Long-term post-liver transplant complications of renal impairment and diabetes mellitus: data from Singapore

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ABSTRACT

Introduction: Patients who survive the initial post-liver transplantation period face the development of chronic diseases in the long run. We studied two important complications of liver transplantation, namely: renal impairment and diabetes mellitus.

Methods: We analysed adult patients followed-up for more than one year using data from our liver transplant clinical records. Long-term post-transplant renal impairment (RI) was defined as glomerular filtration rate (GFR) less than 60 ml/min/1.73 square metres and long-term post-transplant diabetes mellitus (DM) was defined as fasting blood glucose more than 7.8 mmol/L, that existed at least one year after liver transplantation. Pre- and post-transplant factors that could be associated with these conditions were examined.

Results: Altogether, 35 patients were evaluated. Mean age at transplant was 50 years. Mean duration of follow-up was 58.4 months. There was 11.4 percent of pre-transplant RI and 17.0 percent of pre-transplant DM. Prevalence of post-transplant RI was 43.5 percent at one year and 45.0 percent at four years. Long-term post-transplant RI was associated with renal impairment at six months post-transplant (p-value is 0.033). Prevalence of severe post-transplant RI (GFR is less than 30 ml/min/1.73 square metres) at four years was 5.7 percent. Prevalence of post transplant DM was 45.5 percent at two years but declined to 5.3 percent at four years.

Conclusion: Post-transplant renal impairment appears to be a potential long-term problem while post-transplant diabetes mellitus appears to improve with time.

Keywords: diabetes mellitus, glomerular filtration rate, liver transplant, liver transplant complications, renal impairment

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INTRODUCTION

In the current era of liver transplantation, long-term survival of the recipients is the rule rather than an exception. Common medical diseases occurring in the long-term postoperative period after liver transplantation include renal dysfunction, hypertension, neurological and psychiatric complications as well as metabolic complications like obesity, diabetes mellitus, hyperlipidaemia and osteoporosis[1]. Renal failure and cardiovascular complications, in particular, are among the main causes of late mortality after liver transplantation[2]. Thus, complications such as renal impairment and diabetes mellitus in post-liver transplant patients can lead to poor long-term outcomes. A recent study[3] involving 300 patients, and using serum creatinine level of >1.3 mg/dL as definition for chronic renal dysfunction, reported a prevalence rate of post-transplant renal impairment as 30.9% at one year, 41.5% at five years and 38.9% at 13 years. Such renal dysfunction can worsen[4] to end-stage renal disease requiring dialysis in about 10% of patients, 13 years post-transplant. Based on published data[5-7], diabetes mellitus occurs in about 30% of cases post-transplant.

Most of the prevalence studies on post-liver transplant renal impairment and diabetes mellitus were based on non-Asian data, although a recent Korean centre reported that 44% of their post-liver transplant patients had moderate renal dysfunction[8]. Our study objective was to look at the prevalence of renal impairment and diabetes mellitus in our patients who have survived at least one year after their liver transplantation. We used calculated glomerular filtration rates (GFR)[9] to define renal impairment. We also examined the various factors that could be associated with these two important medical conditions.

METHODS

From 1996, there were 36 adult patients who had survived at least one year past their liver transplants and who were followed-up at our centre. Among these, three had their transplants performed overseas.

Table I. Patient characteristics (n=35)

Age at time of transplant (years)	49.9 ± 2.0
Age at last follow-up (years)	54.9 ± 2.0
Male (%)	27 (77)
Race: Chinese/Indian/Malay/Others (%)	69/14/3/14
Post-transplant follow-up (months)	58.4 ± 3.2
Indication for transplant (%)	
Decompensated hepatitis B cirrhosis	8 (22.8)
Decompensated hepatitis C cirrhosis	3 (8.6)
Hepatocellular carcinoma	12 (34.2)
Acute Wilson's disease	2 (5.7)
Autoimmune hepatitis	1 (2.9)
Decompensated cryptogenic cirrhosis	4 (11.4)
Drug-induced acute liver failure	1 (2.9)
Primary biliary cirrhosis	2 (5.7)
Hepatitis B acute exacerbation	1 (2.9)
Primary sclerosing cholangitis	1 (2.9)
Current maintenance immunosuppression (%)	
Tacrolimus-based	26 (74.3)
Cyclosporin-based	7 (20)
Non-CNI-based	2 (5.7)
Pre-transplant hypertension (%)	6 (17)
Pre-transplant diabetes mellitus (%)	6 (17)
Pre-transplant creatinine (umol/L)	84.4 ± 5.4
Pre-transplant GFR (ml/min/1.73 m^2)	92.4 ± 4.4
Pre-transplant renal impairment (%)	4 (11.4)
Pre-transplant severe renal impairment (%)	0
Post-transplant hypertension (%)	24 (68.6)

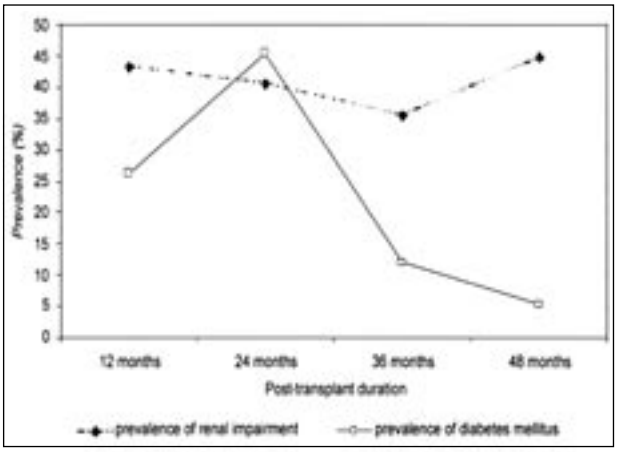

Fig. 1 Prevalence of long-term post-liver transplant renal impairment and diabetes mellitus.

One of the three patients was excluded from the analysis as she was on our registry only after the eighth year post-transplant and had no data in the earlier postoperative period. The other two were seen by us soon after their transplants.

Data from all transplanted patients were captured in a prospective database, which included clinical, laboratory and radiological parameters from the time of referral, pre-transplant period, peri-transplant period and post-transplant follow-up. The immunosuppression drugs were used according to a standardised protocol. The maintenance immunosuppression regime was mostly calcineurin inhibitor (CNI)-based, using either cyclosporin A or tacrolimus. For rejection episodes, patients were given pulses of steroids as well as an increased dosing of the CNI drugs, which were kept at a higher dose for a longer duration before tailing down.

We reviewed the database, querying all instances of renal impairment and diabetes mellitus. A level of GFR of less than 60 ml/mln/1.73 m^2 was defined as renal impairment and a level of <30 ml/min/1.73 m^2 defined severe renal impairment, according to the stratification of chronic kidney disease by the National Kidney Foundation[10]. Chronic renal impairment was defined as mean GFR <60 ml/mln/1.73 m^2 for longer than 12 months post-transplantation. GFR was calculated from MDRD study equation[9] and diabetes mellitus was defined by the hospital reference value: fasting blood glucose >7.8 mmol/L.

Continuous variables were expressed in mean ± standard error (SE) of mean, unless otherwise stated. Factors associated with renal impairment and diabetes mellitus were analysed by univariate analysis. Continuous variables were compared by the Student's t-test whereas categorical variables were compared by either chi-square test or Fisher's exact test as appropriate. p-value of <0.05 was considered to be statistically significant.

RESULTS

35 adult patients were analysed (Table I). Mean age at transplant was 49.9 years. Duration post-transplant was 53.6 months, with a range between 26.1 and 92.1 months. 24 (69%) were Chinese and 27 (77%) were male. The two commonest indications for transplant were decompensated hepatitis B cirrhosis (n=8) and hepatocellular carcinoma (n=12). All patients had used calcineurin inhibitor (CNI)-based maintenance immunosuppression regimes, with 75% of patients using tacrolimus and the remaining using neoral. Two patients had relied on non-CNI monotherapy at a later stage due to their renal dysfunction. The prevalence rate for post-transplant hypertension was 18%. There were three deaths in the group of patients analysed. The causes of death were due to sepsis, recurrent heptaocellular cancer and recurrent hepatitis B liver failure. The latter case had been non-compliant with the anti-viral drug prescribed. The

Table II. Prevalence of long-term post-transplant renal impairment and diabetes mellitus.

Post-transplant GFR (ml/min/1.73 m^2)	
At year 1	70.7 ± 4.6
At year 2	65.9 ± 3.5
At year 3	67.1 ± 3.6
At year 4	60.5 ± 4.8
Long-term post-transplant renal impairment (%)	
At year 1	43.5
At year 2	40.7
At year 3	35.7
At year 4	45.0
Severe post-transplant renal impairment (%) at year 4	5.7
Long-term post-transplant diabetes mellitus (%)	
At year 1	26.3
At year 2	45.5
At year 3	12.0
At year 4	5.3
Post-transplant diabetes mellitus that subsequently resolved (%)	40.0

Table III. Factors associated with long-term post-transplant renal impairment.

	Long-term post-transplant renal impairment		
	Present Mean (SE)	Absent Mean (SE)	p-value
Age at transplant (years)	51.8 (2.6)	47.6 (3.3)	0.286*
Duration post-transplant (months)	58.8 (4.4)	59.1 (4.5)	0.883*

* Mann-Whitney U test

		Long-term post-transplant renal impairment		
		Present (n=19)	Absent (n=16)	p-value
Race:	Chinese	14	10	0.478†
	Others	5	6	
Gender:	Male	15	12	1.000*
Viral Hepatitis B or C		14	10	0.478†
Current immunosuppression				
	FK 506	12	14	0.095*
	Cyclosporin	7	2	
Increase in weight		12	11	0.728†
Rejection		7	9	0.251†
Pre-transplant hypertension		2	4	0.379*
Pre-transplant renal impairment		3	1	0.608*
Post-transplant renal impairment at 6 months		9	1	0.033*
Pre-transplant diabetes mellitus		5	1	0.187*
Post-transplant hypertension		12	12	0.493*
Post-transplant diabetes mellitus		9	8	0.877†

* Fisher's exact test, † Pearson chi-square test

rest of the patients had normal liver graft function at the latest follow-up, defined by a normal prothrombin time (PT <13.3 sec).

11.4% of patients had pre-transplant renal impairment, due to the hepatorenal syndrome (HRS), as they had no prior intrinsic renal disease. These patients had fulfilled the four major criteria for HRS as outlined by the International Ascites Club[11]. Mean GFR level just before liver transplantation (pre-transplant) was 92.4 ml/min/1.73 m^2. The mean values were 70.7, 65.9, 67.1, 60.5 ml/min/1.73 m^2 at 12, 24, 36 and 48 months post-transplant, respectively. The prevalence of long-term post-transplant renal impairment (RI) was 43.5, 40.7, 35.7, 45.0% at one, two, three and four years, respectively (Table II and Fig. 1). Prevalence of severe post-transplant renal impairment was 5.7% at year 4. However, none had required any renal replacement therapy.

Among the cases with pre-transplant diabetes mellitus, only one had a significant long history of non-insulin dependent diabetes mellitus (NIDDM) well before the onset of liver cirrhosis. There was 17.0% (6 out of 35) of pre-transplant DM in the cohort. The prevalence of long-term post-transplant DM was 26.3%, 45.5%, 12.0% and 5.3% at one, two, three and four years, respectively (Table II and Fig. 1). 20% (7/35) of patients required insulin at some stage of their follow-up. Among the patients with DM post-transplant, 41.1% (7/17) had resolution of their DM during follow-up.

Factors that may be associated with the occurrence of post-transplant renal impairment were analysed (Table III). The factors that can possibly affect post-transplant diabetes mellitus are listed in Table IV. Univariate analysis showed that renal impairment at six months post-transplant was associated with chronic renal impairment post-transplant (p=0.033). The prevalence of post-transplant diabetes mellitus was 26.3%, 45.5%, 12.0% and 5.3% at one, two, three and four years post-transplant, respectively. There was significantly less post-transplant diabetes mellitus in the longer follow-up period (p=0.014).

Table IV. Factors associated with long-term post-transplant diabetes mellitus.

	Post-transplant diabetes mellitus		
	Present Median (range)	Absent Median (range)	p-value*
Duration of prednisolone (months)	15.0 (1.0-90.0)	13.5 (0-64.0)	0.757
Duration post-transplant (months)	50.7 (26.1-92.1)	66.3 (26.1-87.8)	0.014

* Mann-Whitney U test

		Post-transplant diabetes mellitus		
		Present n (%)	Absent n (%)	p-value
Race:	Chinese	11 (45.8)	13 (54.2)	0.632†
	Others	6 (54.5)	5 (45.5)	
Gender:	Male	14 (51.9)	13 (48.1)	0.691*
Viral Hepatitis B or C		12 (50.0)	12 (50.0)	0.803†
Current immunosuppression				
	FK 506	13 (50.0)	13 (50.0)	0.413*
	Cyclosporin	2 (28.6)	5 (71.4)	
Increase in weight		11 (47.8)	12 (52.2)	0.903†
Rejection		9 (56.3)	7 (43.8)	0.404†
Pre-transplant hypertension		4 (66.7)	2 (33.3)	0.402*
Pre-transplant renal dysfunction		2 (28.6)	5 (71.4)	0.402*
Pre-transplant diabetes mellitus		5 (83.3)	1 (16.7)	0.088*
Post-transplant renal dysfunction		10 (47.6)	11 (52.4)	0.890†

* Fisher's exact test, † Pearson chi-square test

This indicated that there was resolution of cases of diabetes mellitus over time.

DISCUSSION

The mean age of our transplant patients was around 50 years old. With normal life expectancy exceeding 70 years[6] and the expected ten-year long-term survival for liver transplantation of about 60%[7], patients can look forward to reaching normal life expectancies. However, chronic medical conditions such as renal impairment and diabetes mellitus can jeopardise the situation. In our study, long-term post-transplant renal impairment was seen in 43.5% at one year and remained at 45.0% at four years. About 5% were classified as cases of post-transplant severe renal impairment. The prevalence of post-transplant renal impairment was significantly associated with renal impairment at six months post-transplant. This similar finding has been observed by others[3,4,12-14]. One study found a decreased GFR of >30 ml/min/1.73 m^2 from baseline at nine months post-liver transplant predicted the development of permanent renal impairment[12]. In another study[3], renal dysfunction during the first six months after liver transplant was associated with development of chronic renal disease.

However, none of these studies, including ours, had looked at the renal histology to assess the possible pathogenesis of renal impairment during this stage of the post-liver transplant period. We did perform renal biopsies on two patients with post-liver transplant renal impairment at around 40 months post-transplant. This showed changes of tubular atrophy, interstitial fibrosis and glomerular sclerosis, which were consistent with calcineurin inhibitor toxicity. In our study, almost all of our patients were given calcineurin inhibitor-based immunosuppression, so that it was not possible to test the independent effect of these nephrotoxic drugs. Nonetheless, our observations are important from two perspectives. Firstly, we need to formulate strategies to prevent the development of renal impairment postoperatively before the first year. Secondly, we need to take measures to minimise the progression of renal impairment for the high-risk individuals, identified early in the post-liver transplant period.

One strategy to lessen post-liver transplant renal impairment in the long run is to use non-nephrotoxic immunosuppression agents. One of our two patients with long-term post-transplant severe renal impairment was switched to mycophenolate monotherapy for his maintenance immunosuppression. The use of mycophenolate monotherapy to reduce the progression of nephrotoxicity from CNI chronic administration has been adopted by several liver transplant centres with reasonably good results[15-17]. The use of sirolimus as a renal-sparing immunosuppressive drug has also been evaluated[18,19], and one of our patients was solely on this drug for his maintenance immunosuppression. The prevalence of long-term post-transplant diabetes mellitus was highest at two years post-transplant, about 45% in our series, but this resolved in 40% of the cases with time. The gradual improvement of diabetes mellitus post-transplant has been observed in other studies[5,7] and is likely due to the weaning of immunosuppression drugs, which have diabetogenic potential[5].

In summary, post-transplant renal impairment appears to be a long-term problem, whereas the

prevalence of diabetes mellitus post-transplant improves over time. The major risk for long-term post-transplant renal improvement was the presence of renal impairment at six months post-transplant. More judicious post-transplant use of potentially nephrotoxic immunosuppression drug regimes, particularly in the early post-transplant period and subsequent maintenance phase, is required. With the advent of newer immunosuppressants that have reduced nephrotoxicty and adverse events, the possibility of reducing such long- term complications, and at the same time maintaining good graft survival, may be around the corner.

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