Prevalence and Risk Factors of Renal Dysfunction After Liver Transplant: A Single-Center Experience

Seyed Mohsen Dehghani,[1,2,4] Ali Derakhshan,[1] Seyed Ali Reza Taghavi,[1,3,4] Siavash Gholami,[1] Hamed Jalaeian,[1] Seyed Ali Malek-Hosseini[1]

Abstract

Objectives: **Renal dysfunction is one of the most significant complications after liver transplant. It is attributed mainly to nephrotoxicity caused by calcineurin inhibitors. We evaluated the renal functioning in liver transplant recipients alive for at least 6 months after liver transplant.**

Materials and Methods: **One hundred seventy patients (108 male [63.5%], 62 female [36.5%]; mean age, 31.4 ± 13.3 years; age range, 13-61 years) were included in this study. Patients who had undergone a liver transplant between 1994 and 2006 at the Organ Transplantation Center of the Shiraz University of Medical Sciences in Shiraz, Iran, and had been alive for at least 6 months after surgery were included. Data were collected regarding age, sex, body mass index, underlying liver disease, graft type, immunosuppressive medications, serum creatinine levels, and glomerular filtration rate before, 1, and 6 months after liver transplant. Renal dysfunction was defined as a serum creatinine level above 132.6 µmol/L or a glomerular filtration rate less than 60 mL/min/1.73 m^2, based on our reference range. Glomerular filtration rate was calculated using the Schwartz formula (glomerular filtration rate mL/min/1.73 m^2 = K × Ht (cm) / Cr mg/dL). Data were analyzed with SPSS software.**

Results: **The mean follow-up was 25.9 ± 23.5 months (range, 6-156 months). The main indications for liver transplant were cryptogenic cirrhosis (n=42), hepatitis B infection (n=34), autoimmune cirrhosis (n=30), Wilson's disease (n=21), and primary sclerosing cholangitis (n=18). The mean pretransplant glomerular filtration rate was 93.7 ± 35.6 mL/min/1.73 m^2. The mean glomerular filtration rates in the first and sixth months after liver transplant were 81.6 ± 29.3 mL/min/1.73 m^2 and 83.6 ± 32.9 mL/min/1.73 m^2. Sex, body mass index, type of immunosuppressive medication, and underlying liver disease were not predictors of renal dysfunction (*P* > .05). Posttransplant renal dysfunction was significantly more common in older patients (ie, those aged 38.8 years and older) (*P* = .0001) and those with a family history of renal disease (*P* < .05).**

Conclusions: **Renal dysfunction may be a significant problem for patients after liver transplant, and early detection of renal dysfunction in patients after liver transplant is important. Of all the risk factors studied here, only older age and family history of renal disease were correlated with development of renal dysfunction after liver transplant.**

Key words: *Cyclosporine, Tacrolimus, Nephrotoxicity*

Improved survival after liver transplant has necessitated a re-evaluation of immunosuppressive protocols. Corticosteroids and calcineurin inhibitors are the most frequently used immunosuppressive drugs for liver transplant but are associated with a range of adverse effects including nephrotoxicity (1, 2). Renal dysfunction in this setting may be caused by pre-existing renal disease, hepatorenal syndrome, or posttransplant factors including the use of nephrotoxic drugs, most notably of which are the calcineurin inhibitors cyclosporine and tacrolimus (1-3). The percentages of patients having posttransplant renal

From the [1]Shiraz Organ Transplantation Center, Departments of [2]Pediatric Gastroenterology, [3]Internal Medicine, and [4]Gastroenterohepatology Research Center, Nemazee Hospital Shiraz University of Medical Sciences, Shiraz, Iran

Acknowledgment: *The authors would like to thank Dr. Mehrdad Vosoughi at the Center for Development of Clinical Research at Nemazee Hospital for their help with the statistics in this paper.*

Address reprint requests to: *Seyed Mohsen Dehghani, MD, Assistant Professor of Pediatric Gastroenterology, Gastroenterohepatology Research Center, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, 71937-11351, Iran*

Phone*: +98 711 626 1775* ***Fax:*** *+98 711 647 0207* ***E-mail:*** *dehghanism@sums.ac.ir*

Experimental and Clinical Transplantation (2008) 1: 25-29

dysfunction have been found to range from 22.8% to 50% (3, 4).

The aim of this study was to evaluate the prevalence of and risk factors for renal dysfunction at 1 and 6 months after liver transplant among Iranian liver allograft recipients.

Materials and Methods

All patients followed at the Liver Transplant Unit at the Clinic of Shiraz University of Medical Sciences in Shiraz, Iran, who had undergone liver transplant between 1994 and 2006 were retrospectively studied. The current study included 170 liver allograft recipients (108 male [63.5%], 62 female [36.5%]; mean age, 31.4 ± 13.3 years; age range, 13-61 years) with a survival of at least 6 months after liver transplant. Our center is the only liver transplant center in Iran, and all patients who came from around the country and underwent a liver transplant were followed at our liver transplant clinic.

We gathered preliminary data that included age, sex, weight, height, body mass index, family history of renal diseases (any type of chronic renal failure or renovascular hypertension), diabetes, hyperlipidemia, hypertension, cardiovascular disease, history of alcohol consumption, cigarette smoking, underlying liver disease, type of graft, and type of immunosuppressive medications. Renal function was evaluated with the serum levels of creatinine (Cr) and glomerular filtration rate (GFR), and was calculated using the Schwartz formula (GFR mL/min/1.73 m^2 = K × Ht (cm) / Cr mg/dL). Renal function (serum Cr and GFR) was assessed before, 1, and 6 months after liver transplant. Renal dysfunction was defined as a serum Cr level above 132.6 μmol/L or a GFR less than 60 mL/min/1.73 m^2, based on our reference range.

Our patients received either cyclosporine (n=132) or tacrolimus (n=38) with mycophenolate mofetil and corticosteroids. Blood levels of cyclosporine were maintained at approximately 150 ng/mL for the first 3 months after liver transplant, and then at approximately 100 ng/mL subsequently. However, blood levels of tacrolimus were not monitored at our center, and tacrolimus was administered at a dosage of 0.1 to 0.15 mg/kg/day. A database was created for all patients from their pretransplant days through surgery, follow-up, and readmission; these records included the results of any laboratory tests obtained routinely according to a posttransplant follow-up protocol. The data were kept confidential and analyzed with SPSS software (Statistical Product and Services Solutions, version 15.1, SPSS Inc, Chicago, IL, USA). The Spearman rank correlation and chi-square tests were used; a value for *P* of less than .05 was considered statistically significant.

Results

The mean duration of follow-up was 25.9 ± 23.5 months (range, 6-156 months). The main indications for liver transplant were cryptogenic cirrhosis (24.8%), hepatitis B infection (20%), autoimmune cirrhosis (17.6%), Wilson's disease (12.4%), and primary sclerosing cholangitis (10.6%). Other less-common indications included hepatitis C infection (4.1%), primary biliary cirrhosis (2.9%), progressive familial intrahepatic cholestasis (2.3%), biliary atresia (1.8%), congenital hepatic fibrosis (1.2%), fulminant hepatitis (1.2%), alcoholic cirrhosis (0.6%), and Budd-Chiari syndrome (0.6%). One hundred fifty-two patients (89.4%) received whole grafts from deceased donors, 13 grafts (7.6%) were from living-related donors, and 5 (2.9%) were split liver transplants. Table 1 shows the characteristics of the patients. Immunosuppression in all patients was accomplished with prednisolone, mycophenolate mofetil, and cyclosporine (n=132, 77.6%) or tacrolimus (n=38, 22.4%). Twenty patients (11.8%) initially started on cyclosporine were subsequently switched to tacrolimus. The characteristics of the

Table 1. Characteristics of the patients who underwent liver transplant at the Shiraz Organ Transplantation Center between 1994 and 2006.

Data	Number
Male/female	108/62
Age	31.4 ± 13.3
Body mass index	21.8 ± 4.9
Underlying liver disease	
Cryptogenic cirrhosis	42 (24.8%)
HBV	34 (20%)
AIH	30 (17.6%)
Wilson's disease	21 (12.4%)
PSC	18 (10.6%)
HCV	7 (4.1%)
PBC	5 (2.9%)
DDLT/LDLT	157/13
Immunosuppression	
Prednisolone	170 (100%)
Mycophenolate mofetil	170 (100%)
Cyclosporine	132 (77.6%)
Tacrolimus	38 (22.4%)

Abbreviations: AIH, autoimmune hepatitis; DDLT, deceased-donor liver transplant; HBV, hepatitis B virus; HCV, hepatitis C virus; LDLT, living-donor liver transplant; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

patients receiving cyclosporine or tacrolimus are shown in Table 2.

Table 2. Characteristics of patients receiving cyclosporine vs tacrolimus

	Cyclosporine	Tacrolimus	*P*
Number of patients	132 (77.6%)	38 (22.4%)	
Creatinine (μmol/L)	117.6 ± 63.6	107 ± 53	.272
GFR_1 (mL/min/1.73m^2)	78.6 ± 26.8	87.4 ± 33.1	.061
GFR_6 (mL/min/1.73m^2)	80.3 ± 30.7	89.9 ± 36.2	.071
Male/female	85/47	23/15	.663
Body mass index	21.6 ± 5.1	22.5 ± 4.4	.307
Immunosuppression			
Prednisolone	132	38	
Mycophenolate mofetil	132	38	

Abbreviations: GFR1, glomerular filtration rate 1 month after liver transplant; GFR6, glomerular filtration rate 6 months after liver transplant.

The mean pretransplant serum Cr level was 84 ± 33.6 μmol/L (range, 8.84-291.7 μmol/L), and the mean posttransplant serum Cr levels at 1 and 6 months were 114.9 ± 61.9 μmol/L (range, 35.4-495 μmol/L) and 132.6 ± 70.7 μmol/L (range, 44.2-539.2 μmol/L. The mean pretransplant GFR was 93.7 ± 35.6 mL/min/1.73 m^2 (range 32.3- 202.1 mL/min/1.73 m^2) and the mean posttransplant GFRs at 1 and 6 months after liver transplant were 81.6 ± 29.3 mL/min/1.73 m^2 (range, 16.6-197.7 mL/min/1.73 m^2) and 83.6 ± 32.9 mL/min/1.73 m^2 (range, 11.5-197.2 mL/min/1.73 m^2).

Eleven patients (6.5%) had serum Cr levels higher than 132.6 μmol/L before liver transplant; however, 6 months after the operation, 39 patients (22.9%) who had had normal renal function before the liver transplant developed a high serum creatinine level, and this difference was statistically significant (P = .019). GFRs lower than 60 mL/min/1.73m^2 were found in 39 (22.9%) and 35 (20.6%) patients at 1 and 6 months after liver transplant. The mean ages of patients with normal renal function and renal dysfunction were 29.2 ± 13.2 years and 38.8 ± 11.0 years, and this difference was statistically significant (P = .0001).

Of those with posttransplant renal dysfunction, there were 13 female and 26 male patients; this difference was not statistically significant (P = .395). Posttransplant renal dysfunction was not correlated with a family history of diabetes, hyperlipidemia, hypertension, or cardiovascular diseases (P > .05). Also, posttransplant renal dysfunction was not related to alcohol consumption or to cigarette smoking (P > .05). Underlying liver disease did not correlate with the development of renal dysfunction after liver transplant. However, posttransplant renal dysfunction was significantly correlated with a family history of renal disease (P < .05); 24 patients had such a family history.

Of those patients who were receiving cyclosporine, the mean blood levels of cyclosporine in patients with normal renal function and renal dysfunction were 133.5 ± 48.2 ng/mL and 131.1 ± 34.1 ng/mL; however, this difference was not statistically significant (P > .05). Using cyclosporine or tacrolimus for immunosuppression had no statistically significant bearing on renal function (P = .215 and P = .382).

All patients with posttransplant renal dysfunction had received whole graft transplants from deceased donors (P = .02). Renal dysfunction after liver transplant was not associated with obesity after liver transplant. The mean body mass indexes of patients with normal renal function and those with renal dysfunction after liver transplant were 21.1 ± 5.1 and 23.8 ± 3.7; this difference was not statistically significant (P > .05). Table 3 shows the results of multivariate analyses by logistic regression for those factors that significantly affected the development of renal dysfunction.

Table 3. Multiple logistic regression analysis of liver recipients with and without renal dysfunction.

		95.0% CI for Exp (β)		
Variables	**Exp (β)**	**Lower**	**Upper**	***P***
Age	1.062	1.024	1.102	.001
Sex	0.642	0.291	1.416	.272
Body mass index	0.911	0.825	1.005	.063
Tacrolimus	0.689	0.294	1.613	.391

Abbreviations: CI, confidence interval.
Exp (β), a statistical term for a *P* value in which Exp means exponent and β means beta.

The calcineurin inhibitor was changed from tacrolimus to rapamycin in 6 patients because of renal dysfunction. Of those patients with posttransplant renal dysfunction, 15 needed hemodialysis 1 to 5 times during hospitalization, and 3 died of renal problems before receiving a kidney transplant (all of them had end-stage renal failure). We have not any case of kidney transplant after liver transplant.

Discussion

Although immunosuppressive therapy with calcineurin inhibitors after liver transplant has dramatically improved patient and graft survival rates, the nephrotoxic effects of calcineurin inhibitors in patients receiving these transplants are being increasingly recognized (5, 6). Renal dysfunction

occurs despite advances in perioperative management or attention to cardiovascular risk factors and infectious complications (7). Renal dysfunction is associated with increased morbidity and mortality (8).

Calcineurin inhibitors are believed to cause nephrotoxicity through various mechanisms including an interference with intrarenal blood flow (9), increased expression of certain cyclosporine-binding proteins in kidney cells (10), higher interstitial transforming growth factor-β, and increased extracellular matrix turnover (11, 12).

Many studies have described a gradual decline in renal function following liver transplant (6, 13, 14). In a retrospective study of 834 recipients of a liver transplant who survived longer than 6 months after transplant, there was a progressive decline in renal function after transplant and a high incidence (18%) of severe renal dysfunction (as defined by a serum Cr concentration greater than 221 μmol/L [15]).

In this study, by reviewing renal indicators such as serum Cr level and GFR, we found that 22.9% of liver transplant patients experienced renal dysfunction, which is similar to the data reported by Sutedja and associates (2) and McCulloch and associates (16) but lower than the data reported by Paydas and associates (4).

Sutedja and associates reported that 22.8% of their patients developed renal dysfunction at 1 year after liver transplant. The mean age of our patients (31 years) was lower than that reported by Sutedja and associates (50 years). In their survey, renal impairment was associated with pretransplant disorders, such as hepatorenal syndrome and diabetes mellitus.

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. However, in the present study, risk of renal dysfunction was not significantly different among patients who received cyclosporine or tacrolimus.

It appears that pretransplant complications of chronic liver disease are important for posttransplant renal impairment. However, because our mean follow-up is only approximately 2 years, we cannot say for certain whether posttransplant factors affect renal impairment in the longer term.

In this study, renal function was assessed from the serum Cr level, and the GFR was calculated according to the Schwartz formula (17). Using the Jaffe method, hyperbilirubinemia and hyperglycemia can underestimate the serum Cr level (18).

Levey and associates (19) claimed that serum Cr level or corrected GFR (cGFR) had a low sensitivity for detecting recent renal failure. In addition, the baseline serum Cr concentration is known to be low in patients with end-stage liver disease, secondary to decreased muscle mass and malnutrition due to longstanding fat malabsorption (a characteristic feature of cholestasis) (20). For these reasons, GFR determination on the basis of serum Cr level overestimates the true GFR (which can be assessed by isotopes clearance).

As shown in our study, assessment of renal function using the serum Cr level and the cGFR underestimates the frequency and the severity of renal dysfunction after liver transplant.

In our study, the mean posttransplant GFR 6 months after liver transplant was 83.6 ± 32.9 mL/min/1.73 m^2, which is higher than that reported by Kim and associates (21), who reported a mean GFR at 6 months after liver transplant of 63.7 ± 30.2 mL/min/1.73 m^2.

In a population of 883 adult transplant recipients, Fisher and associates (10) demonstrated a significant role for cyclosporine in the development of chronic renal failure. In that study, as in ours, no other factor (including initial disease, nephrotoxic drugs, arterial hypertension, or rejection episodes) was correlated with impaired renal function.

Independent risk factors for chronic renal failure included calcineurin inhibitor therapy, older age, lower pretransplant GFR, female gender, baseline diabetes mellitus and hypertension, and hepatitis C virus infection (2, 8). In the present study, renal dysfunction was significantly associated with family history of renal disease and older age. However, sex, type of immunosuppressive medications, underlying liver disease, family history of diabetes, hyperlipidemia, hypertension, cardiovascular diseases, alcohol consumption, and cigarette smoking were not predictors of renal dysfunction.

Significant renal dysfunction occurs after liver transplant. Because renal dysfunction is associated with increased cardiovascular events, mortality, and hepatic allograft dysfunction, early recognition of renal dysfunction and implementation of changes may improve long-term outcomes. Early detection is important. To affect the outcomes in liver transplant recipients, it may be important to introduce renal dysfunction management as early as 6 months after

transplant. However, further prospective studies are needed to evaluate other risk factors for developing renal dysfunction after liver transplant.

References

1. Kaliciński P, Szymczak M, Smirska E, et al. Longitudinal study of renal function in pediatric liver transplant recipients. Ann Transplant. 2005;10(2):53-58.
2. Sutedja DS, Wai CT, Teoh KF, et al. Renal impairment and diabetes mellitus after liver transplant. Transplant Proc. 2004;36(8):2324-2327.
3. Wiesmayr S, Jungraithmayr TC, Ellemunter H, et al. Long-term glomerular filtration rate following pediatric liver transplantation. Pediatr Transplant. 2005;9(5):604-611.
4. Paydas S, Balal M, Demiryurek H, Kose F. Renal function in patients with orthotopic liver transplantation. Ren Fail. 2006;28(2):103-105.
5. Jain A, Reyes J, Kashyap R, et al. Long-term survival after liver transplantation in 4,000 consecutive patients at a single center. Ann Surg. 2000;232(4):490-500.
6. [No authors listed] A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. The U.S. Multicenter FK506 Liver Study Group. N Engl J Med. 1994;331(17):1110-1115.
7. O'Riordan A, Wong V, McCormick PA, Hegarty JE, Watson AJ. Chronic kidney disease post-liver transplantation. Nephrol Dial Transplant. 2006;21(9):2630-2636.
8. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med. 2003;349(10):931-940.
9. Youngelman DF, Kahng KU, Rosen BD, Dresner LS, Wait RB. Effects of chronic cyclosporine administration on renal blood flow and intrarenal blood flow distribution. Transplantation. 1991;51(2):503-509.
10. Friedman J, Weissman I. Two cytoplasmic candidates for immunophilin action are revealed by affinity for a new cyclophilin: one in the presence and one in the absence of CsA. Cell. 1991;66(4):799-806.
11. Bicknell GR, Williams ST, Shaw JA, Pringle JH, Furness PN, Nicholson ML. Differential effects of cyclosporin and tacrolimus on the expression of fibrosis-associated genes in isolated glomeruli from renal transplants. Br J Surg. 2000;87(11):1569-1575.
12. Esposito C, Foschi A, Parrilla B, et al. Effect of calcineurin inhibitors on extracellular matrix turnover in isolated human glomeruli. Transplant Proc. 2004;36(3):695-697.
13. Platz KP, Mueller AR, Blumhardt G, et al. Nephrotoxicity following orthotopic liver transplantation. A comparison between cyclosporine and FK506. Transplantation. 1994;58(2):170-178.
14. Fisher NC, Nightingale PG, Gunson BK, Lipkin GW, Neuberger JM. Chronic renal failure following liver transplantation: a retrospective analysis. Transplantation. 1998;66(1):59-66.
15. Gonwa TA, Mai ML, Melton LB, et al. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLTX) using calcineurin-based immunotherapy: risk of development and treatment. Transplantation. 2001;72(12):1934-1939.
16. McCulloch MI, Burger H, Spearman CW, et al. Nephrotoxic effects of immunosuppressant therapy in pediatric liver transplant recipients. Transplant Proc. 2005;37(2):1220-1223.
17. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics. 1976;58(2):259-263.
18. Halstead AC, Nanji AA. Artifactual lowering of serum creatinine levels in the presence of hyperbilirubinemia. JAMA. 1984;251(1):38-39.
19. Levey AS, Perrone RD, Madias NE. Serum creatinine and renal function. Annu Rev Med. 1988;39:465-490.
20. Goulet OJ, de Ville de Goyet J, Otte JB, Ricour C. Preoperative nutritional evaluation and support for liver transplantation in children. Transplant Proc. 1987;19(4):3249-3255.
21. Kim DY, Lim C, Parasuraman R, et al. Renal disease burden following liver transplantation. Transplant Proc. 2006;38(10):3663-3665.