Editorial

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Chronic kidney disease: A major concern in liver transplantation in the XXI century

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With an approximate 12,000 transplants performed annually in Europe and the United States during recent years, liver transplantation has become a very common treatment and in fact the only curative method for most advanced chronic liver diseases [1,2]. Survival rates have increased gradually since the first liver transplants were performed in the 1960's and current survival probability after 10 years of transplantation is above 60% [1,2].

With the steady increase in survival rates after liver transplantation, some complications that were not frequently observed in early years have become progressively apparent. These complications include, among others, cardiovascular events, metabolic diseases, including diabetes mellitus and lipid disorders, extra-hepatic malignancies, and impairment in kidney function. Among them, an important clinical issue is Chronic Kidney Disease (CKD). There is a large body of evidence indicating that patients submitted to a liver transplant have an increased risk of development of chronic and progressive impairment of kidney function, which becomes particularly relevant in long-term survivors [3–16]. The frequency of CKD, as indicated by a marked reduction in glomerular filtration rate (definitions have changed over time) or the need for renal replacement therapy has been estimated to range between 18 and 25% at 10 years of liver transplantation. With the current definition [17], the observed frequency of CKD in liver transplant recipients is even higher [7,10]. Factors associated with an increased risk of development of CKD after liver transplantation include among others, serum creatinine levels at transplant, GFR at one year of transplantation, age, female sex, diabetes mellitus, and arterial hypertension. Non-alcoholic steatohepatitis (NASH) as a cause of transplantation is also associated with an increased risk of CKD after transplant [4–8,10–13,16]. Few studies have provided a histological analysis of kidneys of patients developing severe CKD after liver transplantation. Interestingly, and contrarily to what was expected initially, only a limited proportion of cases of CKD may be attributed to chronic toxicity related to calcineurin inhibitors (cyclosporine or tacrolimus). By contrast, most patients show histological changes characterized by glomerular and/or interstitial abnormalities, suggestive in some cases of diabetes and/or hypertensive nephropathy [14,15]. A consistent observation of all studies reported is that the occurrence of CKD is a major risk factor of death in liver transplant recipients. This finding emphasizes that the impairment of kidney function is not a simple laboratory abnormality but a major clinical issue in these patients that requires strict surveillance and management of conditions associated with progression of kidney dysfunction, particularly arterial hypertension and metabolic conditions, specifically diabetes mellitus and lipid disorders.

In this context, the study by Allen *et al.* published in the current issue of the *Journal of Hepatology*, reports on the frequency and outcome of CKD in all adult patients treated with liver transplantation in a single institution over a 28-yr period [18]. The study has several important strengths that make it a unique investigation to assess the evolution of kidney function after liver transplantation: (1) inclusion of a large and consecutive series of patients (1211 patients); only patients with simultaneous multiple organ transplantation or repeated liver transplantation were excluded, thus avoiding selection bias; (2) long-term follow-up (average follow-up of 6 years); (3) measurement of GFR at several time points (5 measurements per patient in average) after liver transplantation using iothalamate clearance which is a very precise method of measurement of GFR; and (4) use of time-dependent statistical modeling. The main finding of the study is that the proportion of patients with what can be considered a normal GFR (>60 ml/min/1.73 m^2) decreases dramatically over time after liver transplantation, with only 19% of patients having normal GFR after 25 years of transplantation. Moreover, at 25 years after liver transplantation, 9% of the initial population had been treated with kidney transplantation, and among the remaining patients, 57% had stage 3 CKD stage (GFR between 59 and 30 ml/min/1.73 m^2), 19% stage 4 CKD (GFR between 29 and 15 ml/min/1.73 m^2), and 5% stage 5 CKD (GFR <15 ml/min/1.73 m^2) (and only 19% maintained a normal GFR, as stated above). Corresponding percentages for periods of time lower than 25 years can be seen in Fig. 1B of the manuscript [18]. It can therefore be concluded that normal kidney function is the exception and not the rule for patients who survive for long periods of

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time after liver transplantation. The current study also analyzed the relationship between measured GFR and mortality. The risk of death increased significantly with a reduction in GFR below 30 ml/min, and was particularly increased at values of GFR below 15 ml/min. It is important to emphasize that estimated GFR using existing formulas undervalued the risk of death compared to that of GFR measured with iothalamate clearance. In fact, using estimated GFR the increase in the risk of death did not become apparent until it decreased below 45 ml/min.

In view of the findings of Allen *et al.* [18], as well as those from previous studies, the development of CKD must be considered a major clinical issue in the evolution of patients submitted to liver transplantation. Kidney function should be followed-up in these patients with a close attention similar to that devoted to the evaluation of liver function. Although the use of calcineurin inhibitors can without doubt affect kidney function, results of studies aimed at preventing the development of CKD based on the substitution of these drugs by renal-sparing agents, such as mycophenolate mofetil or sirolimus have been inconsistent [discussed in ref [19]]. Therefore, prevention and treatment of CKD requires a multidisciplinary approach based on the adjustment of immunosuppressive drugs combined with an aggressive treatment of factors predisposing to kidney dysfunction, including obesity, arterial hypertension, diabetes mellitus, and lipid abnormalities. With the anticipated reduction in the number of patients transplanted for hepatitis C in the future due to the recent introduction of the direct antiviral agents and the increasing global incidence of obesity and diabetes mellitus, it is plausible that the number of patients transplanted for cirrhosis or hepatocellular carcinoma associated with non-alcoholic steatohepatitis will be on the raise in the next years. Since obesity and metabolic disorders are strongly associated with the development of CKD [20], the prevalence of CKD in liver transplant recipients will probably increase further in the future. An effort should be made to investigate the mechanisms involved in the pathogenesis of CKD in liver transplant patients as well as in therapeutic strategies to prevent its development. Without this research effort, CKD will become one of the major clinical issues in liver transplantation.

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Conflict of interest

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References

[1] Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol 2012; 57:675–688.
[2] Kim WR, Smith JM, Skeans MA, Schladt DP, Schnitzler MA, Edwards EB, et al. OPTN/SRTR 2012 annual data report: liver. Am J Transplant 2014;14:69–96.
[3] Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. Am J Transplant 2010;10:1420–1427.
[4] Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003; 349:931–940.
[5] Gonwa TA, Mai ML, Melton LB, Hays SR, Goldstein RM, Levy MF, et al. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLTX) using calcineurin-based immunotherapy: risk of development and treatment. Transplantation 2001;72:1934–1939.
[6] Gayowski T, Singh N, Keyes L, Wannstedt CF, Wagener MM, Vargas H, et al. Late onset renal failure after liver transplantation: role of post transplant alcohol use. Transplantation 2000;69:383–388.
[7] Burra P, Senzolo M, Masier A, Prestele H, Jones R, Samuel D, et al. Factors influencing renal function after liver transplantation. Results from the MOST, an international observational study. Dig Liver Dis 2009;41:350–356.
[8] Giusto M, Berenguer M, Merkel C, Aguilera V, Rubin A, Ginanni Corradini S, et al. Chronic kidney disease after liver transplantation: pretransplantation risk factors and predictors during follow-up. Transplantation 2013;95: 1148–1153.
[9] Sanchez EQ, Melton LB, Chinnakotla S, Randall HB, McKenna GJ, Ruiz R, et al. Predicting renal failure after liver transplantation from measured glomerular filtration rate: review of up to 15 years of follow-up. Transplantation 2010; 89:232–235.
[10] Pawarode A, Fine DM, Thuluvath PJ. Independent risk factors and natural history of renal dysfunction in liver transplant recipients. Liver Transpl 2003;9:741–747.
[11] Fussner LA, Charlton MR, Heimbach JK, Fan C, Dierkhising R, Coss E, Watt KD. The impact of gender and NASH on chronic kidney disease before and after liver transplantation. Liver Intern 2013. http://dx.doi.org/10.1111/liv.12381, [Epub ahead of print].
[12] Sharma P, Schaubel DE, Guidinger MK, Goodrich NP, Ojo AO, Merion RM. Impact of MELD-based allocation on end-stage renal disease after liver transplantation. Am J Transplant 2011;11:2372–2378.
[13] Cohen AJ, Stegall MD, Rosen CB, Wiesner RH, Leung N, Kremers WK, et al. Chronic renal dysfunction late after liver transplantation. Liver Transpl 2002;8:916–921.
[14] Kim JY, Akalin E, Dikman S, Gagliardi R, Schiano T, Bromberg J, et al. The variable pathology of kidney disease after liver transplantation. Transplantation 2010;89:215–221.
[15] Pillebout E, Nochy D, Hill G, Conti F, Antoine C, Calmus Y, et al. Renal histopathological lesions after orthotopic liver transplantation (OLT). Am J Transplant 2005;5:1120–1129.
[16] Sharma P, Goodrich NP, Schaubel DE, Guidinger MK, Merion RM. Patient-specific prediction of ESRD after liver transplantation. J Am Soc Nephrol 2013;24:2045–2052.
[17] Levey S, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139:137–147.
[18] Allen AM, Ray Kim W, Therneau TM, Larson JJ, Heimbach JK, Rule AD. Chronic kidney disease and associated mortality after liver transplantation – A time dependent analysis using measured glomerular filtration rate. J Hepatol 2014;61:286–292.
[19] Trotter JF, Grafals M, Alsina AE. Early use of renal-sparing agents in liver transplantation: a closer loo. Liver Transpl 2013;19:826–842.
[20] Ix JH, Sharma K. Mechanisms linking obesity, chronic kidney disease, and fatty liver disease: the roles of fetuin-A, adiponectin, and AMPK. J Am Soc Nephrol 2010;21:406–412.