Living Kidney Transplantation: Good for Recipient, How About Donor?

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This is to acknowledge that Nilum Rajora, M.D. has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Rajora will not be discussing off-label uses in this presentation.

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Internal Medicine Grand Rounds

August 1, 2008

1. Introduction

Chronic kidney disease is a worldwide public health problem. Fifty years ago no treatment option existed for patients with end stage renal disease (ESRD). Now, in most developed countries, every patient with chronic kidney disease stage 5 (GFR <15ml/minute/1.73 m2) is, routinely, offered renal replacement therapy option. Once a patient is diagnosed with ESRD and the patient decides to undergo kidney replacement therapy, there are only two treatment options for ESRD. Either the patient can go on Dialysis (hemodialysis or peritoneal dialysis) or get kidney transplant. No treatment is third option if patient chooses for it. Conventional hemodialysis is time consuming commitment and it significantly worsens the quality of life and reduces life expectancy. Patients have to go to outpatient dialysis units at least three times a week and for about 3-5 hours of treatment each time. Peritoneal dialysis requires aseptic technique, persistence and discipline to continue with the daily treatments. The preferred treatment for ESRD is kidney transplant. It provides the opportunity to maintain better lifestyle and is associated with significant improvements in life expectancy.

2. ESRD

There has been significant rise of ESRD in the United states over the past several decades. According to United States Renal Data System (USRDS) , the number of patients enrolled in ESRD medicare funded program has increased from approximately 10,000 in 1973 to 86,354 in 1983 and it was upto 472,099 in December 2004. According to USRDS data (Fig.1) the rate of increase of ESRD since 2004 has started to flatten but still has not started trending down (1) .

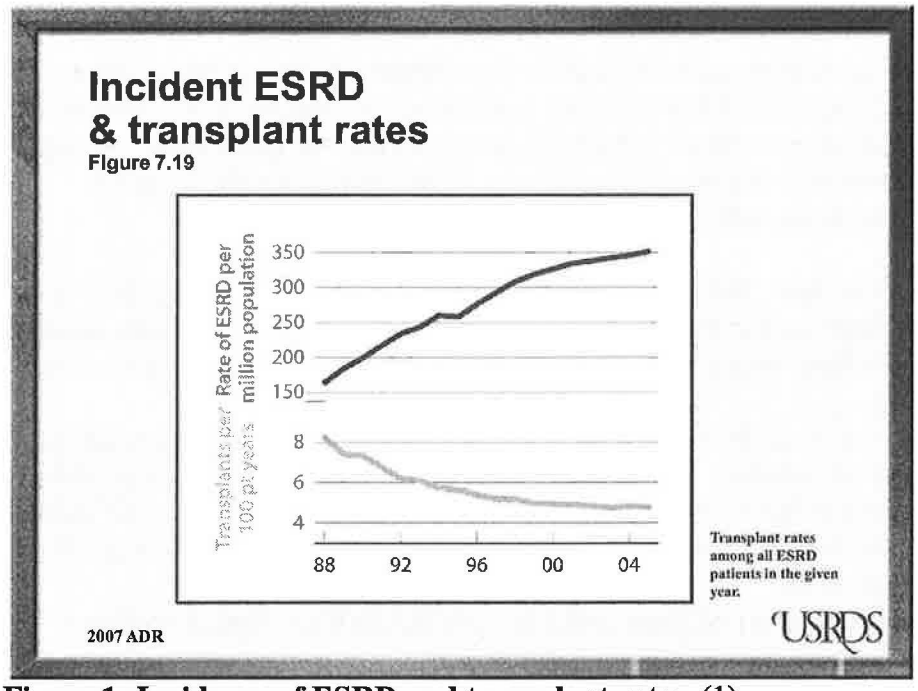

Figure 1: Incidence of ESRD and transplant rates. (1)

Medicare funding was approved in 1972 for renal replacement therapy and since then long term dialysis has evolved as primary treatment of ESRD. ESRD consumes a disproportionate amount of medicare funding i.e. relative to the number of patients being served in the ESRD population. Although the large amount of health care resources are used to take care of the ESRD patients, these patients continue to have reduced quality of life, increased morbidity and mortality on dialysis.

Initially, transplant was considered only experimental procedure as treatment of ESRD. In 1978, Rennie (2) made a comment about the transplant: "Even though it offers a much better quality of life while it works, a transplant in most cases (of kidney failure) can be considered only a temporary respite from the basic form of treatment, which is dialysis." Kidney transplant has evolved tremendously over the years. With the availability of better immunosuppressant drugs allograft and recipient survival has improved significantly. Since then, there have been numerous studies that have examined the outcomes of the ESRD patients with different modalities of treatments. Transplant has been shown to increase the life expectancy and quality of life as compared to long term dialysis treatment (3-5). Now transplant is preferred treatment for ESRD (6). It gives them the option to live independently of dialysis and provides them with longer survival.

3. Organ Shortage

Despite the awareness about kidney transplant most of the patients still undergo dialysis for few months to years prior to transplantation. Why is this so? As the number of the ESRD patients has increased over the years there has been a concomitant increase in the number of patients on transplant waiting lists, yet the number of transplants have not increased.

Although significant efforts have been made to increase the number of kidney transplantation in the Unites States, the inadequate pool of donor organs has limited the number of transplants This severe organ shortage has lead to a progressive increase in the number of patients on waiting list for transplant (Fig.2). The number of deaths of the patients while waiting for the organs to become available has also not decreased over the years (7).

According to UNOS data, as of June, 2008, there are 99,105 patients in USA waiting for organ transplant. Out of these waiting patients 80,798 are waiting for kidney transplant. Since January 2008 there have been 3,054 kidney transplants, among these 1,717 were deceased donors and 1,337 were living donors (8) .
Although every effort has been made to utilize the available deceased donor organs including expanded criteria donor (age ≥60 years or 50 to 59 years with at least 2 of the following: history of hypertension, serum creatinine level >1.5 mg/dL [132.6 μmol/L], and cerebrovascular cause of death), donor after cardiac death and high risk donors with close surveillance, the waiting list for kidney transplant continues to grow.
Given limited and unpredictable supply of deceased donor organs there has been significant interest in living donors to increase the pool of available organs.

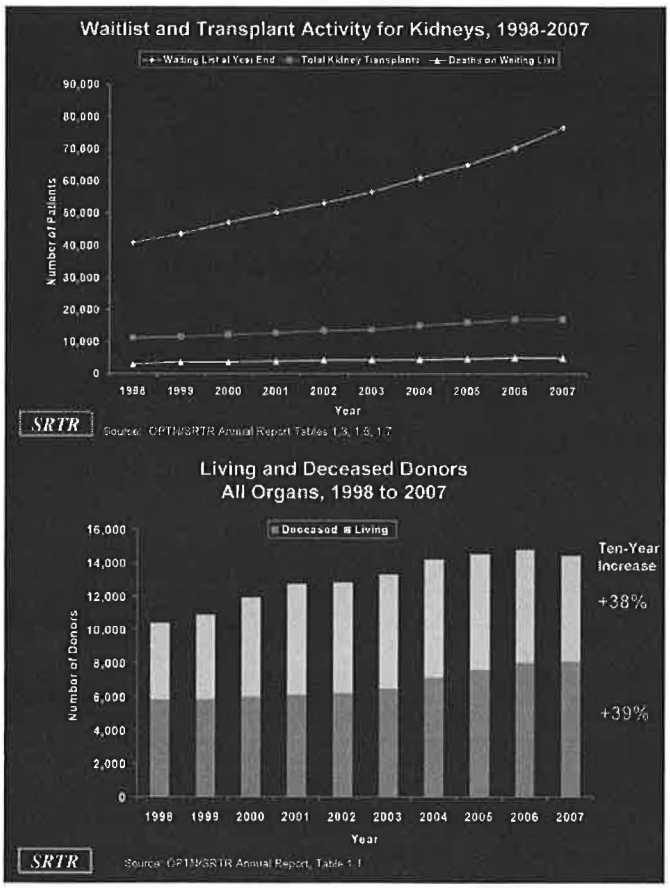

Fig 2 &3: UNOS data

Living donation rates vary worldwide. In Asia and the Middle East few deceased donor transplantations are performed, may be because of lack of organizations like UNOS and OPTN, appropriate transport systems and challenges in co-ordinations between different hospitals. But in western countries it is hoped to be the predominant form of kidney transplant (9-11). In 2001, for the first time, the annual number of live kidney donors surpassed the number of deceased donors in USA (12) but this trend has not been sustained (7).

4. Why Living Donors?

The development of living kidney transplantation was predicted by transplant authorities. They contended that the living donors provide the best opportunity for timely and successful kidney transplant. Transplant from living donors has gradually evolved from being initially limited to identical twins to current state in which organs are now being procured from altruistic living donors. It has been shown that the living donation provides better patient and allograft survival (Figure 4) as compared to deceased-donor transplantation (13).

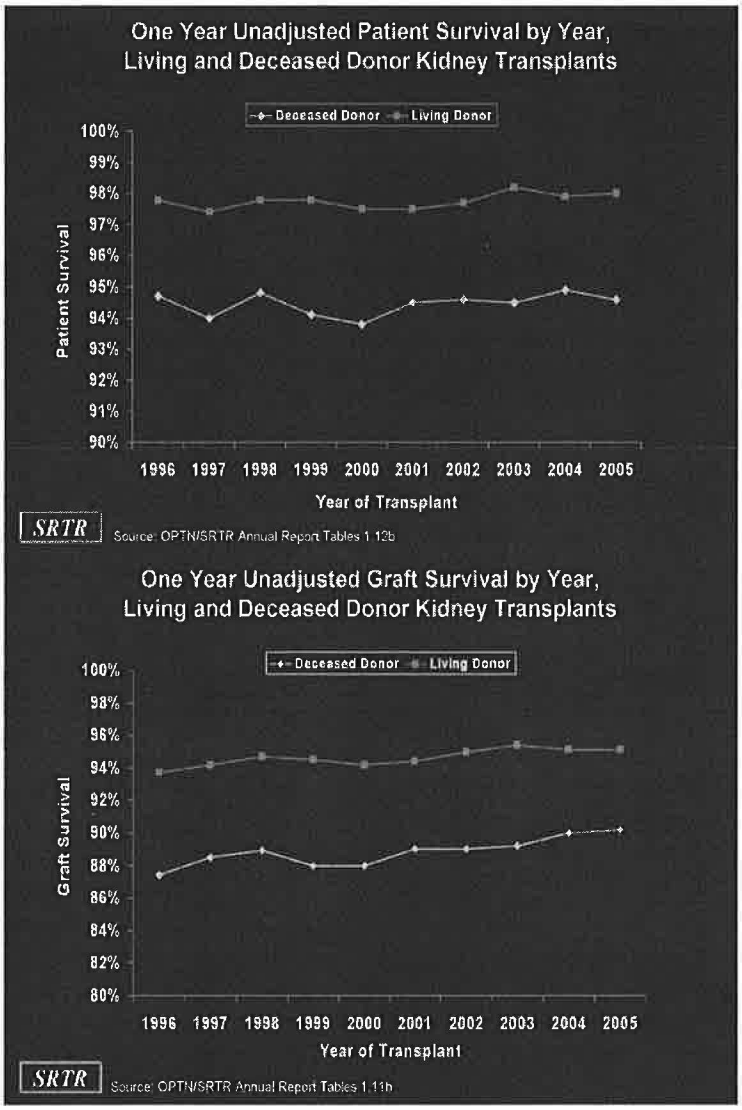

Figure 4: Patient and Graft Survival among Deceased and Living kidney transplants (7).

According to different studies, there are several factors that may contribute to better survival of the allograft and recipient (14,15). As compared to deceased kidney transplants the allograft in living kidney transplant is exposed to none to minimal ischemia and is consequently subjected to less ischemic and reperfusion injury. Short ischemia time is important as it has been shown that cold ischemia time is one of the causes of delayed graft function (16). Delayed graft function has been shown to be negative risk factor for long-term renal allograft survival (17,18). Data relating to deceased donor kidney transplants performed between 1994 to 1998 in USA reveal that the half life of kidneys without any delayed graft function was 11.5 years while it was 7.2 years for kidneys with delayed graft function (17). Other factors that may contribute to the beneficial effects of living kidney transplant include:- a) the vascular anatomy can also be evaluated prior to the donor nephrectomy, b) elective surgery, c) lower recipient age, and d) lower time on dialysis prior to transplantations.

5. Living Donor Evaluation

So, we know it is better for ESRD patients to get living donor kidney but what about the living donors? Are we hurting them by removing one of their kidneys? Are there any psychosocial concerns among donors? One thing to keep in mind is that the donors have to undergo an elective surgical procedure which will not provide them any health benefit. Thus, in addition to medical evaluation, psychosocial evaluation is performed in order to ensure that the donation is completely voluntary. Current standard of practice require that all donors be informed of the potential risks of surgery. The importance of this approach is underscored by the death of living liver donor in 2001 that subsequently led to big public response: it may explain the slight decrease in living donor transplantation over the past five years. There were two big international conferences following that unfortunate event, one is Amsterdam and the other in Vancouver, both of which were aimed at addressing the care and evaluation of the living organ donors. The Amsterdam conference (19) had 100 experts from all over the world representing 40 different countries including participants from Africa, Asia, Australia, North America and South America. After reviewing the available data, the consensus guidelines for evaluation of potential living kidneydonor and care of the donors were developed. In addition to the above focus, these conferences addressed the responsibility of the community for the living kidney donors.

a. Evaluation Protocol

Before proceeding with the donor nephrectomy every effort is made that the donor does not, in any way, have any risks related to the surgery itself ; it is especially important that a donor will not be affected by having solitary kidney. The donor evaluation has mostly been standardized and it includes thorough medical, surgical, and psychosocial evaluation of the prospective donor (19-22). In addition, an assessment of the donor and recipient blood groups and a cross match between the individuals is performed.

All prospective living kidney donors undergo comprehensive evaluation to ensure donor safety (19). This includes history, physical exam, chest X-Ray, UA with microscopic analysis, 24 hour urine for creatinine clearance and albuminuria, EKG and lipid panel. Additional considerations include age, family history and appropriate cardiac stress and cancer screening results. Thorough infectious disease screening is done which includes hepatitis C, hepatitis B, HIV, RPR, CMV, EBV serologies, and PPD placement. Donor also undergoes anatomical studies which can be CT angiogram, renal angiogram or Magnetic resonance angiogram. Our center uses CT angiogram as the study of choice and it has been shown to be reliable test (23).

Absolute contraindications for kidney donation are age <18years, uncontrolled hypertension or cardiovascular disease, hypercoagulable state, bleeding disorder, uncontrolled psychiatric illness, morbid obesity, chronic lung disease, history of melanoma or metastatic cancer, bilateral or recurrent nephrolithiasis, CKD stage 3 or less, >300 mg/day proteinuria, or HIV. I will be discussing some issues with marginal living donors. It will cover potential donors with obesity, HTN, proteinuria, nephrolithiasis, and hematuria.

b. Obese Donors

Obesity is a risk factor for increased mortality and morbidity (24). Likewise, the renal outcome has been shown to be worse in patients with obesity as compared to healthy individuals (25,26). Increased BMI is associated with increased risk for proteinuria, FSGS, diabetes, HTN and metabolic syndrome (27). Affected individuals may also be predisposed to more surgical complications.

Heimbach et al (28) looked at the outcomes in obese kidney donors in Mayo clinic. Renal function of more than 100 obese donors (BMI>30) was not significantly different from that of non-obese donors. Selection criteria of these donors included absence of proteinuria and fasting blood glucose <126 mg/dl. For fasting glucose between 100-125 mg/dl, a 2 hour glucose tolerance test was done. For both groups, comparable trends of rise in BP and GFR persisted as before donation. Higher blood pressure was associated with higher BMI. In this study, blood pressure did not change after donor nephrectomy. The drawback of this study was a short follow up of only 12 months after nephrectomy.

Most of the programs exclude donors with BMI >35. It may be because close attention has been given to medical risks associated with obesity. Praga (29) published a study in 2000 from Spain in which they looked at the patients who underwent unilateral nephrectomy 13.6+/- 8.6 yrs ago. They compared patients with BMI <31 to BMI >31 in that study. Among the obese patients (BMI > 30 kg/m2) at the time of nephrectomy, 92% developed proteinuria/renal insufficiency. In contrast, among the patients with BMI < 30 kg/m2, only 12% developed these complications. Renal biopsy was done in two patients in obese group and it showed focal segmental glomerulosclerosis. Median time of developing proteinuria was 6.1 years after nephrectomy.

Higher post operative complications have been noticed in obese donors especially related to the open nephrectomy leading to wound complications (30). Some centers have reported longer operative time and higher conversion rates from laparoscopic to open nephrectomy (31).

Most of the transplant centers will use obese donors (BMI>30) as long as they have no other co-morbidities. Survey of US transplant centers (32) showed that 52 percent of the centers use a BMI cut off of 35. There were still 20% of the centers which had BMI cut off of 40.

According to Amsterdam Conference obese potential kidney donors (19) patients with BMI>35kg/m2 should be discouraged from donating, especially when other co-morbid conditions are present. They should be encouraged to lose weight and maintain a healthy lifestyle even after kidney donation. These potential donors should be made aware of acute and long term risks of kidney donation.

c. Hypertension

Even mild elevation in BP has been shown to be an independent risk factor for developing ESRD (33). There has been concern that the hypertensive donors may be more prone to worsening renal function after nephrectomy secondary to reduction in kidney mass (34).

One of the largest studies published on hypertensive donors was from Mayo clinic by Textor et al (35) in 2004. 148 donors were followed for 12 months post donation. Out of these 148 donors 21 donors were hypertensive prior to kidney donation. At the interval of 6 months and 12 months after kidney donation the ambulatory BP, iothalamate GFR, Urine protein and microalbumin were measured. The hypertensive donors had slightly lower GFR and slightly more proteinuria as compared to non-hypertensive donors. In 14 of 24 (58%) subjects, antihypertensive drug therapy was initiated with an angiotensin receptor blocker even prior to nephrectomy. Proteinuria could have been higher considering that many of these donors were started on angiotensin receptor blockers (35). The authors concluded that "white subjects with moderate, essential hypertension and normal kidney function have no adverse effects regarding blood pressure, GFR, or urinary protein excretion during the first year after living kidney donation."

As compared to 1995 the exclusion criteria for hypertensive donors seems to be more flexible, as evidenced by the survey of the US transplant centers (Fig.5) (32). Many centers commented that the blood pressure criteria were looser if the donor was older, or if the end organ damage was ruled out. 47% of the programs exclude donors on any antihypertensive medication, 41% exclude donors if they are taking more than one medication, and 8% exclude donors taking more than two medications (32). Many centers use 24 hour ambulatory blood pressure monitoring especially if the potential donor had high BP in office setting and may have "white coat" hypertension. In our transplant center we frequently do ambulatory blood pressure monitoring of prospective kidney donors.

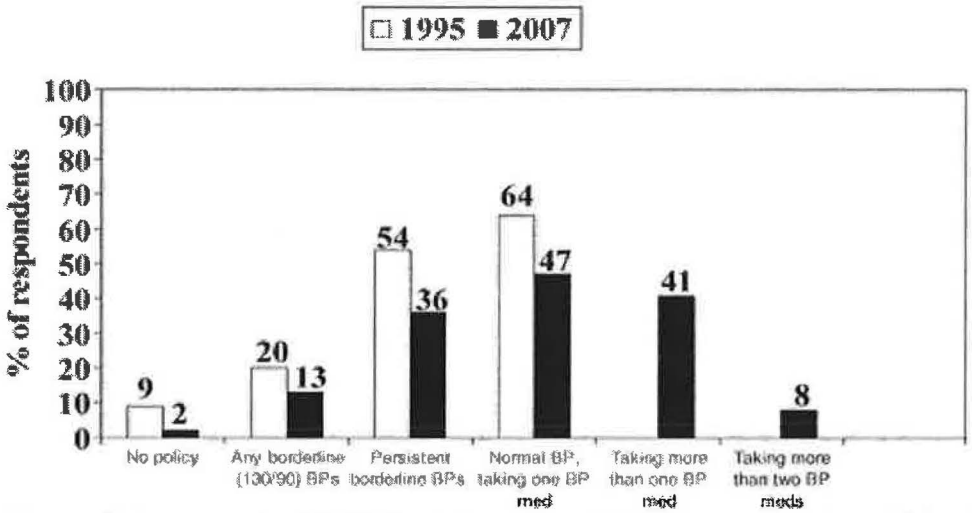

Figure 5: Exclusion criteria by categories of blood pressure (n = 121). (32)

According to Consensus Guidelines from Amsterdam Conference (19) some patients with isolated hypertension may represent a low-risk group for development of kidney disease after donation and may be acceptable as kidney donors if they have easily controlled hypertension, are at least 50 years old, have GFR of <80ml/minute and urinary albumin excretion 30mg/day. Further studies are essential to confirm long-term safety. Based on the current data it may be appropriate to use the non-African American donors with HTN who have no other risk factors for kidney disease.

d. Proteinuria

Isolated proteinuria is not an uncommon finding during donor work up. Urine is tested at least on two different occasions to differentiate between transient or orthostatic proteinuria and persistent proteinuria. Dipstick measurements of proteinuria are not adequate in the assessment of a potential donor. As laboratories vary in normal values of quantified urine protein, it is recommended that 24 hour urine collection be utilized to evaluate for protienuria, albuminuria for potential kidney donor evaluation (19). Urine collection is performed in the absence of fevers, urinary tract infections, or intense exercise. Donors with any amount of proteinuria are usually excluded if the urine analysis also has any other abnormality i.e. hematuria, red cell or white cell casts. It is important to rule out over-collection or under-collection of the urine in 24 hours. Over-collection is suspected if if total urine creatinine–body weight ratio is > 25 mg/kg (220 mol/kg), especially in those with low muscle mass. Under-collection is suspected if total urine creatinine–body weight ratio <15 mg/kg (132 mol/kg). It is important to ensure the adequate urine collection especially in those with 'borderline high' proteinuria (36).

Proteinuria is a strong, independent predictor of ESRD in a mass screening setting (37). Rate of ESRD was only less than 2% in this study. Several follow up studies of the patients with solitary kidney have shown no increase in HTN, chronic kidney disease or proteinuria after unilateral nephrectomy while others have shown slight increase in these outcomes (38-44). In an effort to increase the pool of living kidney donors, slight relaxation of the exclusion for proteinuria has been proposed (45) but it will increase transplantation rate by 3% only in in the face of a risk of about 2% of the donors may develop ESRD. The risk of progressing to ESRD may be even higher in persons with solitary kidneys. If the potential donors have isolated proteinuria between 250-300mg/day then urinary albumin excretion rate should be measured and they may be considered for kidney donation if urinary albumin excretion is negative (36).

We may assume that the actual long-term risk for these marginal donors with proteinuria would be acceptable. But the problem with most of the studies is low retrieval rates of the donors, so at present actual risk may not be quantifiable. At present there is no uniform agreement and the acceptance of these marginal donors is variable between different transplant centers. Our transplant center does not use the potential donors with persistent microalbuminuria.

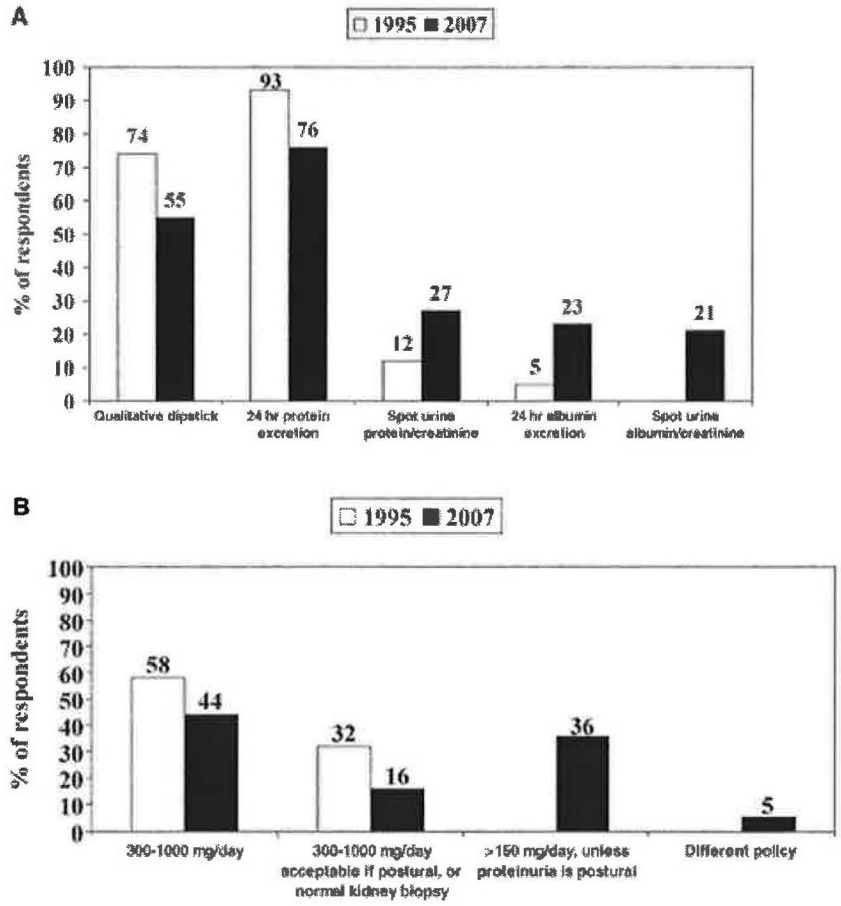

Figure 6A & 6B : (A) Proteinuria—tests routinely performed in all potential donors (n = 131). (B) Exclusion criteria by level of proteinuria (n = 121).(32).

Survey of the US transplant centers (32) showed that most programs (76%) use 24 hour urine collection for evaluation of proteinuria among the kidney donors (Fig.6). Few programs rely on spot urine protein to creatinine ratio. Almost half of the transplant programs use urinary albuminuria as a screen which is increased from 5% in 1995. The exclusion criteria for kidney donation varied among the programs from >150mg/day to >300mg /day unless the proteinuria was postural.

e. Hematuria

Standard donor evaluation includes UA with microscopic exam; dip stick is very sensitive test and can reliably exclude hematuria if dip stick is negative (46). The incidence of hematuria is about 2.7% among donor screening (47). Persistent hematuria is defined as two or more dipstick positive on separate occasion, over at least one month period. Causes of hematuria can be either glomerular or extraglomerular. Glomerular causes include Thin basement memberane disease (TBMD), Alport Syndrome and, IgA nephropathy. Extraglomerular causes include nephrolithiasis, hemoglobinopathy, PCKD, BPH, AVMs, malignancy of bladder, kidney or prostate, infections, hypercalciuria and hyperuricosuria. Work up for hematuria in a donor

includes detailed family history, Urine Culture, 24 hour urine collection to estimate calcium and urate, cytology and, renal imaging (Fig.7). If urological work up is negative donor needs to have renal biopsy to r/o glomerular pathology (48).

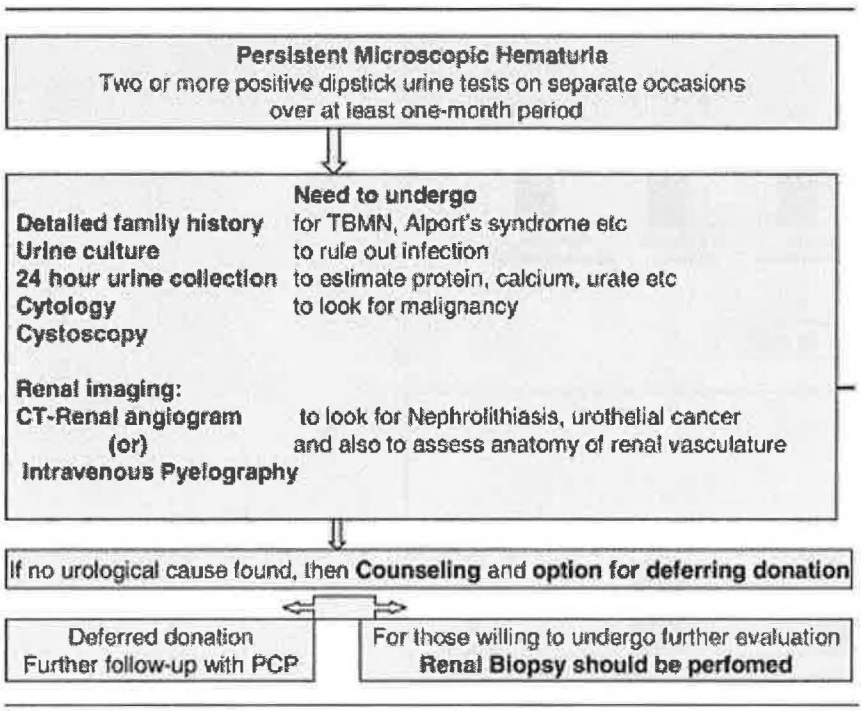

Figure 7: Algorithm to investigate microscopic hematuria in donors (48).

Donors with any glomerular pathology are excluded from kidney donation. This includes donors with IgA nephropathy as 15-40% of these patients may proceed to ESRD (49). Koselj et al (50) has followed 3 living related donors with hematuria who had IgA nephropathy for 7 years and one of the donor developed progressive renal insufficiency. Patients with Thin basement basement membrane disease, in minority of cases, can also progress to kidney failure (51,52).

The renal biopsy is invasive procedure and is not without risks. Nevertheless, patients with isolated hematuria (normal GFR and no proteinuria) may not need renal biopsy. They can be just followed closely, but if they want to be the kidney donor then renal biopsy is necessary to exclude glomerular pathology like TBMD, IgA nephropathy or Alport Syndrome. The complications of renal biopsy are transient hematuria, decrease in hemoglobin, hypotension (1-2%) and requirement for blood transfusion (6%). The risk of mortality is 0.02-0.1% in some studies (53). Another study showed the biopsy related complication in 13% of the patients, major complication rate of 6.4% and minor complication rate of 6.6% (54). Major complications, in this study, were defined as: bleeding severe enough to require a transfusion or invasive procedure, septicemia, acute renal obstruction or failure, or death. In this study patients were 2.3 times more likely to have complication if the creatinine was >5.0 mg/dl. So the risks of the complications may be lower in the healthy kidney donors but not completely absent.

Presently, the most common practice (43% of transplant programs) of transplant centers is to only accept the donors if urological work up is negative and renal biopsy is also normal. Twenty-one percent (21%) of programs automatically exclude donors with >10 RBC/hpf regardless of work-up (32).

f. Nephrolithiasis

In the USA, the prevalence rate of nephrolithiasis is 5.2% (55). It has increased significantly over last two decades from 3.2% in the 1970s. The lifetime risk is about 10-15% in developed country and can be as high as 20-25% in the Middle Eastern countries. It can be a recurrent disease and the likelihood of relapse increases with each episode. Relapse rate (32)can be as high as 50% in 10 yrs and 75% in 20 years (56,57). The recurrence rate is higher in the patients who have metabolic causes of kidney stone formation. There is epidemiological data to suggest that the stone forming population have slight increased incidence of chronic kidney disease especially with BMI> 27 kg/m2. The probability of an overweight stone former having an estimated GFR <60 mL/min/1.73m2 relative to a GFR above 90 mL/min/1.73m2 was found to be nearly twice that of a similar non-stone former (58). The cause of CKD is unknown because this incidence was increased without any obstruction. Also we do not have data available to assume that patients with solitary kidney have higher incidence of CKD (59) as long as they are monitored closely and all risk factors are addressed. These patients do have up to 30% recurrence rate for stone formation but this was not any different than the patients with two kidneys. Nephrolithiasis itself may not be an important cause of renal failure with the exception of bilateral staghorn calculi associated with recurrent urinary tract infection, nephrocalcinosis, or ureteral stricture (60,61).

There are few issues to be addressed while evaluating the potential kidney donors who have a history of nephrolithiasis. Transplant centers consider the frequency of kidney stones occurrence, type of stones and cause of stone. All the potential kidney donors with history of nephrolithiasis are screened for metabolic causes of kidney stones. The screening protocol includes urinalysis, comprehensive metabolic panel (including Ca, phos), PTH, and Uric acid. Also 24-hr urine is collected for total volume, Creatinine, pH, sodium, Calcium, oxalate, citrate, potassium, Uric Acid, phosphorus and sulfate. Attempts are made to get the results of stone analysis, if it was done in the past. The potential donors with a history of cystine stones or struvite stones should not be used as kidney donors as they are at higher risk of recurrent nephrolithiasis. Donor kidneys with struvite stones or infection stones are not recommended for transplantation especially because of high risk of infection after immunosuppressive therapy (61).

The asymptomatic potential kidney donors with history of single stone may be suitable for kidney donation (19) if they have no hypercalciuria, hyperuricemia, cystinuria, hyperoxaluria or metabolic acidosis. Also the donors should not have any UTI, nephrocalcinosis or any evidence of multiple stone on CT scan.

It is not known whether kidney donation by a stone former increases the risk of recurrence of nephrolithiasis or worsening of renal function in the remaining kidney as compared to stone formers with both kidneys(62). The potential donors who are not accepted for kidney donation (19) are the ones with nephrocalcinosis on X ray or bilateral stone disease, cystine or struvite

stones (as higher recurrence rates), systemic disorders such as primary or enteric hyperoxaluria, distal renal tubular acidosis, sarcoidosis, inflammatory bowel disease or history of bowel resection. Likewise, persons who have experienced recurrence while on appropriate treatment (i.e., failed therapy), are not acceptable as potential donors.

According to a survey of the Transplant Centers in US (32) most of the center accept a potential donor with a history of nephrolithiasis if no stones are present and metabolic studies are normal. Only small percent (5%) of programs reported no policy toward stone history in potential kidney donors.

6. Immediate risks to the donor

Living kidney transplant raises concerns about the recipient's and allograft's short term and long term outcomes. One of the most important concerns of the living donor kidney transplant procedure is safety of the prospective donor. This includes the physical, psychological and social well being of the donor (20). First I will focus on peri-operative risks to the living kidney donors.

A survey of 171 UNOS listed kidney transplantation centers, covering the period 1991-2001 has been reported (63). There were 10,828 living donor nephrectomies, 52.3% open, 20.7% hand assisted laproscopic and 27% were total laproscopic. Perioperative mortality in this study was 0.02%, and both deaths were in laproscopic group. This is equivalent to the risk of death when driving a car for 2 years or giving birth to 2 children (64). 22 patients (0.4%) in open nephrectomy group, 1.0% in hand assisted and 0.9% in laproscopic group had to be reoperated. Causes of reoperation are shown in Table 1. Post operative complications not requiring reoperation were 0.3% causes are shown in Table 2.

Table 1: Reasons for reoperation; by donation technique (63)

	Open (n = 5660)	**HA LN (n = 2239)**	**Non-HA LN (n = 2929)**
Bleeding*	9 (0.15%)	4 (0.18%)	13 (0.45%)
Bowel obstruction**	3 (0.05%)	6 (0.27%)	3 (0.1%)
Bowel injury	-	2 (0.1%)	4 (0.14%)
Hernia***	10 (0.18%)	11 (0.5%)	1 (0.03%)
*p = 0.02;**p = 0.03;***p = 0.001.			
HA = hand-assisted; LN = laparoscopic nephrectomy.			

Table 2: Postoperative complications not requiring reoperation, by donation technique (63)

	Open (n = 5660)	**HA LN (n = 2239)**	**Non-HA LN (n = 2929)**
Bleeding*	4 (0.1%)	10 (0.45%)	6 (0.2%)
Rhabdomyolysis**	-	2 (0.09%)	4 (0.13%)
Deep vein	1 (0.02%)	2 (0.09%)	3 (0.1%)

	Open (n = 5660)	HA LN (n = 2239)	Non-HA LN (n = 2929)
thrombosis/pulmonary embolus			
Prolonged ileus	–	1 (0.05%)	2 (0.06%)
Pneumothorax	4 (0.09%)	1 (0.05%)	–
Other	10 (0.18%)	6 (0.27%)	9 (0.3%)
Total***	19 (00.3%)	22 (1%)	24 (00.8%)
*p = 0.03; **p = 0.001; ***p = 0.02.			
HA = hand-assisted; LN = laparoscopic nephrectomy.			

Rate of readmission was higher for laproscopic nephrectomy (1.6%) vs. opennephrectomy (0.6%) donors ($p < 0.001$). Reasons of readmission included nausea, vomiting, dehydration, ileus, constipation, diarrhea, wound dehiscence and small bowl obstruction.

A study from the UK that examined morbidity and mortality among 2509 living kidney donors between November 2000 to June 2006 has been recently reported (65). One death occurred three months post-discharge and was that of a 60 yrs old donor who had myocardial ischemia 10 days post operatively and died of second MI at three months post operatively. The risk of major morbidity was 4.9% in this study. Five other deaths were not related to kidney donation.

Review of other published data shows that the incidence of development of serious complications including bleeding (0.98–6.3%), infections (wound infection 0.6–21%; pneumonia 2.5–9.8%; urinary tract infection 6.7–7.8%) and pneumothorax (0.6–8.8%) (66-69) was variable. Perioperative mortality associated with living kidney donation has been estimated at 0.02% (63)

Laproscopic surgery is the choice of surgery now as it provides several advantages compared to open nephrectomy including shorter hospital stay, less pain, better cosmosis. Laproscopic surgery has evolved significantly over the years and the complications rates are much lower now.

7. Compensatory Adaption After Nephrectomy

How does the remaining kidney compensate after contralateral nephrectomy? Before reviewing the compensation process I will review the basics of GFR. Determinants of GFR in the kidney are: Hydraulic Pressures in the Glomerular Capillaries (PGC) and Bowman Space (PBS), oncotic pressure of plasma in Glomerular Capillary (πP) and Bowman space (πBs), capillary porosity and surface area (70). GFR can be described by following formula:

GFR = (capillary porosity X Surface Area) X (Δ hydraulic Pressure – Δ Oncotic Pressure)
GFR = (Capillary Porosity X Surface Area) X ([PGc – PBs] – s[πp-πbs])
GFR = (Capillary Porosity X Surface Area) X (PGC-PBs - πp)
GFR= K_{uf} (ultrafiltration coefficient) X Pgc (Filtration Fraction)

In the above equation s is the reflection coefficient of proteins across the capillary wall which is a measure of permeability. Since Oncotic pressure of the bowman space (π Bs) is zero as the filtrate is usually protein free and capillary wall is completely permeable to water those two (π Bs and s) can be removed from the final equation. Kuf or Kf is the ultrafiltration coefficient which is the product of hydraulic permeability and filtration surface area. So, any change in the above factors or renal plasma flow can change the GFR. Capillary hydrostatic pressure is affected by afferent and efferent arterioles resistance. Filtration fraction (FF) is the ratio of the GFR to the RPF. FF represents the proportion of the fluid reaching the kidneys which passes into the renal tubules. Catecholamines (Norepinephrine and Epinephrine) increase the filtration fraction by vasoconstriction of Afferent and Efferent Arterioles and that may be the cause of increased FF in the remaining kidney after contralateral nephrectomy.

Ultrafiltration coefficient (Kf), the product of hydraulic permeability and filtration surface area, seemed to be the potential determinant of hyperfiltration. In study by Saxena et al. (71) there was average 60% enhancement in Kf of the remaining kidney after unilateral nephrectomy. But how could the permeability change? If it does change does it explain slightly increased incidence of proteinuria with solitary kidney. As it has been shown that Kf does increase in the remaining kidney it may be secondary to increase in surface area. According to authors, it is possible that the glomeruli also participate in the compensatory hypertrophy which can lead to enhanced flitration surface area. This may explain the limited compensatory response in aged kidney secondary to microvascular changes and atrophic renal cortex because of aging process in the older kidney.

It has been shown by several laboratories in animal studies that there is a progressive increase in the remaining kidney's weight after contralateral nephrectomy (72). There is also vigorous physiological compensatory response in the remaining kidney after the contralateral nephrectomy. There is usually 30-40% increase in glomerular filtration rate among young kidney donors (73-77) (78). Saxena et al (71) looked at the adaptive hyperfiltration response in the remaining kidney after contralateral nephrectomy among the young and aging kidney donors. There was an increase in single kidney GFR (SK-GFR) of 42% in young and 38% in aging donors. They also noticed a trend towards increased urinary albumin/creatinine in the uninephric subjects. SK Renal plasma Flow increased by 38% in uninephric subjects as compared to binephric controls. How does that happen?

There is cellular growth of the remaining kidney after contralateral nephrectomy to compensate for the lost GFR. It has been shown that RNA and DNA synthesis starts within 12 hours of nehrectomy and the synthesis continues till the sufficient compensatory growth occurs (79). Several growth factors have been shown to influence the growth. Hauser et al. (80) have done the microarray studies in the rats and looked at the levels of different transcription factors after the unilateral nephrectomy. 12, 24, and 72 hours after unilateral nephrectomy, the contralateral kidney was harvested for genome wide gene expression analysis and transcription factor analysis. There was dramatic suppression of the genes belonging to growth inhibition within first 3 days after the contralateral nephrectomy. Only few genes were over expressed; these were involved in cell cycle and metabolism. Insulin like growth factor-2 (IGF-2) was one of the few early continuously activated genes. The authors also observed suppression of the protein degradation and metabolism inhibition.

As nephron number is fixed shortly before birth in most species, this gain in kidney weight can be secondary to increased nephron size. Growth is thought to occur largely through cell hypertrophy, accounting for 80% of the increase in renal mass seen in adult rats and, to a lesser extent, through hyperplasia. Renal mass continues to rise for 1 to 2 months until a 40% to 50% increase is achieved.

Hypertrophy is achieved largely through regulation of the G1 cell cycle kinase (cell cycle-dependent mechanism) (81). Liu and Preisig (72) has studied compensatory renal hypertrophy in the rats and mice and they found that there was increase in cdk4/cyclin D kinase activity which may move the cell into G1 phase of the cell cycle and initiate the early stage of G1 phase (Fig. 8).

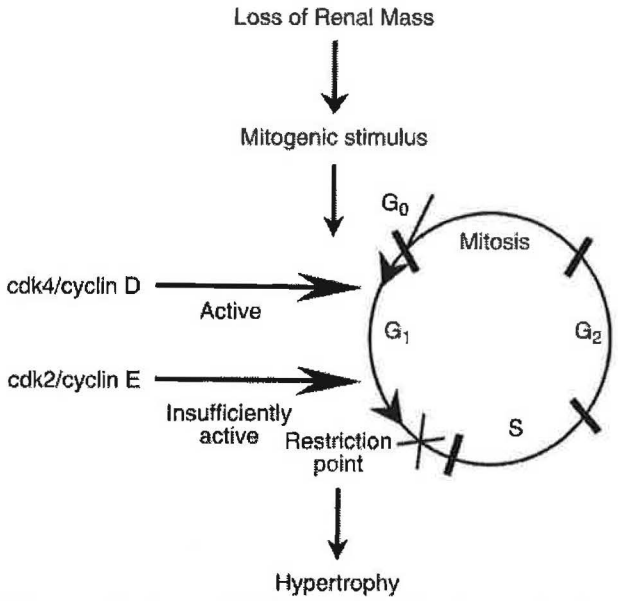

Figure 8: A model for cell cycle-dependent compensatory renal hypertrophy (72).

It was observed that the hypertrophied cells have only single copy of DNA, suggesting that cell cycle must be halted prior to the Restriction Point, so that the retinoblastoma protein remains active and progression into S-phase is prohibited (82,83). Endothelin signaling system through the endothelin B receptor provides the mitogenic signal after the nephrectomy. It was also seen that the endothelin B receptor deficient mice, after unilateral nephrectomy, did not show increase in cyclin D kinase activity or increase in Protein: DNA ratio and did not result in proximal tubule hypertrophy (72).

8. Long Term Risks to The Donors

Living kidney transplantation has been a matter of debate since the beginning (84-86). Initially it was questioned whether physicians should encourage living relatives to donate their organs when families of several brain-dead patients are not being asked to donate. Though we have come far from that era and every effort has been made to utilize the available deceased donor pool, thousands remain on waiting list for kidney transplant. There have been numerous aimed at

evaluating the long term risks of mortality and morbidity in patients after unilateral nephrectomy. At the beginning of the living kidney transplant programs, the long term mortality and morbidity in the living donors was not available. Initially physicians relied on the data from the follow up of persons with congenital unilateral kidney or who had unilateral nephrectomy for reasons other than kidney donation to assess long term medical risks of solitary kidney (87).

One of the longest follow up of solitary kidney patients was published in 1993 (41). This study examined consequences of nephrectomy, secondary to trauma, among US Army personnel. After unilateral nephrectomy the mortality at 45 yrs was not increased in these army personnel. Out of 28 deceased patients 10 had autopsy and there was no increase in glomerular sclerosis. 6/28 patients had kidney disease but the cause of kidney disease was "other than nephrectomy". There was no increase in the prevalence of HTN in living patients. 5/28 living patients had >250mg/day proteinuria and Serum Cr>1.5 mg/dl was observed in three cases.

In another study, even patients with DM and polycystic kidney disease with unilateral renal agenesis or unilateral nephrectomy, did not show any accelerated loss of kidney function (88,89). At the same time another study was published (38) which showed increased incidence of kidney failure, higher blood pressure and increased urinary protein excretion among the patients who had undergone unilateral nephrectomy. Since then there have been other studies published which have shown small increase in blood pressure and increased incidence of proteinuria (40,43,44) after unilateral nephrectomy.

With the reports of increased proteinuria and increased incidence of hypertension reported in patients after unilateral nephrectomy concerns arose about the fate of the living kidney donors. One of the long term follow up of kidney donors was published by University of Minnesota (42) after following donors from 1963 to 1979. Information was available on 464/ 773 (60%) donors. 84 /464 had died, 3 had abnormal kidney function and 2 had undergone transplantation. According to the authors the rate of HTN and proteinuria was similar to age matched general population. The limitations of this study were poor retrieval rate (60%) of the donors and only 50% had creatinine and UA done, representing only 16% of 773 donors. There have been several other follow ups of living kidney donors but with low retrieval rates (50-70%). One of the study which had best retrieval rates of the kidney donors was from Germany (39). In this study, retrieval rate was 93%. Mean time after unilateral nephrectomy was 11 yrs and mean BMI was 26. Among these donors decline in GFR was noted by 25 % after kidney donation and 56% donors had developed proteinuria.

Other criticism of these studies has been that the comparison of the living kidney donors outcome is done with the general population which also includes patients who have diabetes, hypertension, obesity and other risk factors for chronic kidney disease. The most appropriate and accurate way to compare the outcomes of the living kidney donors will be to compare with the population with same risk profile for chronic kidney disease. An excellent study done using the siblings of the donors as controls found no significant difference in blood pressure, but 20% increase in creatinine and increased incidence of urinary protein excretion was noted among donors (90).

Based on the data available it can be assumed that the living kidney donors are at non trivial risk of surgery. The living kidney donors may be at increased risk of proteinuria and hypertension but there is no increased incidence of ESRD with current screening process. Still long term follow ups, with better retrieval rates, of the living kidney donors is needed. Given the lack of data on long term follow ups it is important to have national and international donor registries. Now the UNOS require the follow up of the donors for atleast 2 years after the kidney donation. Our center follows the donors at 3 weeks, 6 months, 12 months and 24 months with basic metabolic panel, UA with micro, albuminuria and BP check.

So, how do the transplant centers do on informing the potential kidney donors about the risks of kidney donation?

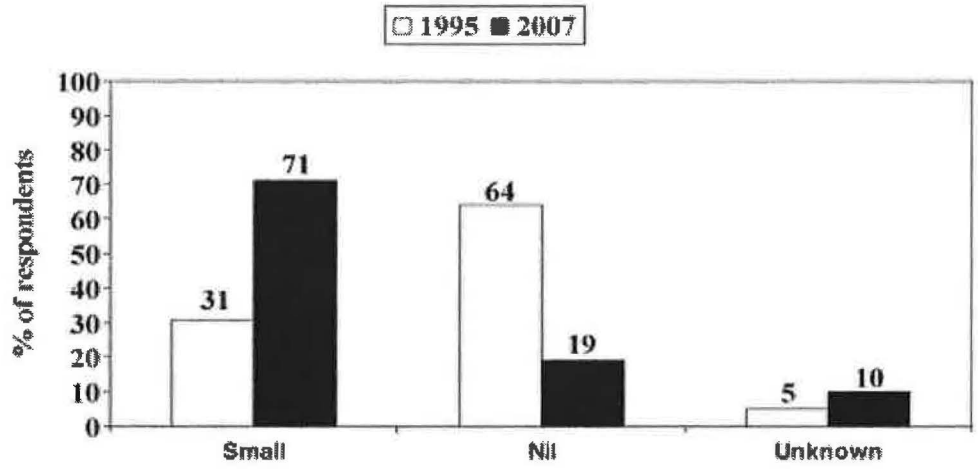

Figure 9 : Donors are told that the long-term risks of renal failure related to donation are (n = 115) (32)

According to the 2007 survey of US transplant centers (32), during the risk counseling of prospective kidney donors, the long-term risk of renal failure related to kidney donation is usually described to donors as 'small' rather than 'nil' in 2007 (Fig.9). This is almost complete reversal of the terms used in 1995.

The long-term risk of hypertension and proteinuria related to kidney donation is also usually described as 'small' (82%, 79% respectively) rather than 'nil' (8%, 7% respectively), with 10% saying the risk of hypertension is unknown and 14% saying that the risk of proteinuria is unknown. This is a significant improvement in informing the risks of kidney donation to potential donors as in 1995, 60–65% of programs informed potential donors that there is a 'small' risk of developing proteinuria or hypertension related to donation.

9. Pregnancy After Donation

Substantial numbers of the donors are young and they frequently ask about the effects of unilateral nephrectomy on their future pregnancies. There have been concerns regarding potential for developing hypertension and progressive renal dysfunction during pregnancy. Given that the remaining kidney compensates by hyperfiltrating after contralateral nephrectomy and that hyperfiltration is an adaptive response to pregnancy, is the risk for development of HTN, proteinuria or worsening renal function among kidney donors compounded with pregnancy? Also during pregnancy right ureteral dilatation occurs more commonly than left and is usually physiological but can be serious especially with solitary kidney. A retrospective review of 6275 pregnancies (91) found only 5 cases of ureteral obstruction secondary to pregnancy and required stent placement. Stones was the cause of obstruction in 4 cases. Overall reported incidence rate of obstruction was 0.007-0.07% only (91,92).

There have been few studies published which has mentioned the outcome of pregnancy in kidney donors. Cleveland Clinic (93) performed kidney transplant from 191 female living donors from 1963 until 1984. They followed the long term outcome among these donors. There were 39 reported pregnancies among 23 living kidney donors. Proteinuria was noted among 9 donors (1+ in 2, and trace in 7), but it disappeared after delivery. Even during follow up of mean 7.9 years (2-14 years) there were no significant changes noted.

Wirenshall et all (94) surveyed 220 women who had donated kidney between 1985-1992. Of the 144 who responded 33 became pregnant, total 45 pregnancies. 75% of the pregnancies had no difficulty. Overall morbidity was 8.8%; miscarriage (13.3%), preeclampsia (4.4%), gestational hypertension (4.4%), proteinuria (4.4%), and tubal pregnancy (2.2%). There were no deaths or fetal abnormality. Infertility was a problem in 8.3% (3/36) respondents, compared with a worldwide incidence of 16.7%.

Recent data related to renal outcome following pregnancy in kidney donors came from University of Minnesota. During the long term follow up of the kidney donors 72 pregnancies were noted. Out of 72 reported pregnancies among 33 donors only two donors reported HTN during first pregnancy and third one had preeclampsia (42).

None of these complications exceeded the incidence of observed among general population. Again the limitations of these studies are low retrieval rate of the donors. Based on the available data it is safe to say that donor nephrectomy does not put donors at any higher risk than general population during pregnancy. Hyperfiltration which occurs with the combination of unilateral nephrectomy and pregnancy does not lead to significant hypertension, proteinuria, change in glomerular filtration rate, or abnormalities of the urinary sediment. However, it is recommended to delay pregnancy until at least 2 months after nephrectomy to assess renal compensation prior to conception with evaluation including blood pressure, GFR, and assessment for microalbuminuria (19). Some transplant centers recommend waiting for 6 months before getting pregnant after kidney donation. It should be verified that postpartum renal function is normal.

10. Who are the donors??

Let us look at the USRDS and UNOS data to see that who are the donors. The most common age group to donate is between 20-44 yrs and, female donate more than males (Fig. 10). Why do we

have gender imbalance in kidney donation? Although it has been shown that spouses are important source of living kidney donation and despite poor HLA matching, the graft survival is similar to that of parental kidney (95). After that finding was reported there should have been increase in living unrelated donation, with equal representation among men and women.

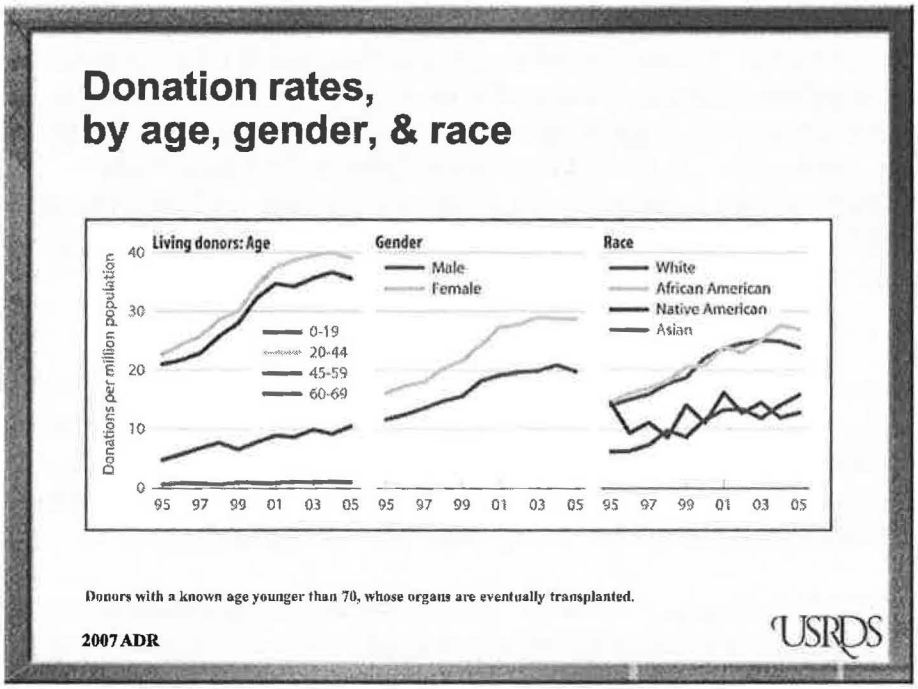

Figure 10: Donation rates by age, gender and race (1).

According to UNOS data more than half of living donors are female. Several studies have shown that wait-listed females are less likely to receive either a deceased or living kidney transplant. There is paucity of male to female donations. Scientific Registry of Transplant Recepients from 1990 to 1999 was analyzed (96). Among 30,258 living donor transplants females comprised of 68% donors. Higher incidence of ESRD among the males and slight female predominance of the population did not explain these differences. Does that mean the men are whimps? Men may be less available to donate secondary to military obligations, incarceration, slight predominance of female population in US or from the ambivalence of men about organ donation. Also women may be specifically sensitized to their husbands from pregnancy which will be contraindication for transplant. Also the loss of wages or vacation time of the donor, around the transplant evaluation and surgery, may be driving factor for both donor and recipient to be reluctant for the process.

11. Donor's Quality of Life

The long term psychological effects on the organ donors have been studied. The long term studies were initially done in nineties. Quality of life (QOL) among the kidney donors has been shown to be equal or better than the general population in USA. Johnson et.al described the QOL among donors (97). A questionnaire (QOL assessment tool, SF-36) was sent to 979 American donors, and 60% responded. Donors scored better than the general US population in 7/8 categories. Only 4% regretted the donation. Further, 4% found the experience extremely stressful and 8% very stressful. Donors who had perioperative complications (odds ratio=3.5, P=0.007) and female donors (odds ratio=1.8, P=0.1) were more likely to find the overall experience more stressful. Vast majority of donors had a positive experience and would readily donate again if it were possible. Parents who donated to offspring had the best scores and donors unrelated to the recipient, the worst; however, all scores were still the same or better than for the US general population.

The quality of life of the donor is also affected by the long term outcome of the allograft and the relationship of the donor to the recipient. Also, the donors were less likely to say that they would donate again (if it were possible) if they were donating to a person who was not a close blood relative or if the recipient of their kidney died in the first year after transplant. Recipients also have more feelings of guilt if transplant came from living donor than deceased donor (98).

Overall, among the surveys in US and Japan <5% donor were dissatisfied after donation and a small number of the donors experienced depression, anxiety and rare cases of suicides (97,99). Although these complications are rare, we need to be aware of their existence and to counsel potential donors and monitor them post-nephrectomy. According to authors, overall, the results of the US study are overwhelmingly positive and have encouraged to continue living donor kidney transplants (97). All of our potential kidney donors are evaluated and presented to Donor Advocate committee which includes nephrologist, ethicist, psychologist, and social worker for thorough screening.

12. How about paying Donors?

There has been much debate about financial incentives to the donors. Reasons for these considerations include the following: a) organ donation is not without risks; b) there is large population in US (especially younger persons), who are uninsured and may be hesitant to be available for organ donation and c) kidney donation requires time off from work for the evaluation and nephrectomy.

Matas and Schnitzler have published cost analysis of transplant (100). They studied the cost effectiveness of paying the living kidney donors by examining what costs would be saved, if any, by removing a patient from the waiting list using a paid (living unrelated: LURD) donor-vendor. A Markov model was developed to calculate the expected average cost and outcome benefits of

increasing the organ supply and reducing waiting times by adding paid LURD organs to the available pool (Fig.11).

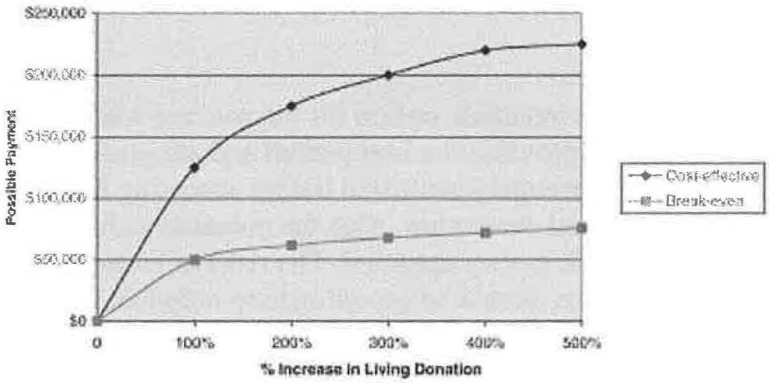

Figure 11: Break-even point to society if all vendors and all current donors were paid. Cost-effective point includes impact of a gain in QALYs (100)

They found that a LURD transplant saved $94 579 (US dollars, 2002), and 3.5 quality-adjusted life years (QALYs) were gained. Adding the value of QALYs, a LURD transplant saved $269 319, assuming society values additional QALYs from transplantation at the rate paid per QALY while on dialysis. According to this analysis, at a minimum, a vendor program would save society >$90 000 per transplant and provides QALYs for the ESRD population. Thus, society could break even while paying $90 000/kidney vendor.

Matas published another article this year with the proposed regulated system of compensation of living donors. His proposal is "government or insurance agencies will provide compensation to the donor and the organ would be allocated to a recipient on the waiting list. An important component of the proposal is the provision of long-term healthcare to the donor." (101). The system will have to be transparent with well defined donor evaluation criteria. This will prevent donors to go from one transplant center to other to get accepted.

Gaston et al. (102) also proposed removal of the financial disincentives from living organ donation. The authors comments that "we believe compensating donor risk in the fashion we propose, or something akin to it, is not only an acceptable alternative to the current impasse, but also the right thing to do." The authors propose providing the living organ donors with health insurance, one year term life insurance policy, compensation for inconvenience, anxiety, and/or pain and small amount of cash or $10, 000 tax deduction.

The above proposal is still very controversial. It does not clearly address the problems with financial incentives to the potential kidney donors. How should we decide the payments to the donors? Should the younger donors be paid higher amount than the older donors? A donor financial compensation scheme may lead to people from poor countries to sell their kidneys to patients in "richer" countries. How these paid kidneys will be redistributed? Will these go to the highest bidder?

It may be reasonable to provide the donors with medicare assistance if they develop any complications from kidney donation. Disability benefits and life insurance will be good for one year after organ donation. For the potential organ donors who have no health insurance,

provision of health insurance will ensure close follow up of the donors and provide appropriate medical care in case of any complications. It will increase the pool of uninsured potential donors.

SUMMARY

There is steady rise in incidence of ESRD. The best treatment option for the patients with ESRD is kidney transplant and the living kidney donation provides the best patient and allograft outcome. The potential living kidney donors are thoroughly evaluated before accepting them for organ donation. It involves medical and psychosocial evaluation. Also the potential kidney donors are well informed of the risks associated with kidney donation. The risks of kidney donation are small but not completely absent. Donors should be encouraged to maintain healthy lifestyle and regular access to health care. The living kidney donors may be at increased risk of proteinuria and hypertension but there is no increased incidence of ESRD with current screening process. Still long term follow ups, with better retrieval rates, of the living kidney donors is needed. Given the lack of data on long term follow ups it is important to have national and international donor registries.

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