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Combined Liver and Kidney Transplantation

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1. Introduction

Combined liver and kidney transplant (CLKT) is the procedure of choice for patients with both liver and kidney end-stage-disease. In addition, patients with polycystic liver or kidney disease or with hyperoxaluria, or those with cirrhosis and acute renal failure, including hepatorenal syndrome receiving hemodialysis (HD) for more than two months, may also benefit of CLKT.

The decision to transplant both, the liver and kidney, is more difficult in cases when kidney dysfunction may be temporary. Hepatorenal syndrome is a potentially reversible renal failure caused by advance liver disease. Currently, the treatment of choice of hepatorenal syndrome is liver transplant alone and not a combined liver/kidney transplant.

The model for end-stage liver disease (MELD) replaced the United Network for Organ Sharing status classification for the allocation of liver organs. Due to the heavily weighted serum creatinine value in the calculation of the MELD score, candidates with renal failure have received organs more rapidly. As a result there has been considerable increase in number of combined liver-kidney transplants in the past few years.

The reason to propose both liver and kidney transplant for patients with cirrhosis and renal failure relays on the negative impact that renal failure has on patients submitted to liver transplant alone (LTA). Results of several studies show that renal failure in patients with chronic liver disease is associated with high mortality and morbidity after liver transplant alone. Nevertheless, it's very hard to identify a cut-off point of renal dysfunction that determines those patients who may benefit from combined liver and kidney transplant instead of liver transplant alone.

In this chapter, we will review the main points to be considered when evaluating candidates for combined liver kidney transplant, as well as some concerns that have not been yet clarified.

2. Assessment of renal function and evaluating of CLKT in patients with end stage liver disease

Renal failure in cirrhotic patients is associated with poor prognosis. It is well known that cirrhotic patients with renal failure have decreased survival when compared to patients

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with normal renal function. This negative effect is also evident when these patients undergo liver transplantation, as shown by reduced graft and patient survival.

Ideally, patients with a high probability of developing end stage renal disease after liver transplantation alone should receive a combination of liver and kidney transplant. However, is still a great challenge to identify these patients who are at higher risk.

The presence and the severity of pretransplant kidney failure are factors independently associated with postoperative sepsis, need for renal replacement therapy and poor graft and patient outcomes.

In addition to the degree of renal dysfunction, duration and cause of renal failure should also be considered when evaluating candidates for liver transplantation alone or combined liver kidney transplantation.

Patients with pretransplant renal dysfunction (defined as pretransplant Scr > 1.5mg/dL) for a period longer than 12 weeks showed higher probability of progression to end-stage renal disease at 3 years post transplant. However in this study the etiology of renal dysfunction was not specified, mainly due to the authors concern of potential bias in classifying renal failure in absence of kidney biopsy.

Renal failure is usually defined by a reduction in glomerular filtration rate (GFR) that can be acute when it occurs in hours to weeks or chronic when it occurs gradually over time.

Currently, serum creatinine remains the most widely used method to assess renal function in cirrhotic patients.

However, patients with liver dysfunction have reduced creatinine production secondary to loss of muscle mass, and therefore, in those patients serum creatinine usually overestimates renal function. As the Cockcroft-Gault and MDRD (Modification of Diet in Renal Disease) formulas are based on serum creatinine concentration, adjusted by race, age, sex and weight, they also overestimate renal function in patients with cirrhosis and should not be used in clinical settings.

In this context, cystatin C has emerged as an option for evaluate renal function since its level is not influenced by muscle mass. Nevertheless, its value has not been well established and is not available as standart test.

More accurate methods, such as determination of inulin clearance or radionuclide markers, represent the gold standard for measuring glomerular filtration rate. Indeed, its use in daily attendance is not feasible, because of its complexity, making repeated measurements that these patients often require difficult. These gold standard methods should be indicated for selected patients when there is a need to accurately assess renal function to decide between performing liver transplantation alone or CKLT. Their routinary use, however, is not mandatory.

Beyond the degree of renal function, the etiology of renal failure should be assessed, as prognosis varies according to the cause of renal failure. In a recent study with a large population of hospitalized patients with cirrhosis, the most common cause of renal failure was due to bacterial infections (46%), followed by hypovolemia (32%), hepatorenal syndrome (13%) and intrinsic nephropathy (9%). Patients with HRS and bacterial infections had lower 3-month survival compare to patients with intrinsic nephropathy. Even though patients with intrinsic nephropathy present better survival among all causes of renal failure in cirrhosis, its chronic form of renal failure has a non-reversible character and are most likely to receive CKLT.

The diagnostic diagram of etiology of renal failure include a complete medical history and physical examination, searching for presence of diabetes and/or hypertension as well as any other evidence of organ damage. Laboratory evaluation should include urinalysis to seek for

signs of intrinsic nephropathy, like hematuria, pyuria, cell and granular casts, and 24h urine collection to assess protein excretion.

In addition to urine test, a renal ultrasonography, is useful in evaluating preexisting renal disease. Findings such as alteration of renal echogenicity and reductions in the size of the kidneys indicate the existence of chronic kidney disease.

Finally, a definitive diagnostic may require the realization of a renal biopsy, which may also give prognostic information. In patients with intrinsic nephropathy, marked tubulointerstitial injury is associated with progression to end stage renal disease, even if the primary disease is a glomerulopathy. Among histological findings, the degree of tubular interstitial fibrosis is the most powerful predictor of subsequent progression of renal impairment. There are very limited data on renal biopsies findings in cirrhotic patients. A study evaluated 23 kidney biopsies performed in liver transplant candidates with renal failure of unknown etiology or persisted HRS (> 4 weeks) demonstrated a variety of pathologic findings. These included membranoproliferative glomerulopathy, IgA nephropathy, diabetes nephropathy and acute tubular necrosis. Of note, 4 patients showed normal histology. In this study CLKT was recommended for 10 of 26 patients with > 40% global glomerulosclerosis, > 30% of interstitial fibrosis or severe glomerular ischemia/injury. Although these histological criteria have not been evaluated in further studies in patients with cirrhosis, it suggests that renal histopathology changes may alter therapeutic management, including the need for combined liver and kidney transplant.

Therefore according to a recent consensus, a renal biopsy should be performed in patients with an estimated glomerular filtration rate less than 30ml/min with a chronic course. The decision to perform a transjugular or percutaneous renal biopsy should take into account professional experience and patient's clinical conditions, mostly platelet count and coagulation parameters.

Hepatorenal syndrome is a form of kidney failure that is secondary to a severe circulatory disorder in patients with cirrhosis. This particular complication of liver disease can be potentially reversible with the combination of systemic vasoconstrictors and intravenous albumin. Even though the definite treatment of this severe condition remains liver transplantation, the importance of pre-liver transplantation treatment should not be underestimate. Patients with HRS treated with systemic vasoconstrictors and albumin before liver transplantation and pretransplant serum creatinine inferior to 1.5 mg/dL had a three year survival similar to patients transplanted with normal renal function.

Finally, the current criteria to perform CLKT according to the consensus conference is shown in table 1.

1. Evidence of chronic kidney disease and renal biopsy demonstrating more than 30% of glomerulosclerosis or 30% of interstitial fibrosis.
2. If the biopsy is not possible, the decision is made based on <i>National Kidney Foundation</i> criteria for chronic kidney disease, which is an eGFR less than 30ml/min for more than 3 months.
3. Patients with end stage renal disease in renal replacement therapy
4. Patients with hepatorenal syndrome or acute kidney injury with creatinine greater or equal to 2.0 mg/dL and on dialysis for more than 8 weeks.

Table1. Indications for combined liver kidney transplant in patients with end stage liver disease.

3. Evaluation of candidates for CLKT in patients with end stage renal Disease (ESRD)

The benefit of combined liver kidney transplantation is not well established for patients with compensated cirrhosis and ESRD. The decision to perform CLKT or only a liver transplant is matter of debate. In a study of patients with chronic hepatitis C on RRT who underwent kidney transplantation alone, the degree of liver fibrosis correlated with patient and graft survival at 3 years .It is recommended that patients with chronic liver disease and ESRD who are candidates for kidney transplantation should be sought for the presence of significant liver fibrosis and cirrhosis. These patients should be submitted to transjugular liver biopsy with assessment of hepatic venous pressure gradient(HVPG). Patients with cirrhosis and/or clinical significant portal hypertension, determined by an HVPG greater than 10mmHg should be referred to CLKT. The option of kidney transplantation alone should be offered for those patients without these characteristics. Even though most of the data regarding these situations comes from patients with cirrhosis due to hepatitis C, the recommendations are generally applied to all patients irrespective of etiology of cirrhosis.

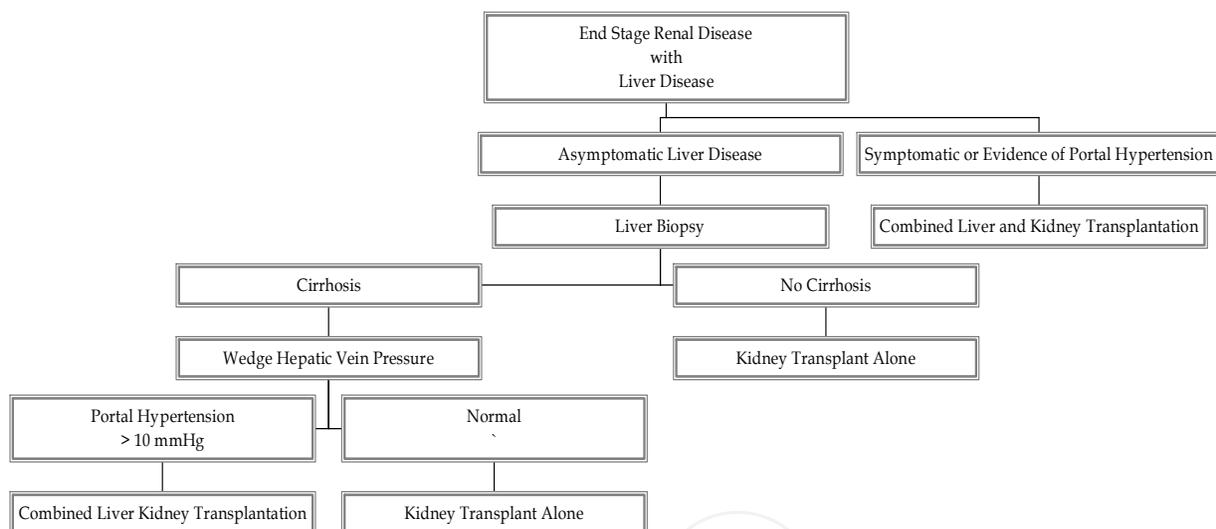


Fig. 1. Diagram for End Stage Renal Disease and Liver Disease (adapted from Consensus Conference on Simultaneous Liver Kidney Transplantation).

4. Outcomes in combined liver and kidney transplantation

Cirrhosis may not be the only indication for CKLT. In a large series of 3520 patients evaluated between 1984-2008, the main indications for combined liver kidney transplantation were: hiperoxaluria type 1 (42.7%), liver cirrhosis and chronic renal failure (23.5%), polycystic liver and kidney disease (15.5%), liver cirrhosis with hepatorenal syndrome (7.1%) and end stage liver disease with renal failure of unknown cause (6%). Hence, prognosis and outcomes of combined liver kidney transplantation are not well known because most of the data came from series that include patients treated with CLKT

not only with end stage liver disease but also patients with inherited diseases without cirrhosis.

In recent years, MELD score has increasingly been used for liver allocation. Due to the presence of serum creatinine in the formula of MELD score, candidates with renal failure are more likely to receive a liver graft. Although pre transplant renal failure is associated with poor outcomes in liver transplantation settings, this modification on organ allocation system was not followed by changes in survival. The 3-year survival of liver transplant recipients remained almost unchanged when compared pre and pos-MELD era (81% vs. 80%, respectively).

A large case-control study compared the outcomes of patients submitted to liver transplant alone with or without renal failure to combined liver kidney transplants (CKLT) between 1987 and 2006. After adjusting for multiple donor (age, race, cause of death) and recipient (MELD, dialysis status at time of transplant) characteristics, recipients of CLKT had a similar one-year survival compared to liver transplant alone (82 vs. 81.8%). However, the degree of renal failure in both groups was not described. The only subgroup in which CLKT had benefit on survival was in patients on long-term pre transplant hemodialysis (defined as a period equal to or greater than 12 weeks). In this subgroup, CKLT recipients had a higher survival than those submitted to liver transplantation alone (84.5% vs. 70.8%, $P=0.008$).

Another study demonstrated that patients on hemodialysis prior to transplantation had a significantly higher 1-year survival for CLKT group when compared to LT alone (79.4% vs. 73.7%, $p=0.004$). This difference, however, was not observed when only patients with renal failure (defined by serum creatinine ≥ 2.5 mg/dL) not on dialysis were analyzed. In this subgroup, 1-year survival was similar for patients who received CLKT or liver transplant alone (81% vs. 78.8%, $p=$ n.s.). An important issue to highlight is that patients receiving CLKT, either on hemodialysis or not, had better liver function at the time of transplant compared to those receiving liver transplantation alone. Mean MELD score of patients receiving LTA or CKLT was 36 vs. 31 for recipients on hemodialysis, and 34 vs. 28 for those with renal failure (serum creatinine >2.5 mg/dl) but not on hemodialysis ($p<0.01$ for both comparisons).

Most studies of survival in combined liver kidney transplantation analyzed a very heterogeneous population respect to the etiology of liver transplantation. Though, a recent study that only included patients with cirrhosis and chronic kidney disease, showed a 1-year survival lower for patients treated with CKLT compared to liver transplant alone group (80 vs. 97%, $p=0.014$). The probability of survival at 3 years was also lower in the CLKT group, but the difference between both groups did not reach statistical significance (75% and 88%, respectively). The incidence of complications was also higher for CKLT. Patients with CLKT had a higher incidence of bacterial infections and transfusions requirements compared to LTA group. Nevertheless, the comparison group (liver transplant alone) did not present renal failure at the time of transplant (mean serum creatinine value of 0.96 ± 0.27 mg/dL), because all patients with cirrhosis and advanced chronic kidney disease (defined by a glomerular filtration rate below 30ml/min) were considered candidates for CLKT.

Another important point is the potential reversibility of renal failure after liver transplantation. As mentioned previously, patients with HRS should be treated to reverse the renal failure before liver transplantation. Many of these patients, however, do not respond to treatment and eventually undergo CKLT. Only a few single-center series had described outcomes of patients with hepatorenal syndrome submitted to CLKT. One of them compared the results of patients with HRS on hemodialysis who received CLKT ($n=22$,

median time of pretransplant hemodialysis of 41 days) to those with HRS on hemodialysis who received liver transplant alone (n=80, pretransplant hemodialysis time inferior to 30 days). The one-year survival for patients undergoing CLKT or LTA was similar (72% vs. 66%, respectively, $p=0.88$). Most of the benefit of performing CKLT was observed in patients on hemodialysis for more than 8 weeks pre transplant. This group had higher survival than those receiving CLKT on hemodialysis for a period inferior than 8 weeks (88% vs.66%, respectively). Among patients receiving liver transplantation alone, recovery of renal function was achieved in 90% of patients at one-month, even though most of them required hemodialysis at post transplant period.

The possible benefit of CLKT on LTA in patients with hepatorenal syndrome was also evaluated in a study comparing patients submitted to CLKT to patients with HRS submitted to LTA. Survival at 5 years was similar for CLKT recipients (48.1%) and patients with HRS receiving LTA (67.1%) ($p=ns$).

Some recent data on patients who received CLKT (n=75) over a 23 year-period show excellent 1-, 3- and 5- year patients survival (81%, 73% and 67%, respectively). However, short-term mortality (< 90 days) was especially high because of sepsis/infection on postoperative period. In addition, there was no difference in patient survival based on whether or not a recipient was on dialysis pre-transplantation. Nevertheless, the need of post transplant renal replacement therapy was significantly associated with poor prognosis ($p=0.0012$).

Regarding graft survival, it seems that the liver graft has an immune protective effect on kidney graft when both organs came from the same donor. A study comparing renal allograft outcomes of patients who undergone CLKT to kidney after liver transplantation (KALT) demonstrated a higher incidence of chronic rejection in KALT group than CLKT group (4.6 vs. 1.2%, $P < 0.001$). One and three-year rejection-free renal graft survival of KALT was lower than CLKT group (77% and 67% KALT vs. 85% and 78% CLKT, respectively; $P < 0.001$). Renal half-life of KALT allograft was shorter than CLKT group (6.6+/-0.9 vs. 11.7+/-1.3 years, $P < 0.001$). It has been speculated that this effect is secondary to the secretion of soluble HLA antigens by the liver and to phagocytosis of these reactive antibodies by kupffer cells.

Although many theories have been described to explain the possible hepatic protection on renal graft, some recent findings have questioned this statement. A case report of acute humoral rejection in kidney allograft in an ABO compatible CLKT was described. Even treating, the humoral rejection with plasmapheresis, intravenous immunoglobulin and rituximab, the kidney required 3 months to recovery function and finally progressed to chronic allograft nephropathy.

5. Combined liver and kidney transplantation in special conditions

Polycystic kidney diseases (PKD) compass a group of inherited diseases that causes an irreversible decline in kidney function. Autosomal dominant polycystic kidney disease (ADPKD) is associated with cysts in the kidneys and, in many cases, cysts in the liver and pancreas. The autosomal dominant form (ADPKD) is the most common genetic cause of chronic kidney disease. As survival with dialysis or transplant increase, incidence of liver disease will also increase. When cysts are diffused, fenestration/resection procedures are not successful and LKA offers a good survival option. For combined liver and kidney transplantation one- and two-year patient survival rates were similar to combined

transplantation for other indications. For patients with acceptable renal function at time of transplantation, solitary liver transplantation has an excellent outcome.

Primary hyperoxaluria (PHO) is a rare metabolic disorder with autosomal recessive inheritance. PHO is induced by one of two enzymatic defects, both of which result in markedly enhanced conversion of glyoxalate to poorly soluble oxalate which is then excreted in the urine. Combined liver-kidney transplantation is probably the treatment of choice for children with type 1 PHO with progressive renal disease. The liver provides the missing enzyme, thereby lowering oxalate production to the normal range. The outcome may be best if transplantation is performed when the GFR falls to 25 mL/min per 1.73 m² and prior to marked tissue oxalate deposition. Isolated liver transplantation has been proposed for patients with rapidly progressive disease who still have a glomerular filtration rate above 30 mL/min per 1.73 m².

6. Conclusion

Since implementation of MELD score as an organ allocation system, a crescent number of cirrhotic patients with renal failure has been submitted to CLKT. Due to increase shortage of organ donors, is of outstanding importance to define which are the patients who benefit most of this procedure.

The decision to perform orthotopic transplant alone or combined kidney-liver transplantation is still challenging, mainly because there is not enough data on factors that can predict renal function recovery. In patients with possible reversible causes of kidney dysfunction, including those with hepatorenal syndrome and acute renal failure, it is difficult to precise the boundaries between functional and irreversible damage. Therefore, in these cases kidney biopsy should be encouraged in order to evaluate interstitial and glomerular injury.

Combined liver kidney transplantation seems to be an adequate treatment in patients with end stage liver disease and chronic kidney disease on renal replacement therapy, as well as for those with inherited disease. The survival advantage in others subsets of patients is not well established and more studies are needed.

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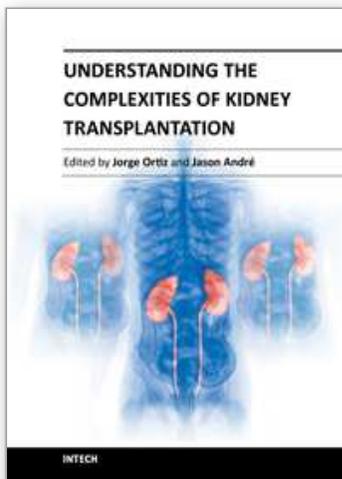
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Kidney transplantation is a complex field that incorporates several different specialties to manage the transplant patient. This book was created because of the importance of kidney transplantation. This volume focuses on the complexities of the transplant patient. In particular, there is a focus on the comorbidities and special considerations for a transplant patient and how they affect kidney transplant outcomes. Contributors to this book are from all over the world and are experts in their individual fields. They were all individually approached to add a chapter to this book and with their efforts this book was formed. Understanding the Complexities of Kidney Transplantation gives the reader an excellent foundation to build upon to truly understand kidney transplantation.

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