Combined Liver and Kidney Transplantation

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Abstract: A significant proportion of patients requiring liver transplantation (LT) present concomitant renal failure. In case of combined end-stage liver and renal disease simultaneous liver and kidney transplantation (CLKT) is indicated. A liver graft may also protect the kidney from recurrence of specific renal metabolic disease.

CLKT is increasingly available, especially since the introduction of MELD score in organ allocation procedures. The long-term results of CLKT are comparable to those of isolated LT. The indications for CLKT are still not well defined, particularly in the cases with potentially reversible renal injury.

The decision to perform CLKT may be difficult due to our inability at the present time to predict the extent of reversibility of acute or functional renal injury. More studies are required to define reliable predictors of renal recovery, and to understand the complex interactions between the background renal impairment and the functional effects on kidney of decompensated liver disease.

Keywords: Renal injury, liver injury, liver transplantation, kidney transplantation, combined liver and kidney transplantation (CLKT).

INTRODUCTION

The first combined liver and kidney transplantation (CLKT) took place in 1984 [1]. Although CLKT is still not uniformly practiced, the proportion of CLKTs performed worldwide (and namely in the USA) has been steadily increasing in the last years [2], both in terms of absolute numbers and of the proportion of overall liver transplants (LT). The recent introduction of MELD-scoring for allocation of livers, which prioritises patients with renal dysfunction [3-5], may probably account for such an increase, since up to 8% of LT candidates are reported to present a dialysis-requiring renal failure at the moment of LT [3].

INDICATIONS TO CLKT

A severe chronic renal failure constitutes an important determinant of post-LT morbidity and mortality, increasing the infectious complications and adversely affecting post-operative long-term renal function and hospital mortality [6-9]. Moreover, the available clinical data suggest that survival of patients with end-stage renal dysfunction (ESRD) receiving CLKT is significantly better than that of those who receive LT alone, with 1- and 3-year survival rates of 83.6 % *vs*. 75.1% and 74.8% *vs*. 68.3%, respectively [10].

Current indications for CLKT have been extensively discussed by Chava e coll. [2], and are further summarized in Table **1**.

As a general rule, they include combined end-stage liver and renal disease. A liver graft may also protect the kidney from disease recurrence and graft loss in specific renal metabolic diseases such as Primary Hyperoxaluria, Amyloidosis or Methylmalonic Acidaemia.

Table 1. Current Indications for CLKT [2]

I. Advanced liver disease with chronic kidney disease:
a) Coincidental:
– Glomerulonephritis/glomerulopathy (membranous, membranoproliferative, IgA-nephropathy, focal glomerulosclerosis, Anti-GbM disease, scleroderma, SLE, diabetes mellitus)
– Interstitial renal disease (chronic pyelonephritis, analgaesic nephropathy, sickle cell anaemia, renal transplant failure, sarcoidosis)
– Structural (obstructive uropathy, medullary cystic disease, nephrolithiasis, malignant hypertension, renal artery thrombosis)
b) Associated:
– Polycystic disease
– Glomerulonephritis/glomerulopathy associated with viral hepatitis (HBV, HCV)
– HCV chronic liver disease in chronic renal failure (patients on haemodialysis)
c) Calcineurin inhibitors toxicity
II. Advanced liver disease with acute renal failure/acute on chronic:
a) Hepatorenal Syndrome
b) Acute Tubular Necrosis
III. Metabolic:
a) Affecting both organs:
– Sickle cell disease
– Alpha 1 antitrypsin deficiency
– Glycogen Storage Disease type I
b) Affecting mainly kidney (liver serving as a gene therapy for correcting the metabolic disorder):
– Primary hyperoxaluria I
– Amyloidosis
– Haemolytic uraemic syndrome
– Methylmalonic acidaemia
IV. Miscellaneous:
– Immunoprotection of kidney in positive cross-match
– Abdominal fibromatosis
– COACH syndrome
– Acute intoxication of chromium-copper

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However, the indications to CLKT are still not well defined, being clearly established only for patients with both liver and kidney end-stage disease on haemodialysis. The indications to CLKT are less clear-cut for patients with mild-to-moderate chronic renal dysfunction or for those with potentially reversible causes of acute renal failure (including hepatorenal syndrome), because of the lack of availability of reliable markers to predict irreversibility or progression of renal disease. Moreover, the serum creatinine is a poor indicator of kidney function in cirrhosis [11, 12].

It may also be difficult to clearly establish a poor prognosis (and therefore an indication to CLKT) in the patients with severe liver disease on haemodialysis, in which transaminase and bilirubin levels are classically low, and ascites may be reduced by renal replacement treatment.

For all these reasons, many questions concerning the appropriate indication and choice of time for combined transplantation still remain unanswered.

Recognising the limitations of available data and the need for more studies, a creatinine clearance <30 ml/min in the setting of chronic kidney disease is currently felt to constitute an appropriate threshold for consideration of CLKT [2].

For patients with hepato-renal syndrome or with acute kidney injury, it is normally agreed that a prolonged duration of renal replacement treatment (i.e. above 8 weeks) could be considered an indication for CLKT, portending lack of kidney recovery [5, 13-15]. Since the longer hepatic-induced kidney ischemia is present the more likely is the permanent renal damage, renal dysfunction of lesser degrees but of prolonged duration may also be associated with a poor kidney function after LT alone. In a recent series [16], the duration of creatinine values of more than 1.5 mg/dL before LT predicted the serum creatinine six months after transplant. However, the actual elevation of the serum creatinine at transplant (not the duration of elevation), predicted the 12-month post-LT creatinine [16].

CLKT OUTCOMES

In CLKT recipients, short-term patient and graft survival rates are generally lower than with LT alone, with a higher post-transplant mortality due to sepsis and multi-organ failure [5, 17, 14], as the patients often present worse general conditions and more co-morbidities.

However, the long-term outcome of CLKT seems to be not different from that of LT alone, with a 5-yr patient survival of 70% and liver graft survival of 65% after CLKT compared to 72% and 64% respectively after LT [14]; the kidney graft half-life has been reported to be slightly less than 10 years for CLKT, compared to 11-12 years for kidney transplants performed from standard donors [18].

However, the results of CLKT are not consistent for all centres, with a 5-year mortality ranging from 48 to 100% in the different series [2, 5, 14, 17, 19-23].

The use of marginal donors (i.e. age>55 years, history of hypertension, donor serum creatinine >2.0 mg/dl, or non heart-beating donors) is however to be avoided in CLKT, since it is associated with a significantly higher rate of persistent kidney dysfunction, need for post-transplant renal replacement treatment and 1-year mortality [24].

It has been claimed by animal studies that liver engraftment may provide immunologic tolerance [25, 26], thus protecting the simultaneously-transplanted kidney from acute rejection [14, 20-22, 27, 28] and permitting lower levels of immunosuppression [21]. The involved immunologic mechanisms may include adsorption and removal of preformed alloreactive antibodies by Kuppfer cells, or their neutralisation by soluble HLA class I antigens expressed by the liver graft [29]. Other potential mechanisms include liver secretion of immuno-modulatory cytokines and the release of donor leukocytes, stem cells or immature dendritic cells, with the subsequent development of haematopoietic microchimerism and donor-specific hypo-responsiveness [30].

Although the 1987-1995 UNOS data did not disclose any reduction in kidney graft rejection in CLKT recipients compared to recipients of the contralateral kidney [31], the analysis of the 1987-2001 UNOS data showed a significantly higher rejection-free survival in CLKT compared to kidney recipients in HLA mismatched groups [17]. Kidney graft loss from chronic rejection seems to be less in CLKT patients (2%) compared to kidney (8%) and polycystic kidney recipients (6%) [17].

NEED FOR A STANDARDIZATION OF THE ORGAN ALLOCATION PROCESS

As stated above, the practice of CLKT is increasing worldwide. However, since the availability of organs for transplant is limited, deep controversies surround the need for standardized strategies for candidate evaluation, selection, and organ allocation procedures in patients with severe liver and kidney disease [5].

Inappropriate CLKT procedures may in fact result in a post-transplant improvement of native kidney function, with some recipients living with three functioning kidneys. Such a possible outcome, demonstrating how easy might be to draw an incorrect decision for combined transplant, may particularly concern the patients having potentially reversible renal failure, in which the heavy weighting of serum creatinine in the MELD-based organ allocation model grants an incorrect and faster organ availability, overestimating the severity of liver disease.

In fact, if in liver patients the pretransplant serum creatinine is significantly related to wait-list and post-LT survival, this is not true in CLKT candidates with ESRD, in which recipient survival is independent of the pre-transplant serum creatinine [10].

Survival after CLKT compared with LT alone shows clear improve only in liver candidates on dialysis at transplant [32, 10]; moreover the data from the Scientific Registry of Transplant Recipients show that only less than 2% recipients of LT alone with a calculated glomerular filtration rate of less than 30 ml/min (but not on dialysis at the time of transplant) required a further kidney transplant within 1 year of LT [4]. Moreover, the need for chronic dialysis (without a listing for kidney transplant) has not been commonly reported soon after transplant [32].

For these reasons, the patients with hepatorenal syndrome not on dialysis should be treated aggressively, reserving CLKT reserved for those with biopsy suggestive of fixed renal damage.

A general consensus has been expressed [2] on the opportunity that any end-stage liver patient with deranged serum creatinine would be studied by a thorough nephrological assessment including urinalysis and imaging.

Newly available markers of kidney failure and renal recovery need to be developed in the evaluation of liver disease [33], in order to grant a reliable assessment of the extent of injury, the risk for progression, and the ability to recover [34-37].

The focus should be on optimal measurements of glomerular filtration (e.g., iothalamate clearances, renal scan), of renal cortical volume, blood flow and oxygen delivery (Duplex-Doppler techniques, paraminohippuric acid clearance, blood oxygen level–determined magnetic resonance imaging), as well as the by-products of injury, matrix protein management, and cytoprotection (i.e. lipid peroxidation products, interleukin 18 and neutrophil gelatinase–associated lipocalin) [33-44].

Renal biopsy is rarely been performed in pretransplant liver evaluation, even when considering a CLKT, probably due to concerns focused upon risks for bleeding [5]. Biopsy safety needs to be carefully evaluated in larger series from experienced centres.

Renal biopsy should be recommended for liver patients in which the cause of a primary renal disease is unclear or the reversibility of renal dysfunction may be uncertain, since its results may potentially alter therapeutic strategies (including the need for CLK) if a progressive kidney disease is diagnosed or substantial renal damage is identified [45-47].

A better way to determine the reversibility of renal dysfunction in liver transplant candidates and the degree of liver disease in end-stage renal disease is certainly needed. More studies are required to delineate the clinical, laboratory or histological predictors of renal recovery, and to understand the complex interactions between the background renal impairment and the functional effects on kidney of decompensated liver disease.

The MELD score should be re-examined as an indicator for the need of LT. Perhaps others than MELD markers of poor liver function (such as sodium serum levels, encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, or diuretic-resistant ascites) could be incorporated into the assessment to improve accuracy of organ allocation [48-50]. This may allow a more accurate picture of the severity of liver disease, especially in candidates with ESRD, and help to prioritize patients for LT before the development of event-related acute kidney failure, avoiding unnecessary CLKT in potentially reversible renal failures.

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