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Editorial

A crystal ball to forecast treatment responsiveness in nonalcoholic fatty liver disease

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Nonalcoholic fatty liver disease (NAFLD) has become the leading cause of chronic liver disease worldwide.[1] NAFLD comprises hepatic steatosis and nonalcoholic steatohepatitis (NASH), the latter of which irreversibly progresses to cirrhosis and hepatocellular carcinoma. Despite the gravity of NAFLD, efforts to develop effective pharmacological interventions have yet to achieve an approval of anti-NASH therapeutics.[2] Given that NAFLD is a hepatic manifestation of metabolic syndrome, the association of NAFLD with obesity and diabetes has been investigated to identify a novel therapeutic target for NAFLD. In this regard, it has been investigated whether different classes of anti-diabetic medications, such as thiazolidinediones, may also have an ability to ameliorate NAFLD.[3,4]

Dipeptidyl peptidase-4 (DPP-4) is an enzyme that catalyzes the cleavage of incretin hormones, such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide. As incretin hormones stimulate insulin release and inhibit glucagon release, DPP-4 inhibitors have attracted attention as an effective option for diabetes without the risk of hypoglycemia.[5] Given that diabetes is a risk factor for NAFLD, and the circulating DPP-4 levels are increased in patients with NAFLD,[6] it is reasonable to speculate that DPP-4 inhibitors might have a beneficial effect on NAFLD. Indeed, several papers have demonstrated that DPP-4 inhibitors attenuated steatosis in experimental NAFLD models.[7-9] However, underlying mechanisms by which DPP-4 inhibitors exert effects on NAFLD improvement remain obscure.

In this issue of *Clinical and Molecular Hepatology*, Oh et al.[10] conducted a study to identify the subgroup population among NAFLD patients who better respond to DPP-4 inhibitors and to verify the biomarkers that characterize the features of the responders. To first determine the benefit of DPP-4 inhibitors in the experimental NAFLD models, the authors performed a basket trial, and evogliptin was administered to different types of murine experimental NAFLD, including the high-fat diet (HFD)-induced, methionine choline-deficient diet (MCD)-induced, and Western-diet-induced models. Among the models chosen, evogliptin was shown to

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reduce the NAFLD activity score and fibrosis stage in HFD-fed mice.

Another important point addressed by Oh et al.[10] was that insulin-like growth factor-binding protein 1 (IGFBP1) could function as a biomarker to predict the efficacy of DPP-4 inhibitors. The authors demonstrated that hepatic expression of IGFBP1 prior to evogliptin treatment was higher in mice that better responded to evogliptin compared with non-responders. Intriguingly, the expression of IGFBP1 was lower in responders after the treatment with evogliptin, suggesting the correlation between the expression of IGFBP1 with the degree of NAFLD as well as diabetes. Indeed, IGFBP1 has been suggested to control blood glucose levels and maintain metabolic homeostasis.[11,12] Stanley et al.[13] reported that transcript levels of IGFBP1 were lower in individuals with higher steatosis grade and NAFLD activity scores. This is corroborated by the notions that IGFBP1 production is inhibited by insulin, and blood levels of IGFBP1 is inversely correlated with metabolic disease.[14] Given the aforementioned biological function of IGFBP1, it is presumed that IGFBP1 could work as a biomarker that predicts the efficacy of DPP-4 inhibitors against NAFLD.

Although Oh et al.[10] elegantly identified the probable biomarker for DPP-4 inhibitors, the current paper also revealed the limitation of the DPP-4-inhibiting approach for NASH treatment. Evogliptin failed to reduce the NAFLD activity score and fibrosis severity in the MCD-induced model and the Western-diet model, which better reflect NASH-associated liver injury, inflammation, and fibrosis than the HFD-induced model.[15] Indeed, 16-week HFD-feeding in mice promotes hepatic fat accumulation, but hardly induces the typical histological feature of NASH. Therefore, the current study provides an indirect evidence suggesting that evogliptin is not an effective option to pharmacologically treat the broad spectrum of NAFLD. In light of the correlation between the severity of metabolic liver diseases with that of diabetes, mild effect of evogliptin on NAFLD improvement could be in line with the lesser glucose-lowering ability of DPP-4 inhibitors than other classes of anti-diabetic medications, such as thiazolidinediones and GLP-1 receptor agonists.

In addition to evogliptin, there are several other DPP-4 inhibitors currently available in market for the treatment of diabetes, including sitagliptin, vildagliptin, linagliptin, and saxagliptin.[16] The study by Oh et al.[10] provided evidence that IGFBP1 is an evogliptin-specific biomarker; however, further studies are required to verify whether IGFBP1 can also function as the biomarker for other DPP-4 inhibitors in general. Successful completion of the study will lead to the identification of IGFBP1 as a class-specific biomarker for NAFLD treatment and accelerate the advent of the tailored application of DPP-4 inhibitors to medical treatments for NAFLD.

Authors' contribution

SH drafted the manuscript. WK revised and finalized the manuscript.

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Conflicts of Interest

The authors have no conflicts to disclose.

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Abbreviations:

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HFD, high-fat diet; IGFBP1, insulin-like growth factor-binding protein 1; MCD, methionine choline-deficient diet; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis

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