Is there any useful surrogate to evaluate metabolic fatty liver disease?

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Nonalcoholic fatty liver disease (NAFLD) is considered as the most common liver illness among developed countries.[1] Distinguishing the spectrum between NAFLD and nonalcoholic steatohepatitis (NASH), conditions which may lead to cirrhosis and liver failure, remains an important challenge for clinical practitioners.

Based on the most recent guideline, liver biopsy remained the most reliable approach for identifying steatohepatitis and fibrosis. Although liver biopsy is regarded as the gold standard of NAFLD assessment, it has been limited by its invasiveness and unsuitability for screening as well as follow-up purposes. Several potential biomarkers have been proposed, such as cytokeratin-18.[1] However, paired liver biopsy in human studies is often infeasible, and refused by the participants. To solve this problem, non-invasive and painless liver ultrasonography, fibroscan, and fatty liver index are applied before and after intervention. Fatty liver index, in particular, is a well-validated surrogate for liver biopsy, and highly feasible in clinical trials to assess NAFLD.[2,3] Other surrogates to appraise NAFLD, such as hepatic steatosis index and lipid accumulation product, may deserve wider use in daily clinical practice.

A recent prospective study brought the concept of circulating soluble interleukin (IL)-2 receptor alpha (IL-2RA, also known as CD25) to our attention.[4] IL-2RA have shown correlation in previous cross-sectional studies[5,6] and Kao et al[4] further demonstrated its ability to predict NASH among morbidly obese patients who received bariatric surgery. IL-2RA expression is absent on naive and memory T cells but is induced after antigen activation,[7] making it an optimal indicator of inflammatory cell activation. The concentration of soluble IL-2 receptor had proven to be elevated during acute viral hepatitis[8] and correlated with disease severity of chronic liver diseases.[9] Adaptive immune response participates in the pathogenesis of liver fibrosis, though the detailed mechanism remained unclear. CD4+ T cells may interact with fibroblasts and macrophages. CD8+ T cells increase hepatic stellate cell activation that perpetuates inflammation and fibrogenesis. IL-2 also enhances B cell survival and therefore leads to further secretion of profibrotic cytokines.[10]

Metabolic syndrome has a close relationship with NAFLD. The coexistence of diabetes was considered as a predictor of steatohepatitis progression and severity of liver fibrosis.[1] The release of proinflammatory cytokine IL-1β by pancreatic β cells and the reduced expression of IL-1 receptor antagonist in pancreatic islets were thought to be fundamental mechanisms of pancreatic β cells destruction. In a randomized controlled trial, recombinant human IL-1 receptor antagonist (anakinra) has shown effects on improving insulin secretion and reducing systemic inflammation among diabetic patients.[11] Moreover, diabetes remission has shown to be IL-1β dependent after bariatric surgery, especially in those receiving sleeve gastrectomy.[12]

The clinical applications of IL-2 pathway on liver disease were limited. The induction with IL-2 receptor antagonist has shown to be safe and effective in reducing acute rejection and decrease dosage of concomitant immunosuppressant use among post-liver transplant pediatric patients.[13] In addition, gut hormone, such as ghrelin,[14] has been demonstrated to exert antifibrotic effects in liver, and may represent a novel antifibrotic therapy for the relief of a hungry liver.[15] It is worth investigating more biomarkers, especially from the blood, as surrogates in the evaluation of NAFLD to replace paired liver biopsy and reduce the suffering of patients.

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