Incidence and outcome of calcineurin inhibitors induced nephrotoxicity after liver transplantation

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Abstract: Background: Renal dysfunction -most often due to calcineurin inhibitors (CNIs) nephrotoxicity- is the most common complication following liver transplantation. **Objective:** To determine the incidence and outcome of CNIs induced nephrotoxicity in patients who underwent living donor liver transplantation (LDLT). **Patients and Methods:** This study was conducted between April 2003 and September 2010, 87 recipients of LDLT in National Liver Institute (NLI) and 23 patients with deceased donor liver transplantation (DDLT) (done outside Egypt as this is not allowed to date in Egypt). **Results:** primary immune-suppression was started using Tactolimus **(**FK) and Cyclosporin A (CsA) in 89 (81%) and 21 (19%) recipients respectively. Most common indication for liver transplantation was due to end stage liver disease due to chronic HCV infection (n=60 (54.5%)), 13 of them (21.6%) developed post-LT Renal dysfunction versus 10 (20%) with non HCV (n=50) (p=0.96). MELD score was higher in recipients with post-LT KD (16.4 ± 5.1) than other recipients (15.6 ± 3.5) but the difference was not statistically significant (p=0.55). Pre-LT total bilirubin did not have significant impact on post-LT RD (P=0.47). Three recipients had pre-LT CKD diagnosed by DMSA scan (chronic parenchymal renal disease and decreased GFR in spite of normal creatinine level), 2 recipients of them developed post-LT KD, with no statistically significant difference (p=0.11), 8 out of 23 diabetic (34.7%) recipients developed nephrotoxicity versus (24.5%) in non diabetics, with no statistically significant difference (p=.091), 7 out of 27 (25.9%) HCC recipients developed post-LT KD 16 patients out of 83 (non HCC recipients) 19.2% developed post-LT KD with no statistically significant difference (p=0.55). 18 recipients were treated by FK (78.3%)), 12 (66.6%) of them improved (normalization of serum creatinine i.e. <1.5mg/dl) with dose modification or with discontinuation or shift to another drug and 6 (33.3%) did not improve, this was better than the recipients treated by CsA (n=5 (21.7%)), 2 (40%) of them improved and 3 (60%) did not improve but this was not statistically significant (p=0.28), dose modification of immune-suppressants was needed in 34 recipients, the most common cause for dose modification was nephrotoxicity (n=23), with statistically significant difference (p<0.001). Recipients with nephrotoxicity had lower 5 year survival rate (67% versus 71% in recipients without nephrostoxicity), this was not statistically significant (p=0.337). **Conclusion:** post liver transplantation nephrptoxicity is highly prevalent, early diagnosis and management is very important. It is usually curable and treated by dose reduction or replacement with other immune-suppressants.

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1. Introduction

Liver Transplantation (LT) is a life saving and quality improving procedure for patients with chronic (ESLD) and acute liver failure (ALF) when there are no available medical and surgical treatment options (1). The first successful LDLT in Egypt was performed at the National Liver Institute in 1991; however, this program did not continue because of poor early results, then the program restarted again in April 2003. Since then, almost 500 cases of living-donor liver transplant have been performed in 9 centers in Egypt (2). Renal insufficiency whether acute kidney failure (AKF) or chronic kidney disease (CKD) is a common complication after LT and represents a major challenge with high morbidity and mortality following LT (3). The cumulative risk of renal failure has been reported to be as high as 20% at 5 years post- transplant (4). ARF has been associated with an eight folds increase in mortality risk, prolonged intensive care unit (ICU) stay, greater risk for infectious complications and greater hospital costs. Others showed an in-hospital mortality rate of 41% for patients with ARF versus 5% for those with preserved renal function (5). The incidence of CKD among recipients of non-renal transplants varies widely, from 10 to 83 % most likely owing to the

lack of a standard definition of post transplantation renal disease, differences in the types of transplantation studied, and variable periods of follow-up. It has been shown that up to 18% of the patients can develop GFR of < 29 ml/min per 1.73 of body surface area (ml/min) by 5 years post-transplantation (6). Nephrotoxicity has become the 'Achilles heel' of CNIs their use in hepatic and cardiac transplantation has led to end-stage renal disease and dialysis with an incidence in large cohorts of recipients directly proportional to the dosage of CsA, higher recipient age and the duration of follow-up. CsA-mediated nephrotoxicity, in the long term course, shows only a weak correlation with elevated CsA blood concentrations. Therefore, at the individual level, CsA nephrotoxicity has to be determined by individual susceptibility (7). CNIs withdrawal is associated with a significant initial improvement and then arrest in long-term decline of renal function. Rejection in this setting is uncommon. The greatest benefit is seen in patients switched within the early years after transplantation (8). De novo CNIs minimization has been proven to be effective at reducing the rate of impaired renal function after transplantation. The reduction in the CNIs doses should be offset by the addition of MMF or enteric-coated mycophenolate sodium. Delayed CNIs minimization in patients with established renal insufficiency may result in a significant improvement in the GFR, even though the increase in the GFR after minimization is generally modest (9).

We aimed in our study to determine the incidence and outcome of CNIs induced nephrotoxicity in patients who underwent (LDLT), and (DDLT) outside NLI-as it is not allowed by political and traditional lows- and who followed up regularly by hepatolgist in liver transplant clinics in National Liver Institute.

2. Patients and methods

This study included 110 recipients who underwent LT. 87 recipients underwent LDLT in NLI, Menoufiya University between April 2003 until September 2010. Another 23 recipients underwent DDLT in China and were followed in the LT clinics in NLI in the same period.

We retrospectively and prospectively reviewed the courses of these recipients who received CNIs as an immune-suppressive either CsA or FK. Data were extracted from preoperative records, post-operative files (in ICU and ward) and from the follow up records of all patients. The Patients with pre LT renal impairment (serum creatinine >1.5mg/dl) were excluded from the study.

2.1. Demographic and clinical data

All patients were reviewed regarding their age, gender, etiology of liver disease, type of transplantation (LDLT or DDLT), diabetes mellitus (DM) (defined as fasting blood glucose > 126 mg/dl) and hypertension (defined as a systolic blood pressure of >140 mmHg and/or a diastolic blood pressure > 90 mmHg).

2.2. Pre-LT investigations

2.2.1. Biochemical investigations

Liver enzymes (Transaminases) (AST, ALT), total & direct bilirubin, serum albumin, prothrombin time and INR, serum creatinine, blood urea, GFR using radio isotope scanning (DMSA & DTPA)&MELD score was calculated within one week prior to transplantation. The standard MELD formula used was: MELD score = 9.57×loge (Creatinine mg/dl) + 3.78 × loge Bilirubin mg/dl) +11.20×loge (INR)+6.43(10).

2.2.2. Imaging studies

Abdominal ultrasound and renal dopplar to exclude primary kidney disease & Renal Isotope Scanning plus the usual pre-transplantation investigations.

2.3. Post-LT assessment

The following were recorded:

- Type of primary immune-suppressive agent used whether CsA or FK based immune-suppression, renal functions were assessed daily in the first 2 weeks then at least monthly till the end of the study. Assessments of renal functions include serum creatinine.

3. Results

3.1. The specific characteristics of the subjects

The recipients were; 89 males (80.9%), and 21 females (19.1%) with mean age = 41.98 ± 1.59 years, ranging from 6 months to 60 years. The one week pre-transplant mean MELD score was 16.2±4.8, 6 recipients (5.5%) of the recipients suffered from pre-LT hypertension and 23 (20.9%) suffered from DM and 3 recipients (3.44%) of the LDLT recipients had CKD.

The main indications of LT included ESLD caused by chronic HCV in 60 (54.5%) recipients, Hepatocellular carcinoma (HCC) in 27 (24.5%) recipients, congenital causes in 12 (10.9%) recipients as following (6 patients with biliary atresia, 2 patients with Byler's disease, 2 patients with congenital hepatic fibrosis, one patient with hepatoplastoma and one patient with giant cavernous haemangioma), 2 (1.8%) cryptogenic decompensated cirrhosis, 2

(1.8%) Budd-Chiari syndrome**,** 1 (0.9%) ESLD due combined HBV and HCC. 1 (0.9%) Wilson disease, 1 (0.9%) ESLD caused by chronic combined HBV and HCV infection, 1 (0.9%) combined HBV, HCV and to chronic hepatitis B Virus (HBV), 1 (0.9%) due to HCC, 1 (0.9%) Alpha-1-antitrypsin deficiency & 1 (0.9%) alcoholic liver disease (Table 2).

Table 1. RIFLE criteria: is an acronym for risk of kidney dysfunction, injury to the kidney (AKI), failure of the kidney (AKF), loss of kidney function and end-stage kidney disease (11)

Class	GFR criteria	Urinary output criteria
Risk	Serum Cr x 1 .5 or GFR decrease >25%.	< 0.5 ml/kg/hour x 6 hours
Injury	Serum Cr x 2 or GFR decrease >50%.	< 0.5 ml/kg/hour x 12 hours
Failure	Serum Cr x 3, GFR decrease > 75% or serum Cr >4 mg/dl with an acute rise>0.5mg/dl.	< 0.3 ml/kg/hour x 24 hours, or anuria x 12 hours
Loss	Persistent acute renal failure = complete loss of kidney function > 4 weeks.	
End-stage kidney disease	End-stage kidney disease > 3 months.	

3.2. Post-transplant renal dysfunction*:*

FK immune-suppression was administered to 89 (81%) recipients and CsA was administered to 21 (19%) recipients as primary immuno-suppressive (Table 3), AKD post LT was seen in 23 (20.9%) recipients, 9 (8.1%) of them progressed to CKD.

3.3. Association of nephrotoxicity with different variables

8 recipients (20.2%) out of the 89 (81%) recipients received FK as primary immunosuppressive developed nephrotoxicity representing 78.2% of total cases of nephrotoxicity. On the other hand, 21 (19%) recipients received CsA, 5 of them (23.8%) developed nephrotoxicity representing 21.8% of total cases of nephrotoxicity, with no statistically significant difference in the incidence of nephrotoxicity among recipients treated with FK or CsA based immunosuppression (P=0.48) (Table 4).

3.4. Association of nephrotoxicity with Pre-LT variables

The age was not statistically significant risk factor for post-LT KD, 16 (14.5%) recipients below 18 years, 2 (12.5%) of them developed post-LT KD and 94 (85.5%) adult recipients 21 (22.3%) of them developed post-LT KD, although the incidence of post-LT KD among the adult recipients is higher but with no statistically significant difference (p=0.51). MELD score was higher in recipients with post-LT KD (16.4 ± 5.1) than other recipients (15.6 ± 3.5) but the difference was not statistically significant (p=0.55) (table 5). Pre-LT total bilirubin had no significant impact on post-LT RD (P=0.47). Pre-LT DM: 8 out of 23 diabetic recipients (34.7%) developed nephrotoxicity, with no statistically significant difference (p=.091). Nephrotoxicity was not affected by the etiology of ESLD: HCV as an etiology of the liver disease was not significantly correlated to post-LT KD, 13 out of 60 chronic HCV recipients (21.6%) developed post-LT KD. On the other side recipients with ESLD other than HCV (n=50), 10 of them (20%) developed post-LT KD (p=0.96). 27 recipients (24.5%) had HCC before LT, 7 (25.9%) of them developed post-LT KD, versus 16 out of 83 (19.54%) of non HCC recipients developed post-LT KD but this was not statistically significant (p=0.55). 3 recipients had pre-LT CKD diagnosed by DMSA scan (chronic parenchymal renal disease and decreased GFR in spite of normal serum creatinine level), 2 recipients of them developed post-LT KD, with no statistically significant difference (p=0.11). Effect of type of LT**;** 87 recipients underwent LDLT (79.1%), 21 (24.1%) of them developed post-LT KD. While 23 recipients underwent DDLT (20.9%), 3 (13%) of them developed KD post-LT with no statistically significant difference (p=0.25) (tables 6, 7 & 8).

3.5. Outcome of nephrotoxicity after LT

AKD happened in 23 out of 110 recipients (20.95%), 14 recipients (60.86%) improved (normalization of serum creatinine level i.e. <1.5mg/dl) with dose modification (10 recipients improved with decreasing the dose and 4 recipients improved with discontinuation and shift to another immune-suppressants), 9 (39.14%) recipients (6 recipients were switched to other immune-suppressants, decreased dose of CNIs in 2 recipients and decreased the dose and added another immune-suppressants in one recipients). Acute cellular rejection episodes developed in 4 recipients after dose modification either reduction or switch to another

immunosuppressant but there was no rejection-associated graft loss. Recipients who needed dose modification of immune-suppressant for different causes were 34 recipients, the most common cause for dose modification was nephrotoxicity in 23 recipients), this was statistically significant (p<0.001) (tables 9, 10, 11, 12 &13).

3.6. Effect of nephrotoxicity on recipient's mortality

The 5 year survival rate was 67% in recipients with nephrotoxicity versus 71% in recipient without nephrotoxicity, this was not statistically significant (p=0.337) (figure 1).

Table 2. Demographic data and pre-transplant clinical characteristics of all recipients (110 recipients)

	Minimum	Maximum	Mean	Std. Deviation
ALT (IU/L)	12	209	57.26	38.864
AST(IU/L)	12	379	101.72	74.099
MELD score	7	28	16.22	4.835
T. Bill (mg/dl)	.5	47.6	5.047	7.5758
D. Bill (mg/dl)	.1	31.11	15.506	21.0172
S.Alb(g/dl)	1.2	5.1	2.889	.6813
INR	1.0	3.1	1.576	.3763
S.Cr(mg/dl)	0.1	1.4	1.31	7.11022
Bl.Urea (mg/dl)	8	98	33.70	18.968

Table 3. Indication of liver transplantation in the studied subjects

Etiology of liver disease	Number	Percent
HCV	60	54.5%
HCV+HCC	27	24.5%
Congenital liver disease	12	10.9%
Cryptogenic	2	1.8%
Budd-chiari syndrome	2	1.8%
HBV	1	0.9%
HBV+HCC	1	0.9%
Wilson disease	1	0.9%
HCV+HBV	1	0.9%
HCV+HBV+HCC	1	0.9%
Alpha-1-antitrypsin deficiency	1	0.9%
Alcoholic liver disease	1	0.9%
Total	110	100.0

Table 4. Incidence of post-LT nephrotoxicity with the type of immuno-suppressants

Immunosuppressive drug	Nephrotoxicity		Total	p-value
	No n=87	Yes n=23		
FK	71 (79.7 %)	18 (20.3%)	89 (81%)	0.487
CsA	16 (76.2%)	5 (23.8%)	21 (19%)	

Table 5. Incidence of post-LT Nephrotoxicity with the age

Nephrotoxicity	Child <18 years	Adult >18years	Total	P value
YES	2 (12.5%)	21 (22.5%)	23	0.51
NO	14 (87.5%)	73 (77.5%)	87	
Total	16	94	110	

Table 6. The incidence of post-LT nephrotoxicity with DM and the type of LT

	Nephrotoxicity		Total	p value
	No n=87	Yes n=23		
Diabetic	15 (65.3%)	8 (34.7%)	23 (20.9%)	0.091
Not diabetic	72 (82.8%)	15 (17.2%)	87 (79.1%)	
LDLT	67 (77%)	20 (23%)	87 (79.1%)	0.25
DDLT	20 (87%)	3 (13%)	23 (20.9%)	

Table 7. Incidence of post-LT nephrotoxicity according to MELD score & total bilirubin for LDLT recipients

	Nephrotoxicity	Mean	Std. Deviation	Std. Error Mean	p value
MELD	NO	15.62	5.18	0.63	0.554
	Yes	16.41	3.57	0.77	
T. Bill.	NO	2.84	1.70	0.37	0.475
	Yes	5.74	8.54	1.05	

Table 8. The incidence of post-LT nephrotoxicity with HCV and HCC

HCV	Nephrotoxicity		Total	p value
	No n=87	Yes n=23		
HCV -ve	40 (80%)	10 (20%)	50 (45.5 %)	0.966
HCV+ve	47 (78.4%)	13 (21.6%)	60 (54.5%)	
No HCC	67 (80.8%)	16 (19.2%)	83 (75.5%)	0.552
HCC	20 (74.1%)	7 (25.9%)	27 (24.5%)	

Table 9. Outcome of post-LT renal dysfunction

Nephrotoxicity	Number	Percentage in patients with nephrotoxicity	Percentage in all recipients
Improved	14	60.86%	12.7%
Not improved (chronic nephrotoxicity)	9	39.14%	8.2%
Total	23	100%	20.9%

Table 10. Outcome of renal dysfunction in association with immunosuppressant drugs

immunosuppressant	Nephrotoxicity outcome		Total	p value
	improved	not improved		
FK	12 (66.6%)	6 (33.4%)	18	0.280
CsA	2 (40%)	3 (60%)	5	
Total	14	9	23	

Table 11. Dose modification of immunosuppressant drugs

modification	NO	Valid Percent	Cumulative Percent
Decreased dose	14	41.2	41.2
Shift to another drug	18	52.9	94.1
Added drug	2	5.9	5.9
Total	34	100.0	100.0

Table 12. Causes of dose modification

Cause	Dose modification			Total	P value
	decreased	shift	added		
chronic cellular rejection	0	0	1	1	P<0.001
D.M	0	2	0	2	
dyslipidemia	0	2	0	2	
dyslipidemia&DM	0	3	0	3	
nepherotoxicity	12	10	1	23	
neurotoxicity	2	1	0	3	
Total	14	18	2	34	

Table 13. Nephrotoxicity outcome related to dose modification

Nephrotoxicity outcome	Dose modification			Total	P value
	decreased	shift	added		
Improved outcome	10 (71.4%)	4 (28.6%)	0	14 (100.0%)	0.033
Not improved outcome	2 (22.2%)	6 (66.7%)	1 (11.1%)	9 (100.0%)	
Total	12 (52.2%)	10 (43.5%)	1 (4.3%)	23 (100.0%)	

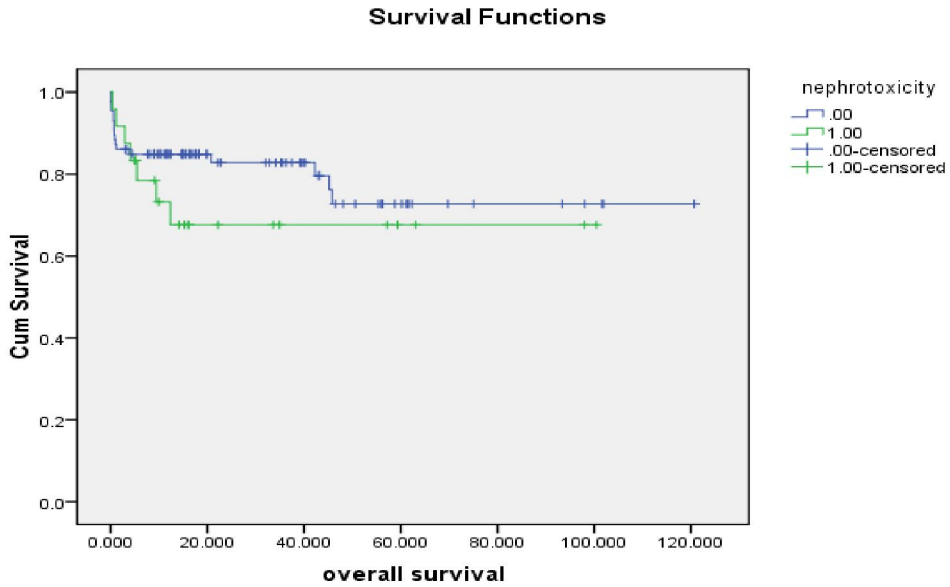

Figure 1. Kaplan-Meier curve of the cumulative patient survival in patients with and without renal dysfunction according to log rank test (p=0.337)

4. Discussion

Our study showed that the incidence of post-LT KD occurred in 23 recipients (20.9%), 9 (8.18%) of these recipients progressed to CKD during the mean follow up period 29 months.

CKD was diagnosed in 9 (8.18%) of recipients over a mean follow-up period after transplantation of 29.09 months. Its incidence was comparable to the results of Lebron et al. (12) who used the same criteria to define CKD (16.7% over a follow up period ranging from 6 months to 6 years, and Abbasy et al. (13) who reported that CKD was diagnosed in 12.5% of recipients over a mean follow-up period after transplantation of 53 months.

On the other hand, Moreno et al. (14) in their study reported an incidence rate of post-LT KD 47.8% although we used the same definition of CKD. The higher incidence could be explained by the longer duration of follow-up and large number of recipients in Moreno's study which assessed the CKD

in all recipients who underwent DDLT between 2002 and 2007 and found that the cumulative incidence of post-LT CRF at 1, 3, and 5 years was 8%, 17% and 22%, respectively.

In the present study 89 (81%) recipients received FK as primary immunosuppressive; 18 (20.3%) developed nephrotoxicity. On the other hand, 21 recipients (19%) received CsA, 5 of them (23.8%) developed nephrotoxicity, with no statistically significant difference in the incidence of nephrotoxicity among recipients treated with FK or CsA as primary immune-suppressive. But the outcome of nephrotoxicity with FK was better than CsA as in recipients treated with FK 66.6% of them improved versus 40% in recipients treated by CsA however this was not statistically significant. Many investigators, in consistent with our study, did not identify any difference in the impact of either CsA or FK on renal function post-LT **(**15 - 18**).** With no added beneficial effect of the use of FK over CsA on the renal function post-LT (14 and 16). However O'Riordan et al., Filler et al. and Lucey et al (6, 20 and 21) found a beneficial effect of FK use, compared with CsA, which retarded the progression of AKD to CKD. Regarding the impact of CNIs on long term renal function, Ojo et al., Moreno et al. and Lee et al. (4, 14 and 22) concluded that the overall risk of CKD development was associated with CsA more than FK.

In our subjects the dose reduction of CNIs significantly improved the renal function than discontinuation or switch to another immunosuppressant drug. Macky et al., Ziolkowski et al. and Kyrsten et al. (8 19 and 23) reported that dose reduction significantly improved the renal function with no acute episode of rejection after conversion and dose reduction.

The occurrence of CKD after LT has a major impact on post-LT mortality. In our study, the 5 years patients survival in recipients with post-LT KD was 67% versus 71% in those without post-LT KD, without significant difference (p=0.337). This finding could be explained by short period of follow up (5 years only) and small number of patients. But Gonwa et al. (24) reported that the 13 years survival rate in recipients with post-LT ESRD was 28.2% versus 54.6% in those without post-LT KD. Similarly, Abbasy et al. (13) in their study reported that the mean survival of patients who developed CKD, was 19.2 months and 65.3 months in recipients without nephrotoxicity (P<0.001).

Ojo et al. (4) with ESRD observed that recipients who remained on dialysis had a 6 year survival rate of only 27% versus 71% in the patients who subsequently received kidney transplants. Campbell et al. and Sharma et al. (25, 26**)** showed that a decrease in post-LT GFR over time was associated with a significant decrease in post-LT survival.

5. Conclusion

Early diagnosis and management of renal dysfunction after LT is very important. CNIs induced nephrotoxicity is usually curable and could be treated by dose reduction or replacement with anther immune-suppressants however a lot of work in needed to identify the suitable immuno-suppressive drug for every recipient to preserve the graft without renal injury.

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