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Editorial: new insights into the relationship between the intestine and non-alcoholic fatty liver—is "fatty gut" involved in disease progression?

Non-alcoholic fatty liver disease (NAFLD) is currently the most frequent liver disorder worldwide. There is a high heterogeneity in the natural history of NAFLD, with only a small fraction of patients progressing to end stage liver disease and/or hepatocellular carcinoma. This high variability is partly explained by metabolic comorbidities and genetic risk factors.[1] Alteration in the gut microbiota and in the intestinal permeability has also been linked to NAFLD. Robust experimental data suggest endotoxemia is a trigger for hepatic inflammation leading to non-alcoholic steatohepatitis (NASH) and NAFLD progression.[2,3] However, data from human studies remained controversial.[4,5]

Pang and coworkers examined the relationship between markers of endotoxemia and liver damage in patients with NAFLD.[6] They measured circulating levels of Lipopolysaccharide (LPS) and LPS binding protein (LBP), a stable biomarker reflecting hepatic LPS exposure in 237 Asian patients with histological NAFLD. First, authors tested whether endotexemia is associated with liver damage, and found that LBP was independently associated with hepatocellular damage and fibrosis, while LPS only with fibrosis. These data lend support to the hypothesis that endotoxemia is involved in the pathogenesis of NASH and promotion of fibrogenesis.

Next, they examined the determinants of endotoxemia. LBP levels were associated with male gender and metabolic risk factors. Carriers of *TM6SF2* rs58542926 C>T, encoding for the E167K loss-of-function protein variant had also higher LBP levels. The E167K variant predisposes to NAFLD by impairing apoliprotein B (APOB) containing lipoprotein secretion by hepatocytes. Indeed, the mutation is associated with reduced fasting circulating lipoprotein concentration.[7,8] *TM6SF2* silencing in the liver results in steatosis due to decreased secretion of very low-density lipoproteins (VLDL)-associated lipids,[7] possibly by decreasing the lipidation of VLDL.[9] Importantly, TM6SF2 is also highly expressed in the intestine, which plays an important role in post-prandial lipid absorption by secreting chylomicrons, and lipid absorption was modestly impaired in T*m6sf2*-/- mice.[9] Therefore, *TM6SF2* variant may also reduce the ability to secrete chylomicrons by enterocytes in humans. In parallel, a retention of chylomicrons occurs in loss-of-function *APOB* mutations[10] also increasing the risk of to steatosis and progressive liver disease.[1]

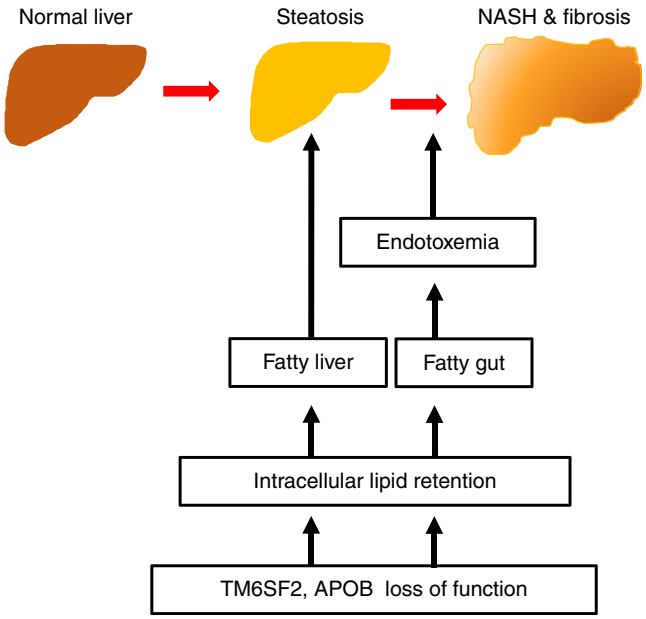

FIGURE 1 Putative model for the mechanism linking the *TM6SF2* E167K variant and APOB loss-of-function (LOF) mutations with endotoxemia and progressive NAFLD

It would thus be tempting to speculate that lipid accumulation in enterocytes, or "fatty gut" due to the diet, insulin resistance or genetic factors causes a damage to the epithelial barrier, increased leaking of bacterial products and consequently liver damage. The potential mechanism linking the *TM6SF2* mutation with endotexemia and progressive liver damage is presented in Figure 1. To prove this model enterocyte fat accumulation, increased intestinal permeability and absorption of intestinal products should be shown in carriers of the *TM6SF2* variant and *APOB* loss-of-function mutations.

Collectively, these new data are consistent with the hypothesis that endotoxemia is involved in the pathogenesis of progressive NAFLD, with potential therapeutic implications. Human genetics may help shedding light into the relationship between altered intestinal environment and liver disease.

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L. Valenti[1,2]
S. Romeo[3,4,5]
[1]*Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy*
[2]*Internal Medicine and Metabolic Diseases, Fondazione IRCCS Ca' Granda Ospedale Policlinico Milano, Milan, Italy*
[3]*Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden*
[4]*Clinical Nutrition Unit, Department of Medical and Surgical Sciences, University Magna Graecia, Catanzaro, Italy*
[5]*Cardiology Department, Sahlgrenska University Hospital, Gothenburg, Sweden*
Email: luca.valenti@unimi.it

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Editorial: hepatitis C direct acting anti-viral agents and the kidney

The evolution of anti-HCV therapy over the past few years has been remarkable because of the development of the direct acting antiviral agents (DAA). The very first DAAs introduced in 2011, specifically, boceprevir (BOC) and telaprevir (TVR), still required a backbone of peginterferon and ribavirin (PR). In patients with advanced chronic kidney disease (CKD), however, these treatments were essentially contraindicated given the necessity of ribavirin, which causes significant haemolysis in this clinical setting.[1] Sofosbuvir, a pangenotypic NS5B polymerase inhibitor marked the beginning of the interferon-free, highly efficacious and well tolerated DAA era. Combination with the NS5A inhibitors, ledipasvir or velpatasvir, pushed the SVR to 95%-99%.[2] Patients with significant renal dysfunction and/or on dialysis, however, were still "out of luck". Sofosbuvir, being renally eliminated, is contraindicated in patients with advanced CKD (GFR<30 mL/min)[3] as pharmacokinetic studies demonstrated a significant increase in the exposure of sofosbuvir (171%), and its major metabolite, GS-331007 (451%), in patients with severe renal impairment compared to patients with normal renal function.[4] Clinically, in the real world setting, sofosbuvir treated patients with severe renal impairment more frequently experienced serious adverse events (19% vs 6%) including acute kidney injury (25% vs 1%).[5] Fortunately, other DAA combinations have been developed that allow these patients access to effective therapy: grazoprevir with elbasvir[6] and glecaprevir with pibrentasvir.[7]

The question that also should be asked is the nephrotoxic potential of the DAAs. Recently, in *Alimentary Pharmacology and Therapeutics*, Maan et al retrospectively examined the renal safety profile of the first generation PIs, TVR/BOC + PR compared to Sofosbuvir (SOF) in patients with normal renal function (eGFR>60 mL/min) at