Renal Dysfunction After Liver Transplant: Is CNI Nephrotoxicity Overrated

With improved survival after liver transplantation (LT), there is a parallel increase in the prevalence of renal dysfunction. Impaired renal function with a glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 is common after LT and documented in up to 70% of the patients five years after LT.[1] Various studies have reported a wide range of prevalence of chronic kidney disease (CKD) in LT recipients which may be due to the different criteria used for diagnosing CKD, and a large study from Mayo Clinic reported that two-thirds of LT recipients developed CKD 10 years post-LT.[2] The 5-year cumulative incidence of CKD in LT recipients is 22%.[3]

Calcineurin inhibitors (CNIs) are the cornerstone of the immunosuppressive regimen after LT, with most LT recipients receiving tacrolimus. While immunosuppression with CNI has been successful in preventing rejection, CNI nephrotoxicity resulting in CKD has been a major concern. The serum drug levels do not corelate with the extent of renal damage. The manifestations could be acute or chronic. Chronic CNI toxicity is structural, progressive, and irreversible. CNI nephrotoxicity affects all three compartments of the kidneys, the glomeruli (focal segmental or global glomerular sclerosis and thickening and fibrosis of Bowman's capsule), the tubulointerstitium (isometric vacuolation of the proximal straight tubules, tubular atrophy, and interstitial fibrosis), and the vessels (arteriolar hyalinosis) (Figure 1). The latter vascular involvement is considered the hallmark of CNI nephrotoxicity, characterized by nodular hyaline deposits in the media of afferent arterioles, also called arteriolar hyalinosis. These nodular hyaline deposits can lead to the narrowing of the arterial lumen.[4] Moreover, vasoconstriction and endothelial cell damage due to tacrolimus can result in necrosis of smooth muscle cells and hyalinization of the vascular walls. These can reduce the vascular lumen, cause chronic ischemia, and contribute to striped fibrosis.[5] The tubulointerstitial involvement may be secondary to the ischemia caused by the vascular lesions resulting in the formation of free radicals or reactive oxygen species that can cause cellular injury and promote cell death by apoptosis. However, CNI can also directly activate the apoptosis genes and induce tubular atrophy. Glomerular ischemia due to CNI-associated arteriolar hyalinosis and arteriolopathy results in glomerular ischemia, and global glomerulosclerosis is the most typical feature of glomerular involvement. Tacrolimus may also cause focal segmental glomerulosclerosis lesions.[6] The features of CNI toxicity also needs to be differentiated from primary and secondary renal diseases due to overlapping histological features. Figure 1 depicts the different features of CNI toxicity in the kidney.

In one of the largest published series of renal biopsies after nonrenal transplantation, the commonest histological renal changes were those of chronic CNI toxicity (nodular arteriolar hyalinosis, mainly striped interstitial fibrosis/tubular atrophy) and hypertension.[7] CNI toxicity has been associated with long-term morbidity and mortality after LT. Many measures have been suggested to prevent post-transplant liver dysfunction due to CNI toxicity. These include maintaining low CNI levels to maintain a reasonable balance between efficacy (avoiding rejection) and CNI nephrotoxicity; and combination therapy such as mycophenolate and mTOR inhibitor (everolimus/sirolimus), which allows the use of lower doses of CNI. In patients with a significant decline in GFR, withdrawal of CNI can be tried, or patients can be switched to monotherapy with mTOR inhibitors, or prednisolone and mycophenolate, or azathioprine.

However, the current study published this month in JCEH by Choudhary *et al.*[8] shows a low incidence of CNI as a cause of renal dysfunction. Choudhary *et al.* retrospectively analysed the renal histology after LT of 26 patients. Of the 25 patients with adequate biopsy samples, the diagnoses on renal biopsies were diabetic nephropathy (n = 7), focal segmental glomerulosclerosis (n = 4), CNI nephrotoxicity (n = 3), IgA nephropathy (n = 4), chronic glomerulonephritis (n = 3), hypertensive nephropathy (n = 1), membranous glomerulonephritis (n = 1), acute on chronic interstitial nephritis (n = 1), and C1q nephropathy (n = 1). The findings of this study are in line with the results of many other authors who found that CNI toxicity forms only a small subgroup of patients with renal dysfunction after LT, while diabetic and hypertensive nephropathy seem to be more important.[1,9–13]

Why is there a lower prevalence of CNI toxicity in LT patients? It has been suggested that we may have been overexaggerating the chronic nephropathy of CNI.[14] There can be many possible explanations for the lower prevalence of CNI toxicity as the major cause of chronic liver dysfunction after LT. LT patients require lower levels of immunosuppression compared to other solid organ transplantations. Moreover, living donor LT recipients have significantly decreased tacrolimus dosing requirements compared to deceased donor LT recipients despite having similar tacrolimus concentrations.[15] All the

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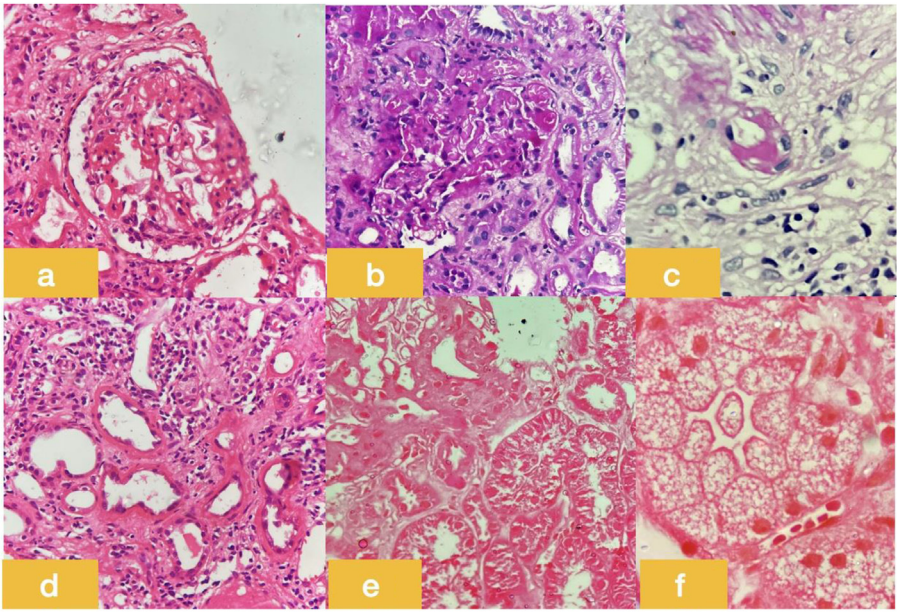

Figure 1 Micrograph showing different features of CNI toxicity on kidney. Figure 1a and b-Showing segmental sclerosis of glomeruli (Figure 1a HEX 40, Figure 1b-PAS X 40) Figure 1c showing arteriolar hyalinosis on PAS stain Figure 1d-Showing areas of tubular trophy and interstitial fibrosis (HE X 40) Figure 1e -Showing areas of arteriolar hyalinosis (HE X 40) Figure 1f Showing Isometric vacuolization of proximal tubule (HEX 100).

transplanted patients in the current study had undergone living donor LT. There are no histological lesions that are specific for CNI nephrotoxicity. Arterial hyalinosis is observed in 70% of CNI-treated patients and 30% of patients who did not receive CNI.[16] CKD after LT can be attributed to various primary lesions, including CNI arteriopathy, diabetic nephropathy, thrombotic microangiopathy, and tubular changes. Multiple simultaneous histological features attributable to more than one primary cause of renal findings can be found in an individual patient.[17] And finally, genetic variations with specific genes involved in the pharmacokinetics and pharmacodynamics of tacrolimus may affect an LT recipient's risk of developing tacrolimus-induced nephrotoxicity.[18] In the current study, as the authors have noted, there was possibly a selection bias against CNIs due to the presence of significant proteinuria in most patients.

Why have most patients progressed to end-stage renal disease (ESRD) despite the histological diagnosis? The authors of the recent study also raised an important aspect of most patients progressing to ESRD. One reason for the poor prognosis mentioned is doing biopsies at a later stage of renal dysfunction (median eGFR was 34 ml/min). Perinephric hematoma was noted in 1/24 patients which was managed conservatively. A study by Lee *et al.*[19] reported histological data in 10 of 544 liver graft recipients with CKD and showed similar results for biopsies performed in the late stages of renal dysfunction. Improvement was noted in 80% of patients following a renal biopsy performed early in the disease course. They also reported no complications following the renal biopsy procedure. Welker *et al.* also performed a biopsy with an eGFR of 39.49 ± 16.88 ml/min/1.73 m^2 (mean ± SD) at the time of the renal biopsy, and most patients performed well with therapy, They thus also emphasized the utility of doing an early renal biopsy. The reported peri-renal hematoma by Welker *et al.*[13] without subsequent interventions was 4/14 (29%). Aggressive management of liver transplant recipients may be helpful to delay the progression of CKD. Is it thus time to say that patients with renal dysfunction after a liver transplant should undergo an early biopsy for better management?

Renal dysfunction remains a major challenge in LT outcomes as it is associated with increased morbidity and mortality. While CNIs play a role in chronic liver dysfunction after LT, it remains unclear what is their actual contribution as the main culprit in causing CKD after LT. Besides the use of CNI, other possible reasons for renal dysfunction after LT include diabetes, hypertension, atherosclerosis, HCV-associated kidney disease, and glomerulonephritis. The cause of renal dysfunction may be multifactorial. Although the current study has shown lower CNI toxicity, it does not mean that we should not be vigilant, as the factors causing renal dysfunction can be additive. Every patient with renal impairment after LT should not be attributed to CNI nephrotoxicity without further investigations, including a kidney biopsy. A kidney biopsy may help avoid an unnecessary blind decrease in immunosuppression which may result in inadequate treatment.

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