Kidney histology and function in liver transplant patients

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Abstract

Background. Chronic kidney disease is a common complication after liver transplantation. However, few reports regarding kidney histology exist for this setting.

Methods. Inulin clearance was measured and a kidney biopsy was performed in 99 patients at 60 ± 48 months after liver transplantation. Kidney biopsies were scored according to the Banff classification, and interstitial fibrosis was measured by a computerized quantitative method.

Results. There was a steep decrease in kidney function within the first 6 months following transplantation, but this lessened thereafter. At kidney biopsy, inulin clearance and estimated glomerular filtration rate (eGFR) (using the abbreviated Modification of Diet in Renal Disease equation) were highly correlated ($r^2 = 0.47$, $P < 0.0001$). A decrease in eGFR at 6 months post-transplant was the sole predictive factor for inulin clearance of <60 mL/min/1.73 m$^2$ at 5 years post-transplant. Few patients had a specific pattern of kidney histopathology and all patients had complex primary lesions. Lowered eGFR at 6 months post-transplant was a predictive factor for >50% sclerotic glomeruli on the kidney biopsy. The duration of tacrolimus therapy, as compared to cyclosporine A, was a protective factor for <20% interstitial fibrosis on the kidney biopsy.

Conclusion. In the setting of liver transplantation, this is the largest kidney-histology study to confirm that histological kidney lesions are complex, multiple and interrelated. Kidney function at 6 months post-transplant can predict long-term kidney function and histology.

Keywords: calcineurin inhibitors; fibrosis; inulin clearance; kidney biopsy; liver transplantation

Introduction

Chronic kidney disease (CKD) is a common complication after non-kidney solid-organ transplantation that increases the risk of mortality, and may require dialysis and kidney transplantation [1]. At 5 years after liver transplantation (LT), Ojo et al. showed that the incidence of CKD was at 18.1% [1]. In liver transplant patients, calcineurin inhibitors (CNIs) have long been considered to be the main and sole cause of post-transplant CKD; however, many other factors also contribute. These include pre-transplant kidney function, pre-transplant hepatorenal syndrome, perioperative haemodynamic injuries, diabetes mellitus, hypertension, hyperlipidaemia and hepatitis C virus (HCV)-induced kidney disease [2].

Kidney biopsies, performed in liver transplant patients who either have severe CKD or significant proteinuria, show that, beyond some of the specific histopathological features such as nephroangiosclerosis, diabetic nephropathy, thrombotic microangiopathy (TMA) and CNIs nephrotoxicity, there are other complex pathological findings [3–5]. This has prompted us to assess histological primary kidney lesions in liver transplant patients who both have or do not have CKD, and to describe these lesions using the Banff classification rather than trying to identify a single kidney disease. Furthermore, for the first time, we have calculated, and not estimated, interstitial fibrosis using an automated computerized quantification method.

Materials and methods

Between January 2006 and December 2007, about 300 liver transplant patients were followed up at our institution. In this study, we included those who had received a first isolated liver transplant. Exclusion criteria...
were as follows: an estimated glomerular filtration rate (eGFR) (using the abbreviated Modification of Diet in Renal Disease equation—aMDRD [6]) <15 mL/min, the use of mTOR inhibitors (mainly for post-transplant hepatocellular carcinoma relapse), an ongoing relapse of hepatocellular carcinoma, inclusion in a clinical trial and absence of informed consent. During the study period, patients who were receiving mTOR inhibitors were converted from calcineurin inhibitors to mTOR inhibitors late after transplantation. Consequently, histological findings do not reflect the sole effect of mTOR inhibitors on the kidney. Therefore, they were excluded from the study. The study was approved by the local institutional review board. Hence, all patients who met the inclusion criteria and did not decline the kidney biopsy were included in the study (n = 99).

All patients had normal liver function. There were 67 men and 32 women. Their mean age at transplantation was 51.6 ± 10.4 years. At inclusion, their mean time since transplantation was 60 ± 48 months. The causes for transplantation were alcohol-induced liver disease in 41 patients (41.4%), viral hepatitis in 34 patients (34.3%, 6 infected by hepatitis B virus and 28 infected by HCV) and other causes in 24 patients (24.2%). At transplantation, 46 patients (47%) had hepatocellular carcinoma, and the distribution of the Child–Turcotte–Pugh classes was 34 patients for A, 20 patients for B and 45 patients for C.

At commencement of the study, blood pressure, 24-h microalbuminuria, creatinine level and inulin clearance were collected from all patients. eGFR was calculated using the aMDRD equation. In addition, microscopic haematuria was tested and a percutaneous KB was performed. Patient characteristics and treatments were collected at and after transplantation.

Histopathological analysis of kidney biopsies

All KB were reviewed by a single pathologist (CGF). Biopsy specimens for light-microscopy examination were fixed in Bouin’s solution, embedded in paraffin, cut into 2-μm sections and stained with light green trichrome. All biopsies had more than 10 glomeruli and at least two arterial sections. All biopsies were scored according to the 2005 Banff classification [7]. We determined the percentages of sclerotic glomeruli (SG) and acute tubular necrosis (ATN). Furthermore, the percentage of interstitial fibrosis (IF) was calculated using an automated computerized quantification method, as previously described by Servais et al. [8]. Briefly, a cortical section was imaged using a colour video camera (Nikon DXM1200) mounted on a light microscope (Nikon Eclipse E1000M). Images were acquired using the 40× objective. Images of the entire cortex of the biopsy (defined as the region inside the renal capsule and outside the medulla) were obtained, starting at one end of the tissue and working toward the other with microscope stage remotely controlled by software (Lucia G481; Nikon, France). The medulla was eliminated at the acquisition phase or during analysis by the observer. For each biopsy, the entire cortical region was analysed in a stepwise fashion as a series of consecutive fields. Images were analysed by a new programme of colour segmentation image analysis (Patent EU number 2004292513-1) [8]. We used clustering techniques in the H1H2H3 colour space and colour image quantization, whereby a programme automatically extracts green colour areas characteristic of IF. The segmentation procedure is sufficiently robust for the various degradation factors that can affect image quality such as histological section quality and colour staining. Renal capsule, tubular basement membranes and SG are recognized and automatically excluded from analysis. Tubular membranes are removed from the green pixels according to their thickness. The capsule is recognized by its colour and location, and SG are detected by their shape. The proportion of green/non-green pixels in the image is calculated and used as an index of IF. An index of surface IF was defined as the ratio between the surface area of green pixels in the mask of IF and the total number of pixels in the original biopsy minus pixels from tubular lumen. The inter- and intra-operator standard deviations were 4.07 and 3.89%, respectively [8]. Routine immunofluorescence studies were also done using polyvalent antibodies to IgA, IgG, fibrin, albumin, C3, C4 and Clq. There were no biopsy-related complications.

Measurement of inulin clearance

The procedure used to measure inulin clearance has been described previously [9]. Plasma and urine levels of inulin were determined using a Novaspec II spectrophotometer (Pharmacia Biotech, Cambridge, UK).

Statistical analyses

Results are presented as mean ± standard deviation or median (ranges). Proportions were compared using the chi-squared or Fischer’s exact test. Quantitative variables were compared by Student’s t-test. A P-value <0.05 was considered statistically significant. Correlations were sought using Spearman’s test. We determined the parameters that were associated with inulin clearance of <60 mL/min/1.73 m², those associated with >50% SG and those associated with >20% IF. We used Student’s t-test, with two-tailed independent samples, to assess univariate analyses between the two groups, and the significance was taken as P = 0.05. All recorded parameters at transplantation and at the KB were tested. Risk factors for inulin clearance of <60 mL/min/1.73 m², of SG >50% and of IF >20% were defined using a multivariate, stepwise, logistical regression analyses that used initial inclusion criteria that had a significance of P <0.05.

Results

Kidney function after liver transplantation

Before LT, only one patient had hepatoportal syndrome, and 11 patients had ascitis (11%). After LT, only five patients (5%) required acute dialysis. Serum creatinine level increased from 82.2 ± 27.4 μmol/L at transplantation to 114 ± 35 μmol/L after 6 months, and to 124 ± 40 μmol/L at the KB (P < 0.0001). Similarly, eGFR decreased from 92 ± 33 mL/min at transplantation to 63 ± 19 mL/min after 6 months, and to 57 ± 17 mL/min at the KB (P < 0.0001; Figure 1).

Kidney function at the kidney biopsy

Patient characteristics, biological parameters and immunosuppressive therapies at KB are presented in Table 1. At KB, serum creatinine level was 124 ± 40 μmol/L. aMDRD eGFR was 57 ± 17 mL/min. Inulin clearance was 60.5 ± 22.6 mL/min/1.73 m². Inulin clearance and aMDRD

Fig. 1. Kidney function after liver transplantation. (A) Serum creatinine level. (B) Creatinine and inulin clearance. LT, liver transplantation; KB, kidney biopsy.
eGFR were highly correlated ($r^2 = 0.47$, $P < 0.0001$). Twenty-four-hour microalbuminuria was 35 ± 77 mg/day (range: 0–482 mg/day). Twenty patients (21.2%) had microalbuminuria of >50 mg/day and three patients (3.03%) had microalbuminuria of >300 mg/day. Only 10 patients (10%) had a microscopic haematuria.

Based on aMDRD eGFR, according to the Kidney Disease Outcomes Quality Initiatives/Kidney Disease: Improving Global Outcomes classification [10,11], at transplantation, 50% had CKD stage 1 (≥90 mL/min), 33% had stage 2 (60–89 mL/min), 17% had stage 3 (30–59 mL/min) and none had stage 4 (15–29 mL/min) or 5 (<15 mL/min). Based on aMDRD eGFR, at the KB, 3, 42, 52, 2, and 1% had CKD of stages 1, 2, 3, 4 and 5, respectively ($P < 0.0001$), compared to transplantation.

**Histopathologic kidney lesions**

Only five patients had features of a specific kidney disease: IgA nephropathy ($n = 1$), cryoglobulinemic membranoproliferative glomerulonephritis ($n = 1$), nephroangiosclerosis ($n = 1$), signs of TMA ($n = 1$) and tubulointerstitial nephritis ($n = 1$). The mean percentages of SG and ATN were 47 ± 21 (ranging from 0 to 97) and 13.8 ± 19.21 (ranging from 0 to 80), respectively. The percentage of IF, as calculated by computerized quantification, was 22.7 ± 10.6%.

All biopsies were graded according to the 2005 Banff classification: mean arteriolar hyaline thickening (aah) was 1.7 ± 0.98, mean IF (ci) was 1.2 ± 1.05, mean tubular atrophy (ct) was 1.48 ± 0.79, mean vascular fibrous intimal thickening (cv) was 1.02 ± 0.9, mean mesangial matrix increase (mm) was 0.17 ± 0.43 and mean tubulitis (ti) was 0.17 ± 0.43. The proportions of patients with ci >1, ct >1 and cv >1 were 37.4, 36.4 and 34.4%, respectively. There was a strong correlation between IF calculated by computerized quantification and IF estimated by the Banff classification ($r^2 = 0.51$, $P < 0.0001$). There was also a significant correlation between the number of SG observed by the pathologist and the one detected automatically ($r^2 = 0.41$, $P < 0.0001$).

### Correlations between inulin clearance and histological findings

There was a significant inverse correlation between inulin clearance and the percentage of SG ($r^2 = -0.13$, $P = 0.003$), the percentage of IF calculated by computerized quantification ($r^2 = -0.08$, $P = 0.006$), ci ($r^2 = -0.1$, $P = 0.015$) and cv ($r^2 = -0.1$, $P = 0.01$). No correlation was observed between inulin clearance and aah, ct, mm, ti or the percentage of ATN.

### Correlations between the duration of exposure to calcineurin inhibitors and histological findings

There was a significant correlation between the time receiving CNIs and the percentage of SG ($r^2 = -0.08$, $P = 0.004$) and aah ($r^2 = -0.24$, $P = 0.0001$). There was an inverse correlation between the time receiving CNIs and ct ($r^2 = -0.04$, $P = 0.03$), and the percentage of IF calculated by computerized quantification ($r^2 = -0.07$, $P = 0.009$). No correlation was observed between the time receiving CNIs and ci, cv, mm, ti and the percentage of ATN. No correlation was observed between CNI levels at kidney biopsy and either kidney function or the percentage of ATN. Since all patients were receiving CNIs since transplantation, the correlations between the time since transplantation at kidney biopsy and histological findings were similar to those observed between the time receiving CNIs and histological lesions.

**Predictive factors for inulin clearance of ≤60 mL/min**

Statistically significant differences observed in the univariate analysis and variables included in the multivariate ana-
lysis model are presented in Table 2. Only a lower eGFR at 6 months post-transplantation has been identified as an independent predictive factor for inulin clearance of <60 mL/min/1.73 m².

Predictive factors for ≥50% sclerotic glomeruli

Because the SG rate was 47 ± 21%, we looked for predictive factors for SG ≥50%. The statistically significant differences observed in the univariate analysis and variables included in the multivariate analysis model are presented in Table 2. A lower eGFR at 6 months after transplantation, the use of diuretics and the use of statins were identified as independent predictive factors for SG of ≥50%.

Predictive factors for ≥20% interstitial fibrosis

Because the IF calculated by computerized quantification was 22.7 ± 10.6, we looked for predictive factors for IF >20%. The statistically significant differences observed in the univariate analysis and variables included in the multivariate analysis model are presented in Table 3. A lower eGFR at 6 months after transplantation, the use of diuretics and the use of statins were identified as independent predictive factors for IF >20%.
the univariate analysis and variables included in the multivariate analysis model are presented in Table 4. A higher inulin clearance value at the time of the KB and a longer duration of tacrolimus therapy as compared to cyclosporine A (CsA) have been identified as independent protective factors for IF >20%.

**Discussion**

Within the last few years, it has been shown that CKD in the setting of LT is multifactorial and that histological kidney lesions are multiple and interrelated. Herein, we assessed kidney function by means of measured inulin clearance and histopathological lesions in 99 liver transplant patients. We found that (i) there is a steep decrease in kidney function within the first 6 months following transplantation, which lessens thereafter; (ii) eGFR at 6 months post-transplant was the sole predictive factor for inulin clearance of <60 mL/min/1.73 m² at 5 years post-transplant; (iii) few patients had a specific histopathological kidney pattern and all patients had complex primary lesions; (iv) lower eGFR at 6 months post-transplant was a predictive factor for >50% SG on the KB; and (v) the duration of tacrolimus therapy, as compared to CsA, was a protective factor for IF of >20% as assessed on a KB.

After heart transplantation, it has been shown that kidney function deteriorates most quickly within the first 6 months post-transplant and declines more slowly thereafter [12,13]. In the TRY study, which included 1598 liver transplant patients, the mean GFR (according to the MDRD formula) decreased by 30.6 and 34.8% at 1 and 6 months, respectively, from baseline [14]. Similarly, in the present study, a steep decline (31.5%) in kidney function was observed within the first 6 months post-transplant, though impairment of kidney function slowed thereafter. The steep decline within the early period post-transplant is probably related to hypotension and hypoperfusion during transplantation, which both induce acute kidney injuries [2]. In our study, 5% of patients required transient dialysis after LT. However, the decrease in eGFR is also probably overestimated. Indeed, liver transplant candidates often have a low muscle mass and, therefore, low creatinine generation. Consequently, serum creatinine level is a poor marker for kidney function as it is often underestimated [2]. Similarly, the accuracy of equations developed to estimate GFR rate is also limited in this setting. Gonwa et al. have shown that when equations that estimate or measure GFR (by I¹²⁵ iothalamate before LT) are compared, only 66% of estimates are within the 30% of measured GFR values [15].

After LT, CNI-induced nephrotoxicity is the main incriminating cause of CKD. Other factors such as hypertension and diabetes can also induce histological lesions. For this reason, all nephrologists who perform kidney biopsies in this setting conclude that histopathological kidney lesions are complex and interrelated. In the studies published so far, all biopsies performed after LT were clinically indicated, i.e. a GFR of <30 mL/min/², a steep decrease in kidney function and heavy proteinuria [4], or a serum creatinine level of ≥1.5 mg/dL or new proteinuria in a dipstick [5]. This prompted us to perform kidney biopsies in liver transplant patients whatever the patient’s kidney function was, in
order to describe histological lesions and establish a specific therapy (if necessary), i.e. better control of hypertension, more aggressive anti-diabetic therapy or anti-HCV therapy for patients with mild HCV-associated glomerular disease. Because the histological pattern is complex in this setting, we preferred to score all biopsies according to the Banff classification. We also calculated IF by means of a computerized method.

Pillebout et al. performed kidney biopsies in 26 liver transplant patients who had CKD (eGFR ranging from 5 to 69 mL/min) at 4.8 ± 0.7 years post-transplant [3]. IF was estimated to be 45 ± 3%, and the percentage of SG was 45 ± 4%. The percentages of patients with the following major lesions were 65% with vascular lesions, 61% tubulointerstitial lesions related to hydroxyethyl starch, 50% TMA, 46% CNI nephrotoxicity, 34% diabetic lesions and 34% lesions of focal segmental glomerulosclerosis. More recently, O’Riordan et al. performed kidney biopsies in liver transplant patients who had experienced rapidly deteriorating kidney function over the previous year, high proteinuria and hypoalbuminaemia. Among 2100 liver transplant patients, 54 (2.57%) were referred to nephrologists at 5.3 ± 4.6 years after transplantation. Of these, 23 underwent a KB. Almost all these patients had severe kidney failure and nephrotic syndrome. SG and IF were observed in, respectively, 39 and 45% of patients. Histological findings included hypertensive changes (44%), CNI nephrotoxicity (48%), IgA nephropathy (9%), membranoproliferative glomerulonephritis (MPGN, 17%), acute tubular necrosis (4%), crescentic glomerulonephritis (4%) and diabetic nephropathy (9%).

Very recently, Kim et al. have reported the results of kidney biopsies performed in 81 liver transplant patients who had either a serum creatinine level of ≥1.5 mg/dL or new onset proteinuria on dipstick analysis [5]. Their mean time since transplantation was 4.89 years. The eGFR by MDRD was 38.7 ± 13.7 mL/min. The 24-h proteinuria was 1.37 ± 1.8 g. All kidney biopsies demonstrated arterial and glomerular abnormalities. Tubulointerstitial abnormalities were observed in 53% of patients, 46% had primary glomerular disease and only 16% had features of CNI toxicity [5].

In the present study, 99 patients underwent a KB at 5 ± 4 years post-liver transplantation. None of them had severe CKD. Only five patients had features of specific kidney disease (5%): IgA nephropathy (n = 1), cryoglobulinemic MPGN (n = 1), nephroangiosclerosis (n = 1), signs of TMA (n = 1) and tubulointerstitial nephritis (n = 1). The mean percentages of SG and acute tubular necrosis were 47 ± 21 and 13.8 ± 19.2%, respectively. The percentage of IF, calculated by computerized quantification, was 22.7 ± 10.6%. According to the Banff classification, the proportions of patients with IF (ci), tubular atrophy (ct) and fibrous intimal-thickening (cv) scores >1 were 37.4, 36.4 and 34.4%, respectively (Table 5). Interestingly, even in patients with an inulin clearance >60 mL/min/1.73 m², severe histological findings were observed (Table 2). This suggests that kidney function impairment is delayed as compared to histological lesions.

Kim et al. found that HCV-positive status was not associated with the type of renal pathology, and they did not observe any cases of MPGN [5]. Pillebout et al. found more glomerular lesions in patients infected by HCV [3]. In the present study, only 10% of patients were HCV-positive RNA positive, and half were receiving anti-viral therapy. HCV-associated cryoglobulinemic MPGN was observed in only one patient. Pillebout et al. found histological features of unrecognized chronic TMA, which may be related to CNI toxicity or interferon-alpha [3]. In the present study, one patient who was treated by α-interferon for HCV infection had histological signs of TMA. Finally, similar to Pillebout’s findings [3], we found a significant negative correlation between kidney function and the rate of SG, and the percentages of IF and fibrous intimal thickening (arteriosclerosis). There was also a correlation between the duration of receiving CNIs and the percentage of SG, and between the time of receiving CNIs and arteriolar hyaline thickening.

Even though the definition of CKD varies in other studies, patient factors, such as age, female gender, diabetes, hypertension and a high Model for End-Stage Liver Disease score, have been found to confer a higher risk of CKD after LT [1,14]. In the present study, because inulin clearance was

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### Table 5. Review of recent published reports on primary histopathological kidney lesions after liver transplantation

<table>
<thead>
<tr>
<th>Studies</th>
<th>Patient numbers</th>
<th>Time between KB and LT (years)</th>
<th>Creatinine clearance at kidney biopsy (mL/min)</th>
<th>Sclerotic glomeruli (%)</th>
<th>Interstitial fibrosis (%)</th>
<th>Tubular atrophy (%)</th>
<th>Patients with severe vascular damage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pillebout et al.</td>
<td>26</td>
<td>4.8 ± 0.7</td>
<td>36 ± 3 (5–60)</td>
<td>45 ± 3</td>
<td>45 ± 4</td>
<td>44</td>
<td>65</td>
</tr>
<tr>
<td>O’Riordan et al.</td>
<td>23</td>
<td>5.3 ± 4.6</td>
<td>22.9 ± 15.2</td>
<td>39</td>
<td>45</td>
<td>45</td>
<td>65</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>81</td>
<td>4.89</td>
<td>38.7 ± 13.7</td>
<td>&lt;20% SG: 50% of pts</td>
<td>53% of pts</td>
<td>45% of pts</td>
<td>100</td>
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<tr>
<td>Present study</td>
<td>99</td>
<td>5 ± 4</td>
<td>57 ± 17</td>
<td>47 ± 21</td>
<td>22.7 ± 10.6</td>
<td>36.4% of pts</td>
<td>34.4</td>
</tr>
</tbody>
</table>

KB, kidney biopsy; LT, liver transplantation; SG, sclerotic glomeruli; pts, patients.

*aCockcroft–Gault Formula.

*bModification of Diet in Renal Disease.
not measured before transplantation, we looked for predictive factors for an inulin clearance of $<60 \text{mL/min/1.73 m}^2$ at the time of KB. Only a low eGFR at 6 months post-transplant was identified as an independent predictive factor for an inulin clearance of $<60 \text{mL/min/1.73 m}^2$ at 5 years post-transplant. It has been also identified as an independent factor associated with $\geq 50\%$ SG. These findings suggest that long-term kidney function outcome depends on kidney function in the early post-transplant period. The uses of diuretics and statins at the time of a KB have been also identified as independent factors associated with $\geq 50\%$ SG. This reflects the more aggressive therapies used in patients with worse kidney function.

Low inulin clearance and the time of receiving CsA therapy, rather than tacrolimus, were independent factors associated with $>20\%$ IF. This finding is in line with previous reports. Ojo et al. have shown that the risk of CKD was 25% higher in liver transplant patients receiving CsA compared to those treated with tacrolimus [1]. In de novo liver transplant patients, Lurcey et al. found improved renal function from Months 3 through to 36 in patients receiving tacrolimus compared to those treated with CsA [16]. In the TRY study, CsA treatment was associated with worse kidney function at both 12 and 60 months post-transplantation [14]. Klein et al. found that tacrolimus does not influence renal haemodynamic parameters, whereas CsA causes potentially serious renal vasoconstriction, which may be harmful for long-term kidney function [17]. Finally, Epstein et al. have shown that CsA, but not tacrolimus, may selectively induce renal artery smooth muscle contraction [18].

In summary, similar to previous reports, our study, which is the largest kidney-histology study in the setting of LT, confirms that kidney lesions are complex and multiple. It is impossible to attribute kidney lesions to a single pathology. However, histological analysis of kidney biopsies before and early after liver transplantation may allow a better understanding of histological lesions observed later after liver transplantation. Careful management of kidney function is required at different periods after liver transplantation. Hypertension and diabetes should be aggressively treated. Investigating different immunosuppression regimens with regard to their association with long-term kidney function is required.

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References


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