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Kidney dysfunction after non renal solid organ transplantation

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Summary

Chronic kidney disease developed after non renal solid organ transplantation in a significant issue. Evaluation of kidney function starting form a complete history and physical examination, then an accurate measurement of renal function and a urinalysis, followed by kidney imaging study should be performed prior to transplantation. Moreover, probability of reversibility of kidney dysfunction and the risk of progression to end stage renal disease should be assessed. During peri- and postoperative period hypotensive episodes should be avoided or at least minimized. Good blood pressure control (however, no guidelines for target blood pressure values for non solid organ transplants are available) as well as tight control of diabetes and hyperlipidemia should be implemented. Proteinuria, if present, should be attenuated by the use of therapeutic modalities (RAS blockade) to prevent or delay the progression of renal failure. The ability to identify CKD may allow early implementation of treatments that could arrest or delay the progression of renal damage, enable effective treatment of its complications, and reduce the risk of drug-induced nephrotoxicity. Kidney function should be monitored in nonrenal solid organ transplant recipients as an important risk factor comparable with diabetes for cardiovascular mortality and morbidity. In presence of existing nephron sparing immunosuppressive regimens, early detection of deteriorating kidney function gives the opportunity to tailor the treatment. A multidisciplinary approach for these patients including also a nephrologist should be considered.

Key words: **chronic kidney disease • heart transplantation • kidney transplantation • liver transplantation**

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Background

Nonrenal solid organ transplantation (SOT) is now established method of therapy with significantly improved outcome over the last years [1,2], however, an increasingly prevalent complication in this population appears chronic kidney disease-CKD [1–3]. In all end-stage organ failures transplantation is the best and practically only method of treatment. It also does not exists methods of long last support similar to dialysis. Chronic kidney disease (CKD) is an important long-term complication of all forms of nonrenal organ transplantation [4]. This has been attributed to long-term treatment with calcineurin inhibitors (CNI) [5,6]. However, CKD occurs despite advances in immunosuppression, tailored and CNI-free regimens, advancements in peri-operative management as well as attention to cardiovascular risk factors and infectious complications [7]. The development of CKD is associated with enhanced morbidity and mortality [4].

Evaluation of Kidney Function Before Nonrenal Solid Organ Transplantation

As a general rule, the preoperative evaluation of kidney function in candidates for nonrenal solid organ transplantation is mandatory. It should focus upon establishing the likelihood of being left with adequate kidney function post-transplant and the chance of progression to end-stage renal disease (ESRD). Kidney dysfunction is one of the major risk factor for any kind of surgery. It is also one of the major problems in cardiac surgery were hypothermia, hypotension and organ hypoperfusion are part of vast majority of cases. Patients with established primary kidney disease before solid nonrenal organ transplantation with high likelihood of progression to ESRD or with a high risk of CKD stage 4 or 5 after the early post-transplant period (i.e. GFR below 30 or 15 ml/min, respectively) and thereby with a great probability to require renal replacement therapy shortly post-transplantation, should be considered for a combined organ transplant. However, in the era of organ shortage, increasing time on the waiting list for a kidney transplantation, every decision should be very judicious. Vast majority of candidates for nonrenal solid organ transplantation with normal of mildly impaired kidney function (i.e. GFR in the range of 60–90 ml/min) should be considered for transplantation without nephrological indications. However, normal or near normal serum creatinine levels do not necessarily reflect normal kidney function, especially in states of heart failure or liver disease, where affected patients frequently have poor nutritional status, low muscle mass, weight loss, and edema. Patients with cardiovascular diseases often exhibit renal dysfunction due to concomitant diabetes, hypertension, congestive heart failure, while patients with liver cirrhosis may show signs of hepatorenal syndrome.

Candidates for non renal solid organ transplantation should have their kidney function evaluated starting form a complete history and physical examination, then an accurate measure of renal function and a urinalysis should be performed, followed by kidney imaging study [3]. In some cases, on the basis of the findings form initial evaluation other studies, including kidney biopsy may be required.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend estimating GFR in patients who are at risk for kidney disease using the Modification of Diet in Renal Disease (MDRD) study formulas [8]. Within the 5^{th} and 95^{th} percentile for age, both formulas MDRD and Cockcroft-Gault formula provide similar measurements which were consistent with age-specific historic inulin clearance values [9]. The Cockcroft-Gault equation provided higher estimates at younger ages, and lower estimates at older ages (eg. greater than 70 years of age) than the obtained with the simplified MDRD formula [9]. However, the accuracy of MDRD formula in patients populations outside of the United States is also unclear [10], Despite this, the use of the MDRD or the Cockcroft-Gault formulas to estimate GFR may provide a better assessment of kidney function than the serum creatinine concentration alone [11]. A 24-hour collection for the creatinine clearance is also likely to overestimate GFR in patients with renal disease as the contribution of tubular secretion of creatinine to total clearance is increased in this subset of patients. In a urinalysis a particular attention has to be paid on the presence of microscopic hematuria and proteinuria. Active urinary sediment with significant proteinuria and/or hematuria should prompt a full evaluation to elucidate the nature and the prognosis of the kidney disease with subsequent consideration on performing renal biopsy. Moreover, kidney biopsy should also be considered in the event of renal failure in which the cause is not evident from routine clinical data [12,13].

In patients with abnormal kidney function, anatomic evaluation of kidneys using imaging

techniques should be performed, mainly due to exclude renal obstruction and irreversible or end-stage renal disease (small and echogenic kidneys). In some patients assessment of urinary electrolytes is helpful to estimate the effective volume status of patients and renal concentrating ability of patients with abnormal renal function. Moreover, urinary sodium or fractional excretion of sodium may also provide important diagnostic information for hepatorenal syndrome in patients awaiting liver transplantation, or for low cardiac output states in heart transplant candidates. In these conditions, some degree of recovery of kidney function after transplantation may be expected.

CKD Before Non Renal Solid Organ Transplantation

In liver disease kidney dysfunction may be due to mainly to hepatorenal syndrome, but other conditions should be taken into account such as membranous glomerulonephritis in the course of hepatitis B, membranoproliferative glomerulonephritis in the course of hepatitis C, or cryoglobulinemia in hepatitis C positive patients.

In patients with liver failure and more than 40 percent glomerulosclerosis or more than 30 percent interstitial fibrosis on kidney biopsy some suggests to perform combined liver and kidney transplantation [12,14]. However, lack of correlation between clinical parameters and renal histology in patients with decompensated liver disease is highlighted [15,16]. Moreover, is has not been established whether post-liver transplant progression of kidney disease is better predicted by histological damage or clinical judgment.

Because serum creatinine is a component of the Model for End-Stage Liver Disease (MELD) scoring system (adopted in 2002 to prioritize patients for liver transplantation), the number of candidates for liver transplantation with kidney dysfunction has increased [17], leading to concern that some recipients who receive combined liver and kidney transplantation may have reversible renal injury and that some patients with ESRD receive liver transplants prematurely [18].

In 2008, the proceedings of a consensus conference on simultaneous liver-kidney transplantation were published in American Journal of Transplantation [19]. Automatic approval for listing for simultaneous liver-kidney transplantation is recommended to the following patients: ESRD with cirrhosis and symptomatic portal hypertension or hepatic vein wedge pressure gradient ⩾10 mmHg; hepatic failure and GFR ⩽30 mL/min due to chronic kidney disease; AKI or hepatorenal syndrome with serum creatinine ⩾2 mg/dL (177 μmol/L) and dialysis ⩾8 weeks; hepatic failure and chronic kidney disease with a kidney biopsy showing >30 percent glomerulosclerosis or >30 percent fibrosis.

Evaluation of kidney function prior to orthotopic heart transplantation is less well defined that in the case of liver failure. Chronic kidney disease is common in patients with chronic heart failure (CHF) due to prolonged low ejection fraction and secondary kidney hypoperfusion. Moreover, drugs used to treat heart failure such as ACE inhibitors or angiotensin II receptor antagonists may also contribute to the observed fall in GFR. Congestive heart failure and chronic kidney disease appear to act together in a vicious circle in which each condition causes or exacerbates the other, therefore. the nature of the kidney disease, in terms of chronicity and reversibility, must be determined. Patients with mainly hemodynamically mediated renal failure and without obvious intrinsic kidney disease can recover sufficient native kidney function after restoration of renal perfusion to not need subsequent kidney replacement therapy for several years. Recently in many transplant centers mechanical circulatory support is one of the most important parts of multidisciplinary treatment of end-stage heart failure. Today the patient with revealed shock and multiorgan failure is not consider as a good candidate for heart transplantation. Contemporary systems for short and long term circulatory support gives satisfactory cardiac output and in many cases the kidney function recover. The recent data suggest also better outcome and kidney function after transplantation. However, for patients with heart failure and irreversible renal failure combined heart-kidney transplantation could be considered as a viable option.

CKD After Non-Renal Organ Transplantation

The degree of functional impairment in kidney function after non renal solid organ transplantation and the rate of progression of CKD post-transplant depend to a large extent on the pretransplant kidney function (i.e. stage of preexisting CKD), the type of the organ transplanted, and the immunosuppressive protocol (use of calcineurin inhibitors), presence of comorbid conditions such as diabetes, hypertension, HCV

infection, older age, surgical issues, [4] and individual clinical features determining susceptibility to renal injury, even nephropathy resulting from BK virus infection.

Kidney Function After Orthotopic Heart Transplantation

Cardiovascular disease and kidney disease seem to be lethally synergistic and both approach level of epidemy. Patients with cardiovascular disease have often impaired kidney function, while on the other hand cardiovascular disease is the single best predictor of mortality in patients with chronic kidney disease. The risk in a patient with moderate impaired renal function is comparable in magnitude with that of a patient with diabetes mellitus [8]. Heart transplantation has become an established treatment for advanced heart failure, often associated with impaired kidney function [20]. Studies have shown that a GFR (glomerular filtration rate) less than 60 ml/min is a harbinger of premature cardiovascular death [8]. The recent DOQI (Dialysis Outcomes Quality Initiative) publication on the evaluation, classification, and stratification of chronic kidney disease states that individuals with a reduced GRF (glomerular filtration rate) is at greater risk for CVD and cardiac deaths [8].

There are limited data on kidney function in OHT. The major available database of ISHLT showed that is the increasing problem. Between 1994–1997, 20.4% of patients had kidney dysfunction within 1 year after transplantation and almost a decade later between 2002–2006 this percentage reach 38.7% [21]. The reported incidence of CKD (GFR<60ml/min) after OHT has varied between studies ranging from 54% early postransplant till 93% 10 years post transplant in the prospective study [22] or in 38.3–73.3% in cross-sectional study. The criteria for assessing CKD have varied between studies (e.g. serum creatinine concentration, calculated eGFR or creatinine clearance by the Cockcroft-Gault formula). These differences in methodology make direct comparison between studies difficult. In the recent cross-sectional study in 162 prevalent OHT patients, vast majority of patients had significantly impaired kidney function. In the recent paper, Hamour et al. [22] retrospectively analyzed the renal function for 352 OHT in single center from January 1995 to January 2005 to determine the incidence and risk factors for CKD including the influence of the CsA regimen. They concluded that incidence of CKD increased over time was not influenced by the CsA regimen (full dose vs lower dose). In their population mean GFR (MDRD) was 48 ml/min at year 1 and 41 ml.min at year 10 after transplantation. In other study, Przybylowski et al [23] assessed kidney function using two formulas and 24-houres creatinine clearance and found that mean eGFR was higher (any formula) in the population reported by Hamour et al. [22]. They do even have patients with normal kidney function, however, it was a minority, while Hamour et al. [22] reported that 40% of patients before OHT had significant CKD. They demonstrated a progressively increasing incidence of both moderate and severe CKD with time after transplantation. They also found in multivariable logistic regression model that the risk factors for development of CKD stage 3 were post-operative renal replacement therapy for acute renal failure; pretransplant diabetes; increasing recipient age; female recipient; female donor, but not CsA regimen (normal versus low dose). In other study, Przybylowski et al. [24] found in multiple regression analysis, that the predictors of kidney function were age, time after transplantation and haemoglobin. Increasing recipient age as a risk factor for future CKD was found in the ISHLT registry report [21] and other studies [25,26]. In other studies, dealing with kidney function after OHT, the overall conclusion was that patients after OHT had significant decrease in kidney function [27–29]. Veillon et al. [30] reported a 59% incidence of moderate CKD with an eGFR <70 ml/min per 1.73 m^2 at 1 year following heart transplantation, however, it was not clear why cut-off of 70 ml/min for eGFR was chosen. Similar findings have been reported in other, relatively old studies from 80s [31,32]. Hamour et al. [22] in the recent study found that 12% of their patients developed ESRD (end-stage renal disease) by 10 years, whereas in the study of Lubitz et al. [33] a cumulative probability of ESRD was 4.5% at 5 years, 19.6% at 10 years and 44.6% at 15 years following OHT. In the ISHLT registry report a 27% cumulative probability of developing severe renal dysfunction (creatinine >2.5 mg/dl [~220 µml/l], dialysis or renal transplant) by 5 years, 34% by 7 years and 42% by 10 years was demonstrated [34]. According to ISHLT registry, 4.4 percent of heart transplant recipients were on chronic dialysis and 0.9 percent of patients received a renal transplant within eight years after heart transplant [35]. Similar data were reported by Canadian and French Registries with the incidence of dialysis after heart transplantation of 4% [36,37]. In all these registries survival of heart transplant recipients on dialysis was significantly worse than a matched dialysis cohort.

As reported, at least 25 percent of cardiac transplant recipients will develop CKD within the first year after transplant. According to latest ISHLT database report from 2008 is 38,7% [21]. Cardiac transplant recipients usually suffer an initial rapid decline in renal function in the first two years post-transplant, which is followed by a less pronounced decline afterwards [27–32,38–40]. The mechanism for this biphasic pattern appears to be due to the renal response to early versus late effects. The GFR rapidly declines in the first few months after transplant mainly as a result of exposure to perioperative and postoperative insults plus exposure to calcineurin inhibitors [41]. Renal function later stabilizes. In general, the GFR at one year is a better reflection of renal functional reserve, which is also predictive of long term renal outcome and mortality [26]. Lindelow et al. [15] followed 200 patients for up to nine years post heart transplant. The average loss of GFR in the first year post-transplant was 14 mL/min, while the average loss of GFR in the subsequent eight years was 14 mL/min. Severe kidney dysfunction (GFR <20 mL/min per 1.73 m^2) developed in 20 percent of the patients, which was predicted by the recipient age at time of transplantation plus the GFR one year after transplantation. Cirillo et al [29] reported that pre-transplant creatinine clearance was not significantly associated with 5-year mortality in 160 patients after heart transplantation. They suggested that the relation between kidney function and mortality after heart transplantation was affected by several confounders with inclusion of cause of heart disease, co-morbidity, anemia, and post-transplant decrease in kidney function. Calcineurin inhibitor (cyclosporine and tacrolimus) therapy, still the cornerstone of immunosuppressive regimen in most organ recipients, has been implicated as a predominant cause of CKD after transplantation [4,27,32,42]. It should be stressed that histological findings of calcineurin inhibitors toxicity such as vascular obliteration, glomerulosclerosis, tubular atrophy, striped interstitial fibrosis or focal hyalinosis of small arteries and arterioles in the kidney did not differ between renal and non renal solid organ transplant recipients [5,6,43,44]. However, some other studies [7,45] no statistically significant association between the chronic renal failure and the use of a calcineurin inhibitor were observed.

Kidney Function After Lung/Heart-Lung Transplantation

It has been reported that CKD is common following lung transplant [46–50]. As in the case of orthotopic heart transplantation, the decline in renal function is usually biphasic, with a steep decline in the first year after transplantation and a slower decline thereafter. Ojo et al. [4] reported the cumulative incidence of severe CKD (eGFR below 29 ml/min) in 16% lung transplant recipients. Canales et al. [51] found that 54% of the patients following lung or heart-lung transplantation who survived at least 1 year, developed CKD stage 3 or higher, with 7.3% of subjects who developed ESRD. After 7 years posttransplant 59% of patients developed CKD. Hypertension (elevated diastolic blood pressure) and elevated serum creatinine at one month after transplantation were associated with impairment in kidney function, whereas predictors of a shorter time to doubling of the serum creatinine were older age, lower GFR at one month posttransplant and use of cyclosporine within the first 6 months posttransplant [51]. According to the International Society for Heart and Lung Transplantation 17.8 percent of heart-lung recipients developed some degree of renal dysfunction, 3.6 percent required maintenance dialysis, and 0.4 percent received a renal transplant within one year after transplantation [33]. In the same report of this registry, 25% of heart-lung recipients, developed severe CKD (defined as serum creatinine over 2.5 mg/dl, or renal replacement therapy in a form of dialysis or kidney transplantation) within 5 years posttransplant.

As observed with other non renal solid organ transplants, the tapering and withdrawal of calcineurin-inhibitors could improve renal function [52].

Kidney Function After Orthotopic Liver Transplantation

As in the case of orthotopic heart transplantation, calcineurin inhibitors has dramatically improved patient and graft survival in liver transplant recipients, however, their use is associated with nephrotoxicity and many studies have described a gradual decline in renal function following orthotopic liver transplantation [53–55]. In the population-based cohort of 69,321 persons who received nonrenal transplants (heart, lung, liver, and intestine) in the United States between 1990 and 2000 [4] among patients who had received liver transplants, the excess risk of chronic renal failure associated with the use of a calcineurin inhibitor was greater with cyclosporine than with tacrolimus therapy. This association was not statistically significant in recipients of

heart, heart-lung or lung transplants. The prevalence of CKD (eGFR below 60 ml/min), after orthotopic liver transplantation is not precisely known. Diez et al.[56] found stage 3 CKD in 56% of patients within the first year posttransplant, while Ojo et al. [4] reported the cumulative incidence of severe CKD (eGFR below 29 ml/min) in 18% of liver transplant recipients and 23% of intestine transplant recipients. In other study, O'Riordan et al. [7] reported that overall prevalence of CKD among 230 liver recipients followed for a mean period of approximately six years was 2% at 10 years with stage 5, 6% with stage 4 and 57% with stage 3, whereas Fisher et al. [57] found that 8% of liver transplant recipients surviving more than 10 years developed severe CKD (defined as serum creatinine above 2.8 mg/dl) with 50% of those developing ESRD. Gonwa et al. [55] studied 834 liver transplant who survived beyond six months and found that severe CKD, in this study defined as serum creatinine greater that 2.5 mg/dl, was diagnosed in 18% of patients. The risk of developing severe CKD was associated with a higher preoperative serum creatinine, presence of hepatorenal syndrome pretransplant and requirement of renal replacement therapy early posttransplant. Impaired renal function prior to orthotopic liver transplantation is a predictor of decreased patient survival post-transplantation based on the UNOS/OPTN data [17,58]. Decreased GFR was associated with increased 30 day and two year mortality in one study [58], while in the other elevated preoperative serum creatinine concentration was associated with the increased relative risk of death [17]. Generally speaking, presence of impaired kidney function before transplantation, particularly presence of hepatorenal syndrome, is a significant predictor of posttransplant CKD or even requirement of renal replacement therapy. About 10 percent of patients with hepatorenal syndrome prior to liver transplantation eventually develop ESRD posttransplantation [55,59,60]. Five year survival of patients with preoperative creatinine over 2 mg/dl pretransplant in UNOS data base was significantly better in cases of combined kidney-liver transplantation than liver alone [58], with superior renal allograft half-life survival in combined liver-kidney transplantation versus kidney after liver transplantation [61]. As in the case of patients after heart transplantation, survival of liver transplant recipients who develop ESRD requiring renal replacement therapy was significantly worse than a matched dialysis cohort [55]. In addition, acute kidney injury posttransplant requiring renal replacement therapy is a significant predictor of CKD. The reported incidence of hemofiltration for posttransplant acute kidney injury in solid organ recipients varied in different studied ranging from 2–15% in OHT, 8–10% in lung transplantation and 20–25% in liver transplantation [62–65].

Pancreas Transplantation and Islet Transplantation

The is a paucity of data on renal function following islet or pancreas transplantation alone performed for diabetes mellitus. There are a limited number of studies on a relatively small number of patients with relatively short follow up period. In this particular setting, post-transplant renal function is principally influenced by two competing factors such as beneficial effects of sustained normoglycemia and nephrotoxic effects of immunosuppressive protocol and transplantation procedure itself. It has been reported that even five years of sustained normoglycemia after pancreas transplantation alone did not improve kidney function and did not resolve diabetic changes in kidneys [66]. It was probably due to adverse effects of cyclosporine, as it was revealed in the another study where a fall in creatinine clearance correlated with cyclosporine blood levels and dose [67]. In the next study performed by the same investigators, they found that despite a decrease in creatinine clearance after 5 years posttransplant, the kidney function stabilizes thereafter [68]. Ten years after pancreas transplantation alone in the kidney biopsy thickness of the glomerular and tubular basement membranes decreased when compared with the findings after 5 years [68]. It should be stressed, that practically all patients listed for pancreas transplantation alone have normal or near normal kidney function. However, in the case of type 1 diabetes mellitus complicated by significant CKD, patients are considered for either kidney transplant alone or simultaneous kidney-pancreas transplantation or pancreas after kidney transplantation. Scanty reports on kidney function following islet transplantation revealed no rise in serum creatinine in a short-term posttransplant and a rise in serum creatinine after 10 years posttransplant (but still within normal range), complicated also by proteinuria *de novo* or worsening of proteinuria. This phenomen was attributed to the use of mTOR inhibitors since proteinuria resolved after discontinuation of sirolimus [69]. Moreover, successful islet transplantation improved also kidney graft survival [70].

KIDNEY FUNCTION AFTER INTESTINAL TRANSPLANTATION

In a few report on kidney function after intestinal transplantation, all of these studies suggested that kidney function deteriorated among intestinal transplant patients [71–74].

CONCLUSIONS

Chronic kidney disease developed after nonrenal solid organ transplantation is a significant issue. Evaluation of kidney function starting form a complete history and physical examination, then an accurate measurement of renal function and a urinalysis, followed by kidney imaging study should be performed prior to transplantation. Moreover, probability of reversibility of kidney dysfunction and the risk of progression to end stage renal disease should be assessed. During peri- and postoperative period hypotensive episodes should be avoided or at least minimized. Good blood pressure control (however, there are no guidelines for target blood pressure values for non solid organ transplants are available) as well as tight control of diabetes and hyperlipidemia should be implemented. Proteinuria, if present, should be attenuated by the use of therapeutic modalities (RAS blockade) to prevent or delay the progression of renal failure.

The ability to identify CKD may allow early implementation of treatments that could arrest or delay the progression of renal damage, enable effective treatment of its complications, and reduce the risk of drug-induced nephrotoxicity. Kidney function should be monitored in non renal solid organ transplant recipients as an important risk factor comparable with diabetes for cardiovascular mortality and morbidity.

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