Editorial

Non-alcoholic fatty liver disease and risk of developing chronic kidney disease: a new piece of a recent puzzle from a large Asian study

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In a recent cross-sectional study published on *J Hepatol*, Yeung *et al.* have showed that advanced liver fibrosis (detected by transient elastography), which is a severe form of non-alcoholic fatty liver disease (NAFLD), was associated with an increased risk of albuminuria in a cohort of approximately 1,800 Chinese patients with type 2 diabetes mellitus, independent of several cardio-metabolic risk factors (1). To date, NAFLD is the most common chronic liver disease observed in clinical practice worldwide, affecting approximately 30–35% of adult general population (2). Importantly, among patients with type 2 diabetes, the prevalence of NAFLD is much higher, affecting roughly 70–75% of these patients (2). In addition, of note, patients with type 2 diabete have also an increased risk of developing the severe forms of NAFLD, including nonalcoholic steatohepatitis (NAFLD), advanced fibrosis and cirrhosis (2,3).

Over the last decade, it has become increasing evident that the clinical impact of NAFLD is not only restricted to the liver-related morbidity and mortality, but that NAFLD is a multi-systemic disease, which is strongly associated with an increased risk of developing cardiovascular disease and other relevant extrahepatic complications, including chronic kidney disease (CKD) (3,4).

At present, both in non-Asian and Asian countries, CKD is a relatively frequent condition, that is strongly associated with a high health-care costs and with an increased risk of developing end-stage renal disease (ESRD) and other important comorbidities, including cardiovascular complications (5,6). For all these reasons, the early identification of the traditional and non-traditional risk factors for CKD is important and essential in clinical practice.

In literature, there are several observational studies, finding that the prevalence of CKD [defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and/or abnormal albuminuria or overt proteinuria) is much greater in patients with NAFLD than in those without NAFLD (4). In such studies, the prevalence of CKD spanned from 20% to 55% among patients with NAFLD (as detected by ultrasound or liver biopsy), while it ranged from 5% to 30% among those without NAFLD (4). However, at present, only small case-control studies and few meta-analyses showed a relationship between the histological severity of NAFLD (e.g., advanced fibrosis) and the presence of either decreased eGFR or albuminuria, independent of several cardiovascular risk factors (4). For instance, in a very recent meta-analysis incorporating nine observational cohort studies with a total of 96,595 adult individuals (34.1% with NAFLD) of predominantly Asian descendent and 4,653 cases of incident CKD stage 3 (i.e., defined as occurrence of eGFR <60 mL/min/1.73 m^2 and/or overt proteinuria) over a median follow-up of 5.2 years, Mantovani *et al.* documented that NAFLD patients had a higher risk of incident CKD compared to those without NAFLD [random-effects hazard ratio (HR) =1.37, 95% confidence interval (CI): 1.20–1.53; I^2 =33.5%) (7). In addition, notably, patients with more

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"severe" NAFLD were more likely to develop CKD (7).

On the basis of this evidence, the cross-sectional study of Yeung *et al.* gives additional pivotal information by supporting that type 2 diabetic patients with severe forms of NAFLD are more likely to have persistent albuminuria, which is a relevant marker observed in diabetic nephropathy and it is also a strong predictor for ESRD, cardiovascular events and overall mortality (8). In a cross-sectional study including 1,763 Chinese patients with type 2 diabetes (mean age of 61 years and mean diabetes duration of 11 years) from the Hong Kong Diabetes Registry, free of secondary causes for liver steatosis and excessive alcohol consumption, who performed a transient elastography (Fibroscan®), the investigators found that the prevalence of persistent albuminuria was much higher in type 2 diabetic patients with advanced fibrosis compared to those with liver steatosis and those with no NAFLD (no NAFLD *vs.* liver steatosis *vs.* advanced fibrosis: 41.4% *vs.* 46.2% *vs.* 64.2%, respectively; P<0.001) (1). In addition, after adjustment for several cardio-renal risk factors, advanced fibrosis, but not liver steatosis, was significantly associated with an increased risk of persistent albuminuria [odds ratio (OR) =1.52, 95% CI: 1.02–2.28, P=0.039] (1). Notably, the investigators also observed that the relationship between advanced liver fibrosis and albuminuria was found only in patients with body mass index (BMI) ≥25 kg/m^2, but not in those with BMI <25 kg/m^2 (1), suggesting that, as described below, liver and kidneys share multiple pathophysiological pathways that could explain such relationship.

The findings of Yeung *et al.* are, at least in part, in contrast with the results of Targher *et al.*, showing that NAFLD (as detected by ultrasound) was associated with an increased prevalence of CKD (defined as eGFR <60 mL/min/1.73 m^2 and/or abnormal albuminuria or overt proteinuria) and proliferative/laser-treated retinopathy in approximately 2,100 type 2 diabetic Italian individuals (9). However, it is important to highlight that there are important differences between the two observational studies, mainly in terms of simple size, outcome definition, population characteristics and diagnostic tools for detecting NAFLD.

In the paper, the investigators reported with clarity the limitations and the strengths of their study. Among the limitations, it is important to remember that the study of Yeung *et al.* is a cross-sectional study (hence, it is not possible to understand any causal and temporal relationship between NAFLD and persistent albuminuria) and that the Authors included only a single-ethnic Asian population. Seeing that Asian and non-Asian individuals tend to have different adipose tissue distributions as well as specific genetic settings, additional studies are timely required to corroborate these findings in other ethnic groups of patients (10). Furthermore, it is important to point out that the use of non-invasive fibrosis markers still needs being properly validated in the adult general population (10). Therefore, future studies conducted in large cohorts of patients with NAFLD, as detected by magnetic resonance-proton density fat fraction and magnetic resonance elastography, are urgently required to better elucidate if the severity of NAFLD has a specific effect on the risk of developing CKD (7,10). In fact, the question regarding whether the increased risk of developing CKD is present to all NAFLD patients or if it is only restricted to patients with more severe NAFLD (i.e., NASH and/or advanced fibrosis), is very pertinent due to the recent drastic increase of NAFLD patients worldwide (7,10).

Despite these considerations, the results of Yeung *et al.* are clinically relevant, as they furnish additional evidence for the view that the identification of the severe forms of NAFLD, especially advanced fibrosis, could be advantageous for detecting a subgroup of NAFLD patients at very high risk of developing CKD, who might need more intensive surveillance and treatment in order to reduce their CKD risk.

To date, it is not known if NAFLD is causally linked to CKD development or if it is merely a marker of multiple shared cardio-renal risk factors. The liver and kidneys, in fact, share multiple pathophysiological pathways, that are strongly related to each other (4,7,10). Several experimental and clinical data suggest that NAFLD, mainly NASH with varying amounts of liver fibrosis, may: (I) worsen the hepatic insulin resistance; (II) induce hypertension; (III) and contribute to atherogenic dyslipidemia and the release into bloodstream of several pro-inflammatory molecules, pro-coagulant factors and pro-oxidant mediators (4,7,10).

All these NAFLD-related factors may play a part in the pathophysiology of CKD and other extra-hepatic vascular complications (4,7,10).

In order to conclusively determine the causal relationship between NAFLD and CKD (or albuminuria), future well-designed, adequately prospective and randomized clinical studies of cohorts of patients with biopsy-proven NAFLD from Asian and non-Asian countries are required. Lastly, studies designed for establishing whether the presence and severity of NAFLD increases the risk of CKD, or if the amelioration of NAFLD will prevent or procrastinate the development and progression of CKD are needed.

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