Editorial

Non-alcoholic fatty liver disease: a pandemic disease with multisystem burden

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Non-alcoholic fatty liver disease (NAFLD) is a leading cause of liver-related morbidity and mortality in the United States and globally (1,2). A large body of literature currently exists to suggest at the clinical burden of NAFLD is not only confined to liver but may rather represent a major part of a multisystem disease (3). Along with the well-known association with metabolic syndrome (MetS), NAFLD has proven to strongly correlate with cardiovascular disease (CVD), chronic kidney disease (CKD), type 2 diabetes (T2D) and potentially osteoporosis and extra-hepatic malignancies (4,5).

Over the last decade, remarkable advances have been made in the understanding of the pathophysiology of NAFLD (6,7). However, the exact mechanism of hepatic fat accumulation and the progression to nonalcoholic steatohepatitis (NASH), the more severe form of the disease, is only partially elucidated. NAFLD progresses when hepatic lipid accumulation overcomes the combination of intra-hepatic lipid oxidation and lipid export (8,9). Emerging evidence shows that hepatic fat is essentially the primary ectopic fat driving the formation of visceral adipose tissue (VAT) (8,10). Furthermore, multiple cross-sectional studies link liver fat and VAT with other metabolic complications of obesity, including insulin resistance, T2D, and even CVD (11,12).

In their recent article, Adams and colleagues examine the magnitude of the associations between NAFLD and several extra-hepatic conditions. In this comprehensive review of the literature, the authors focus on the epidemiologic data and clinical implications of NAFLD as a manifestation of multi-systemic disease (13).

The association that carries the most significant clinical relevance is the one between NAFLD and CVD, which has been the focus of multiple studies recently. A strong association between NAFLD and several markers of subclinical atherosclerosis was reported by a meta-analysis of multiple cross-sectional studies. Those markers included increased carotid intima-media thickness, increased coronary artery calcification, impaired flow-mediated vasodilation and arterial stiffness. This association was independent of the classical CVD risk factors (14). Moon *et al.* reported a significant and independent association between NAFLD and carotid artery inflammation through a cohort of healthy adult men, using ^{18}F-fluorodeoxyglucose positron emission tomography (15).

In recent years, there has been abundant evidence on the potential links between NAFLD and impaired kidney function. An increased incidence of CKD in patients with NAFLD was found by the Valpolicella Heart Diabetes Study which followed patients with T2D who had normal kidney function over a period of 6 years (16). This was supported by another retrospective study on a cohort of non-diabetic, non-hypertensive men with normal kidney function. The study revealed that NAFLD was associated with increased incidence of CKD, independent of age, sex, and other factors (17). Additionally, studies have shown

that NAFLD is a risk factor for developing CKD after liver transplant (18). An article by Houlihan *et al.* demonstrated that approximately 30% of patients with NASH progress to stage III CKD compared to 8% of non-NASH patients two years after liver transplantation (19).

NAFLD is strongly associated with insulin resistance and T2D. Ballestri *et al.* conducted a study of a large population of patients from 20 prospective studies and found that the presence of NAFLD (diagnosed by enzyme levels or US) was associated with 1.6–2.0-fold increase in the risk of developing T2D (20). Another example is a similar study which revealed that the presence of NAFLD increased the incidence of MetS (17).

NAFLD was found to be associated with increased incidence of colorectal adenomas in a large Korean study by Hwang *et al.* (21) Same results were revealed by a cross-sectional study, in addition to the association with high risk of colorectal neoplasm (22).

Malignancies are the second most common cause of death among NAFLD patients. They include both gastrointestinal and extra-intestinal cancers. Fatty liver significantly increased all-cancers risk based on the Danish Study. Obesity is believed to play the major role in predisposing to cancers per a recent review (23). NAFLD and its parallel extra-hepatic conditions are emerging as one very common and progressive multi-systemic disease. The impaired hepatic functions in patients with NAFLD may actually be the primary driver for this expansive multi -systemic process. Cardiac events and extra-hepatic malignancy are not only more common in NAFLD patients, but also the leading causes for death in this patient population. CKD and T2D incident and prevalence are also higher in fatty liver patients, but they tend to improve with the improvement/resolution of NAFLD; a very strong argument that liver fat is the main trigger in this process. It is of extreme significance to raise awareness of these associations in order to initiate the appropriate screening methods and apply early medical interventions necessary to improve long-term outcomes and prevent complications in patients with NAFLD.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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