Editorial: Noninvasive Fibrosis Biomarkers in Patients With NASH With Diabetes

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Patients with type 2 diabetes mellitus (T2DM) are at high risk of developing nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH), and progress faster to cirrhosis.[1,2] With the rapidly increasing numbers of patients with T2DM, early diagnosis of significant fibrosis is an unmet clinical need. There have been few studies focusing on noninvasive fibrosis tests, specifically in the diabetic population, and most data have been extrapolated from larger studies that included both diabetic and nondiabetic patients with NAFLD/NASH.[3]

Abbreviations: APRI, aspartate aminotransferase–to-platelet ratio index; COL4-7S, type IV collagen 7S; ECM, extracellular matrix; ELF, enhanced liver fibrosis test; FIB-4, Fibrosis-4 index; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PRO-C3, pro-collagen III peptide neoepitope; T2DM, type 2 diabetes mellitus.

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Although liver biopsy still is a gold standard for fibrosis staging, it is fraught with several issues including sampling error, interobserver bias, and the fact that it is not measuring fibrosis as a dynamic process but instead describes architectural changes. Noninvasive fibrosis tests have been developed and used with various success over the last 20 years. Several surrogate composite scores have been devised that take into account easily accessible clinical lab values (e.g., the age of the patient, NAFLD fibrosis score, aspartate aminotransferase–to-platelet ratio index [APRI], and Fibrosis-4 index [FIB-4] score), whereas others reflect direct biomarkers of fibrosis (e.g., enhanced liver fibrosis test [ELF] score). Of these, only the NAFLD fibrosis score takes into consideration the presence of T2DM.

The other major group of surrogate fibrosis markers focuses on "products" of matrix turnover. In a simplified way, the extracellular matrix (ECM) of the liver can be divided into interstitial and basement membrane matrix. The main components of the interstitial matrix are fibrillar collagens I, III, V (produced by fibroblasts and myofibroblasts), glycosaminoglycans, and fibronectin, whereas the basement membrane matrix is composed primarily of collagen IV, laminins, and specific proteoglycans such as heparan sulfate. During fibrogenesis, there is an extensive remodeling of the ECM that is dynamic and involves both interstitial and basement membrane matrix. Proteolytic fragments of different collagen subtypes can be released during fibrogenesis and/or fibrolysis that can serve as direct, noninvasive markers (Fig. 1). These fragments can present neoepitopes that are differentially involved in the fibrosis process, such as by binding to integrins, thereby eliciting new signaling pathways. Most studies have focused on type III collagen, as this is abundant in the liver, whereas collagen I is also present in high quantities in the bone and skin. Pro-collagen III peptide neoepitope (PRO-C3), which reflects collagen formation, has been shown to correlate to fibrosis stage and disease activity in

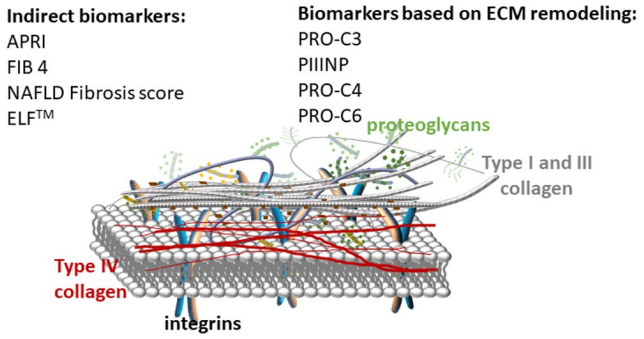

FIG. 1. Examples of serum biomarkers used to detect fibrosis in NASH trials. Abbreviations: PIIINP, N-terminal collagen III propeptide; PRO-C4, C-terminal pro-peptide of type IV collagen; and PRO-C6, C-terminal pro-peptide of type VI collagen.

NAFLD/NASH.[4,5] In addition to PRO-C3, other collagen fragments are being studied, including PRO-C5 (C-terminal pro-peptide of type V collagen) and PRO-C6 (C-terminal pro-peptide of type VI collagen). The ELF combining hyaluronic acid, N-terminal collagen III propeptide, and tissue inhibitor of MMP-1 was shown to have high sensitivity, but limited specificity, to exclude advanced fibrosis at low cutoffs in patients with NAFLD/NASH.[6] Because fibrogenesis may follow a different course depending on the patient population studied, data from the general population of NAFLD/NASH patients may not be directly extrapolated to patients with T2DM/NAFLD.[3]

In this paper, Ishiba et al.[7] describe type IV collagen 7S (COL4-7S) as a serum marker of fibrosis in patients with NAFLD and T2DM. In the 311 patients enrolled with biopsy-proven NAFLD, COL4-7S measurements resulted in a significantly higher area under the curve (AUROC), compared with the FIB-4 score, NAFLD fibrosis score, and APRI. In addition, the AUROC for COL4-7S was significantly higher compared with the other noninvasive tests in patients with diabetes/NAFLD, compared to those without diabetes.

COL4-7S is a fragment of type IV collagen that is the most abundant structural component of the basement membrane. Type IV collagen is very different from the fibrillar collagens, as it forms loose "networks" around the sinusoids. It is known to be significantly induced and remodeled during the fibrogenic process. Enzyme-linked immunosorbent assay–based immunoassays were developed to detect the COL4-7S,[8] and these have been used to study fibrogenic activity both in animal models[8] and in patients.[9,10]

Detecting liver fibrosis in patients with T2DM has been challenging, as serum biomarkers may not be specific to the liver and can reflect matrix remodeling, such as in the kidneys or other organs. In fact, PRO-C4 was studied in patients with diabetic nephropathy, and was linked to matrix remodeling at the glomerular or tubular basement membranes. In the present study, patients had biopsy-proven NAFLD, and COL4-7S levels correlated with the presence of advanced fibrosis, especially in patients with T2DM. Interestingly, COL4-7S levels also correlated with inflammation and hepatocyte ballooning, both in diabetic and nondiabetic patients.

The authors compared COL4-7S to the commonly used indirect noninvasive serum markers FIB-4 score, NAFLD fibrosis score, and APRI. However, none of these markers are based on ECM remodeling. In the future, it would be interesting to include PRO-C3 or ELF score in these studies, as these may reflect intrinsic liver matrix remodeling. Furthermore, combining several markers may increase the robustness of the data. Studies with omics-based, microbiota, or circulating extracellular vesicle–related biomarkers are emerging, and including these will enrich clinical studies.

Finally, further longitudinal multicentric trials are needed to study noninvasive fibrosis markers in the population with diabetes. Studying a population with higher likelihood of disease progression may increase the efficiency and power of clinical trials.

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