age or sex could be a confounding variable accounting for the overall result of decrease in GFR post kidney donation. Though the donors with age > 45 years had a slight higher fall in GFR compared to younger donors, but this did not amount to statistical significance. Probably the greater decrement in GFR in elderly could be explained by the normal age related decline. Similarly, there was no statistically significant difference in fall of GFR between males and females.

Blood pressure

Our study showed a statistically significant rise in systolic blood pressure from predonation values of 124.1±7.2 to postdonation of 129.8±10.7 mmHg. However, there was no significant change in mean diastolic blood pressure. The incidence of new onset hypertension was 7.5%. Two additional renal donors who were hypertensive predonation had increase in requirement of number of anti-hypertensive agents.

In rats, surgical reduction of the number of nephrons leads to hyperfiltration, proteinuria, and progressive destruction of the remaining nephrons [14]. Findings in human beings have not been conclusive.

Kasiske et al did a meta-analysis to assess the long term effect of kidney donation on remnant kidney function and blood pressure in donors. Nephrectomy did not affect the prevalence of hypertension, but there was a small increase in systolic blood pressure (2.4 mm Hg; -0.3 to 5.1 mm Hg, P > 0.05) which rose further with duration of follow-up (1.1 mm Hg/decade; 0.0 to 2.2 mm Hg/decade). Diastolic blood pressure was higher after nephrectomy (3.1 mm Hg; 1.8 to 4.4 mm Hg), but this increment did not change with duration of follow-up. They concluded that this procedure does not cause progressive renal dysfunction but could be associated with high blood pressure [59].

Boudville and co-workers have reinvestigated the risk of new-onset hypertension in living kidney donors. In a meta-analysis of 48 studies from 28 countries, including 5145 donors, the researchers' identified ten controlled studies with more than 5 years of follow-up after donation. In these studies, the increase in weighted mean systolic blood pressure (four studies) was 6 mm Hg (95% CI 2–11), and the rise in weighted mean diastolic blood pressure (five studies) was 4 mm Hg (1–7). Furthermore, the relative risk for new-onset hypertension was reported as 1·9 (1·1–3·5) in one study. Prognostic features associated with larger increases in blood pressure, higher blood pressure, or hypertension at follow-up included older age at the time of donation, age (usually > 60 years), male sex, higher predonation blood pressure, higher than ideal body weight, and a lower predonation GFR. Potential associations were described for a family history of hypertension and black compared with white ethnicity. No association was shown for increased predonation uric acid level or cholesterol level. The proportion of female donors, average donor age at the time of surgery, and average pre-donation systolic or diastolic blood pressure were not associated with the incidence of hypertension after donation, nor were they associated with a change in systolic and diastolic blood pressure [19].

Although the report by Boudville and colleagues is the most comprehensive so far, however, this meta-analysis has several limitations. First, the analysis is inherently limited by the quality of the included studies, because most studies were retrospective and did not have appropriate controls. Moreover, in controlled trials, loss to follow-up was high, about 31% overall. This factor could introduce bias because studies with higher attrition rates showed higher increases in blood pressure in donors.

Sahay et al from India in their study of 50 donors reported that there was a rise of 9.96 mmHg in mean arterial pressure ($p<0.05$). Hypertension was noted in 23(46%) post nephrectomy ($p<0.05$). The mean increase in systolic blood pressure was 9.96 ± 12.61 mmHg (p = ns) and diastolic blood pressure was 7.18 ± 8.94 mmHg (p = ns). All donors with a family history of hypertension became hypertensive post nephrectomy. However, in our study the mean increase of 5.7 mmHg of systolic blood pressure was statistically significant probably because of relatively larger sample size. There was no statistically significant change in diastolic blood pressure in our study similar to Sahay et al [53].

Rizvi et al reported their data from the subcontinent. Hypertension developed in 10.3% of 736 kidney donors at a mean follow up of 3±3.2 years (range 6 months to 18 years). However, in contrast to our study, their donors had statistically significant decrease in systolic blood pressures post nephrectomy (126±13; 123±15; p value 0.0001) and a significant increase in diastolic blood pressure (79±9; 81±10; p value 0.0001). Among 76

(10%) donors who became hypertensive postdonation, isolated systolic hypertension was seen in one patient only. Diastolic alone and combined systolic and diastolic hypertension was seen in 21 (28%) and 54 (72%) patients, respectively. They also compared hypertensive donors with normotensive counterparts. On univariate analysis, hypertensive donors were older and had high predonation diastolic blood pressure readings and longer duration of donor nephrectomy. They were significantly more obese. Their mean GFR was lower, and there were a higher number of subjects with GFR below 60mL/min [39].

Our results are in concordance with the results of Najarian et al. In their retrospective data of follow up of 23 years from University of Minnesota, they showed that for all donors, and for the subgroup not currently on anti-hypertensives, the mean pretransplant systolic blood pressure was significantly lower than the current mean systolic blood pressure. There was no significant difference in diastolic blood pressure [10]. However, even though our results show concordance to their data, but it is difficult to estimate its value in view of relatively short follow up of 1 year.

Similar to our study, Gossman et al analyzed 152 donors at a single center in Germany. Compared to the values before kidney donation systolic blood pressure rose significantly from 125 ± 15 to 134 ± 19 mmHg. Diastolic blood pressure increased nonsignificantly from 79 ± 11 to 81 ± 9 mmHg. However, the percentage of donors with hypertension (blood pressure above 140/90 mmHg or treatment with anti-hypertensive drugs) increased from 7% to 30% in their study and from 2% to 8% in ours. [25]

Hypertension does; however remains an issue of concern in kidney donors. Untreated hypertension is a known risk factor for nephrosclerois and renal failure in the general population. It is possible that this risk is enhanced in those with a solitary kidney. Renal reserve is reduced even if serum creatinine remains within normal limits. It seems reasonable that glomeruli of uninephrectomized donors are exposed to greater systemic blood pressure than are those of hypertensive individuals with two kidneys. So, in essence, hypertension, although not caused or accelerated by kidney donation, may predispose donors to mare adverse renal consequences.

In the general population, every 10–mm Hg 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 [81]. Whether an increase in blood pressure from kidney donation is similarly prognostic requires future consideration, because closer surveillance and early intervention in otherwise healthy adults could offset any such risk.

Proteinuria

In our study, the mean 24 hour proteinuria increased statistically significantly from 0.138±0.042 to 0.197±0.185 g/g creatinine. Thirteen percent donors developed proteinuria > 300mg/day.

In the data of 70 living kidney donors from Cleveland Clinic, Goldfarb et al showed that there were 13 (19%) subjects who had a 24-hour urinary protein excretion greater than 0.15 g/ day. 24-hour urinary protein excretion after donation were higher in males compared with females. No differences existed in urinary protein excretion between donors younger or older than 50 years at donation, and no significant difference in proteinuria was found between values before and after donation [22]. However, our results are not in concordance with their results. In our study, it was seen that younger donors (age ≤ 45) had statistically significant increase in proteinuria of 0.078±0.213 as compared to older group (> 45 years) of donors i.e. 0.014±0.091. But this was statistically non-significant amongst males and females (0.021±0.094 vs. .079±0.221). Probably more hyperfiltration in younger kidneys could account for this increase in protein excretion.

Also our results are similar to an Indian study by Sahay et al where they also found out that 14% of the donors developed significant overt proteinuria (>300 mg/day). They also noted 40% incidence of microalbuminuria post nephrectomy. [53]

Another early analysis of proteinuria after kidney donation from Brigham and Women′s Hospital examined 52 donors at least 10 years after nephrectomy. Thirteen (25%) donors excreted in excess of 250 mg urinary protein over 24 hours and four excreted more than 500 mg/day (maximum 1012 mg/day). Significant proteinuria was commoner in those donors (n=11) examined 15 or more years after donation than in those investigated at less than 15 years [49]. In comparison our study results of 13% proteinuria may not be better, in view of short mean follow up of a year.

However, our results contradict a report from the Mayo clinic 8% donors at 10-20 years post nephrectomy excreted urinary protein in excess of 150 mg/day (maximum 1334 mg/day) [54].

Whether proteinuria occurs as a consequence of hyperfiltration damage, presence of comorbid conditions, such as hypertension or incipient diabetes mellitus, or as a new renal disease, remains to be confirmed by renal biopsy. A retrospective analysis of 24 subjects who underwent nephrectomy as a consequence of urological diseases showed the development of pathological proteinuria in seven subjects, with focal glomerulosclerosis being the underlying cause, as demonstrated by renal biopsy, in four of the seven patients [57]. These data suggest that hyperfiltration damage may occur in nephrectomized subjects.

Furthermore, the observation of a high prevalence of focal glomerulosclerosis in subjects affected by unilateral renal agenesia has led to consider that subclinical abnormalities of the contralateral kidney may predispose a minority of subjects to develop progressive damage, even in the absence of other pathological conditions [58]. But the age at which a kidney is lost is important, to evaluate the frequency of evolution of secondary focal glomerulosclerosis.

Homocysteine

Serum homocysteine levels significantly increased from predonation value of 5.89±1.38 to 8.12±3.46 µmol/L postdonation. Five (4.6%) donors had moderate hyperhomocysteinemia and one (0.9%) had intermediate hyperhomocysteinemia (serum homocysteine 50 µmol/L).

Tsai et al studied 10 living kidney donors and measured fasting plasma total homocysteine (tHcy), 24 hours before nephrectomy and 2 days, 6 weeks, and 6 months after nephrectomy compared to the values 24 hours before nephrectomy. Mean fasting tHcy were significantly higher in donors 2 days, 6 weeks and 6 months after nephrectomy than they were 24 hours before nephrectomy. Though there was initial rise of tHcy by 47% over baseline after 2 days of nephrectomy, it settled to 27% by the end of 6 months [28].

However, in our study there was an increase of 37% tHcy over a mean follow up of one year. The results of significant increase in homocysteinemia post nephrectomy in our study could be attributed to one donor, who had serum homocysteine level of 50 µmol/L.

The rise in homocysteine after donor nephrectomy could be due to a parallel decrease in GFR. Numerous studies have demonstrated that a strong association exists between renal function and the plasma tHcy level. In fact, renal disease is by far the most frequent cause of moderate and intermediate hyperhomocysteinemia (30–80 µmol/L). Existing data

suggest that a decrease in intrarenal homocysteine metabolism by the kidney is the primary cause of hyperhomocysteinemia in individuals with impaired renal function. However, this conclusion has been drawn largely from the observed correlation between GFR and the plasma tHcy level among patients with kidney disease, including end-stage renal disease and its accompanying uremia [82,83].

During the past few years, elevated blood levels of homocysteine have been linked to increased risk of premature coronary artery disease, stroke, and thromboembolism, even among people who have normal cholesterol levels. Abnormal homocysteine levels appear to contribute to atherosclerosis in at least three ways: (1) a direct toxic effect that damages the cells lining the inside of the arteries, (2) interference with clotting factors, and (3) oxidation of low-density lipoproteins (LDL). [66,84] In view of such deleterious effects of homocysteine, even intermediate and moderate hyperhomocysteinemia needs to be looked into.

Fractional excretion of calcium, phosphorus and uric acid

Our study shows that there is no statistically significant change in fractional excretion of calcium and phosphorus. The hypothesis behind measuring urinary calcium and phosphorus lies in fact that the amount of 1 α hydroxylase might be diminished by removal of one kidney putting kidney donors at an increased risk for secondary hyperparathyroidism. But earlier study done by Gossmann et al did not find any statistically significant correlation between parathyroid hormone and 1,25 $(OH)_2$ vitamin D_3 or the tubular reabsorption of phosphate. However, 30% of their donors had a reduced renal tubular reabsorption of phosphate. (25)

Friedlander et al in contrast to our results, noted that tubular reabsorption of phosphate fell from 83.4% to 72.3% at 1 month and remained at this level throughout the study. At 6 months, several changes developed that were suggestive of increased parathyroid hormone effect [24].

The data is scarce on fractional excretion of uric acid and we also did not have any significant change in FeUa postdonation.

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