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Chronic kidney disease (CKD) and NAFLD: Time for awareness and screening

To the Editor:

We read with interest the article by Allen *et al.* reporting on the high prevalence and associated mortality of chronic kidney disease (CKD), in patients who had undergone liver transplantation [1].

We believe a thorough interpretation of these findings, which are consistent with recent liver transplant literature, should take into account the evolving aetiological spectrum of liver disease in both patients candidate for liver transplantation as well as in those with milder stage disease [2]: in either case, non-alcoholic steatohepatitis (NASH) is as an emerging risk factor for renal dysfunction, as compared with other aetiologies of cirrhosis. An analysis of the United Network Organ Sharing (UNOS) database, during the years 2002–2011, shows NASH-related cirrhosis as an increasing indication for simultaneous liver-kidney transplantation (SLKT) [3]. A concerning observation was the reduced 5-year liver graft, kidney graft, and patient survival in NASH patients in comparison to transplantation for other causes of cirrhosis (HR of 2.50 (95% CI 1.10–5.80), 2.30 (1.10–5.10), and 2.20 (1.02–5.79) respectively), for loss of liver transplant, loss of kidney graft, and death. These findings are consistent with European data suggesting NASH as a risk factor for severe renal impairment after liver transplantation; Houlihan *et al.* [4] reported more rapid loss of renal function in patients receiving a liver transplant for NASH-related cirrhosis in comparison to other aetiologies of cirrhosis (OR for incident CKD in NASH *vs.* controls of 2.43 (95% CI 1.05–5.63)) 2 years after liver transplantation, independent of BMI, diabetes, hypertension, hepatocellular carcinoma, and tacrolimus levels. Remarkably, 35% of patients transplanted for NASH-related cirrhosis progressed to stage 3b-4 CKD within 2 years after liver transplantation, compared to 10% of patients transplanted for other aetiologies of cirrhosis.

The evidence connecting NAFLD to CKD is also emerging in the general population: we recently subjected studies, assessing the association of NAFLD with CKD, to meta-analysis [5], which included 33 studies (63,902 participants, 16 population-based and 17 hospital-based, 20 cross-sectional and 13 longitudinal). For 20 studies, individual participant data were obtained and NAFLD was defined by liver histology in 13 studies (2205 participants). NAFLD was associated with an increased prevalence (OR 2.12, 95% CI 1.69–2.66) and incidence (HR 1.79, 95% CI 1.65–1.95) of CKD. In non-cirrhotic biopsy-proven NAFLD patients, NASH was associated with a higher prevalence (OR 2.53, 95% CI 1.58–4.05) and incidence (HR 2.12, 95% CI 1.42–3.17) of CKD than simple steatosis. Similarly, NAFLD with advanced fibrosis was associated with a higher CKD prevalence (OR 5.20, 95% CI 3.14–8.61) and incidence (HR 3.29, 95% CI 2.30–4.71) than NAFLD with milder fibrosis stages. Remarkably, the severity of NAFLD was positively associated with CKD stages, with NASH and advanced fibrosis conferring a greater risk of developing stage 5 CKD (renal failure) than simple steatosis and milder fibrosis stages, respectively.

In all analyses, the magnitude and direction of effects remained unaffected by diabetes status (present *vs.* absent) and after adjustment for other traditional risk factors for CKD (including age, obesity, metabolic syndrome components, smoking, hypertension, race).

The prevalence of CKD, as well as NAFLD, is continuously rising in concert with the epidemic of its risk factors, including diabetes, obesity and metabolic syndrome. Although early recognition and treatment of CKD have been shown to reduce the staggering cost of CKD and related hospitalizations [6], CKD often goes unrecognized, and in the Third National Health and Nutrition Survey (NHANES III), among all individuals with moderately decreased GFR (stage 3 CKD), the awareness approached 8.2% [7].

Since current therapeutic options to reverse CKD in liver transplant recipients are limited, the findings discussed above emphasize the need for practicing hepatologists to recognize early CKD in chronic liver disease patients and in NAFLD in particular, to optimize the management of these patients by delaying renal disease progression. From a therapeutical stand-point, promising preliminary evidence from randomized trials suggest several available pharmacological classes provide incremental benefits on renal disease progression over others, with statins [8] and angiotensin receptor blockers slowing renal function decline and ameliorating proteinuria [9], in addition to the

amelioration of markers of steatosis and liver histology in non-cirrhotic NASH [10]. Future trials should also evaluate the impact of experimental drugs on renal function, which is currently reported in less than 10% of available randomized trials in NASH.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Reply to: "Chronic kidney disease (CKD) and NAFLD: Time for awareness and screening"

To the Editor:

We appreciate the comments of Musso *et al.* related to our manuscript "Chronic kidney disease and associated mortality after liver transplantation - a time-dependent analysis using measured glomerular filtration rate" [1]. The authors call attention to the accumulating evidence of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) as a risk factor for chronic kidney disease (CKD). As NASH cirrhosis is emerging as the most common cause of liver transplantation (LT) [2], the incidence of subsequent CKD may increase.

Whether the changing trends in the etiology of end-stage liver disease requiring transplantation will impact the risk of CKD post LT remains to be determined. The anticipated decline of hepatitis C as a main cause of end-stage liver disease will reduce the prevalence of well-defined HCV-associated kidney diseases, such as cryoglobulinemia and membranoproliferative glomerulopathy [3]. On the other hand, the increasing prevalence of obesity and NASH is likely to offset this effect. A growing number of observations have linked NASH to the development of CKD [4]. While the exact mechanism of this association is unclear, both share common cardiometabolic risk factors and the ultimate clinical consequence of increased risk for cardiovascular morbidity and mortality.

Efforts to minimize the comorbidity burden associated with NAFLD may consequently decrease the risk of developing CKD. Once CKD develops, we agree that statins and angiotensin receptor blockers are helpful in select patients [5]. Unfortunately, more effective treatments for preventing CKD progression are still needed. Indeed, a GFR decline into stage 3 CKD (moderately decreased GFR) is the expected consequence of normal aging [6] and the American College of Physicians does not recommend routine screening for moderately decreased GFR in the absence of risk factors [5]. However, liver transplantation is an unequivocal risk factor and monitoring for CKD is warranted.

The evolving epidemiology of end-stage liver disease presents new challenges for the transplant community. Optimization of long term outcomes of liver transplant recipients may be improved with vigilant management of pre and posttransplant metabolic syndrome and careful adjustment of the immunosuppression regimen. In order to improve the medical care in this population, we fully agree that renal function should be an investigated endpoint for randomized trials of novel treatments for NASH.