EnM
ENDOCRINOLOGY AND METABOLISM

Editorial

Endocrinol Metab 2022;37:858-860
https://doi.org/10.3803/EnM.2022.605
pISSN 2093-596X · eISSN 2093-5978

DPP-4 Inhibitor in Type 2 Diabetes Mellitus Patient with Non-Alcoholic Fatty Liver Disease: Achieving Two Goals at Once?

Ji Cheol Bae

Department of Internal Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Korea

The clinical impact of non-alcoholic fatty liver disease (NAFLD) is not confined to liver-related morbidity and mortality, but also extends to serious adverse extra-hepatic outcomes, increasing the risk of chronic kidney disease and cardiovascular disease [1]. Over the last decades, it has been shown that these risks are higher in patients with fatty liver disease associated with metabolic dysfunction [2]. For this reason, the term "metabolic (dysfunction) associated fatty liver disease (MAFLD)" has recently been proposed as a replacement for the term "NAFLD" [3]. The definition of MAFLD emphasizes the importance of overweight/obesity, type 2 diabetes mellitus, insulin resistance, and other metabolic risk abnormalities that fuel the risk of liver disease progression and the development of serious adverse extra-hepatic outcomes [2,3].

Advanced liver fibrosis is more common in patients with type 2 diabetes mellitus (T2DM) [4]. T2DM is closely associated with disease progression to steatohepatitis and advanced fibrosis in patients with fatty liver disease [5]. Patients with hepatic steatosis have a higher risk of fibrosis when insulin resistance is present [6]. *In vitro*, insulin and glucose have been shown to stimulate hepatic stellate cells (HSCs) and increase the expression of connective tissue growth factor [7]. These findings collectively indicate that T2DM itself is an important risk factor for the progression of fatty liver disease; therefore, antidiabetic agents are being investigated as possible treatments for NAFLD.

There is accumulating evidence that the dipeptidyl peptidase 4 (DPP-4) enzyme, which is highly expressed in the liver, is involved in the development of NAFLD [8]. The expression and serum levels of DPP-4 are elevated in steatohepatitis patients, and also correlated with hepatic steatosis, fibrosis, and hepatocyte apoptosis [9]. Elevated hepatic DPP-4 activity also has been shown to promote insulin resistance, and genetic ablation of *Dpp-4* in mice results in improved insulin sensitivity and liver function [8,10]. DPP-4 reduces the level of active glucagon-like peptide 1 (GLP-1), which is associated with the development of NAFLD [8]. These findings support the hypothesis that DPP-4 inhibitors may improve the histological features of steatohepatitis and fibrosis and prevent disease progression. In the current issue of *Endocrinology and Metabolism*, Nguyen et al. [11] report the results of various experiments, in which they aimed to investigate the effects and mechanism of the DPP-4 inhibitor gemigliptin on alleviating the progression of liver fibrosis. Immortalized human HSCs (LX-2 cells) were treated with succinate and co-treated with gemigliptin. Succinate activated HSCs and increased the expression of fibrogenesis markers and cell proliferation, but these changes were attenuated by gemi-

Received: 11 December 2022, **Accepted:** 16 December 2022

Corresponding author: Ji Cheol Bae
Division of Endocrinology and Metabolism, Department of Internal Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, 158 Paryong-ro, Masanhoewon-gu, Changwon 51353, Korea
Tel: +82-55-233-5100, **E-mail:** drkuri10@skku.edu

gliptin. Gemigliptin also reduced the succinate-induced production of mitochondrial reactive oxygen species (ROS), intracellular ROS, and mitochondrial fission in HSCs. In addition, in a mouse model of steatohepatitis-induced liver fibrosis, gemigliptin alleviated both liver fibrosis and mitochondrial dysfunction. These findings suggest that the DPP-4 inhibitor gemigliptin protects against HSC activation and liver fibrosis by alleviating mitochondrial dysfunction and ROS production. The results of this study are encouraging, as it provides new insights regarding the protective effects of gemigliptin against liver fibrosis.

DPP-4 inhibitors are incretin-based antidiabetic agents that lower blood glucose levels by blocking the breakdown of GLP-1 and gastric inhibitory polypeptide, thereby increasing active hormone levels [12]. In this study, however, the *in vitro* effect of gemigliptin on preventing HSC activation and liver fibrosis resulted from an incretin-independent effect. In addition to its role in the degradation of incretin, DPP-4 has been reported to be directly involved in hepatic inflammation and fibrosis [8,9]. Elevated expression of DPP-4 in the liver promotes insulin resistance [8]. In an insulin-resistant state, ROS production is increased, which promotes HSC activation and fibrosis progression [13]. The study by Nguyen et al. [11] revealed that gemigliptin reduced the succinate-induced production of mitochondrial and intracellular ROS. In this respect, the lack of testing DPP-4 activity in this experiment is a limitation of this study because it is uncertain whether the effect of gemigliptin resulted from a reduction in DPP-4 activity. Likewise, it is unclear whether the impact of gemigliptin in the diet-induced steatohepatitis mouse model resulted from an incretin-dependent or incretin-independent effect. In my opinion, the effect of gemigliptin on hepatic fibrosis should have been explained in relation to DPP-4 activity.

Despite growing *in vivo* and *in vitro* evidence suggesting the potential of DPP-4 inhibitors for NAFLD treatment, there have been only a few clinical trials demonstrating the significant efficacy of DPP-4 inhibitors in patients with NAFLD, and DPP-4 inhibitors are not yet generally recommended for the treatment of NAFLD. This raises an important question: what are the clinical implications of these experimental studies? It is through these results that we obtain an additional rationale for the use of DPP-4 inhibitors in patients with diabetes who have NAFLD. This is because there is currently no approved drug for its treatment.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Ji Cheol Bae *https://orcid.org/0000-0002-4763-5797*

REFERENCES

1. Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol 2015;62(1 Suppl):S47-64.
2. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020;73:202-9.
3. Eslam M, Sanyal AJ, George J; International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020;158:1999-2014.e1.
4. Lomonaco R, Godinez Leiva E, Bril F, Shrestha S, Mansour L, Budd J, et al. Advanced liver fibrosis is common in patients with type 2 diabetes followed in the outpatient setting: the need for systematic screening. Diabetes Care 2021;44:399-406.
5. Barb D, Repetto EM, Stokes ME, Shankar SS, Cusi K. Type 2 diabetes mellitus increases the risk of hepatic fibrosis in individuals with obesity and nonalcoholic fatty liver disease. Obesity (Silver Spring) 2021;29:1950-60.
6. Bae JC, Beste LA, Utzschneider KM. The impact of insulin resistance on hepatic fibrosis among united states adults with non-alcoholic fatty liver disease: NHANES 2017 to 2018. Endocrinol Metab (Seoul) 2022;37:455-65.
7. Paradis V, Perlemuter G, Bonvoust F, Dargere D, Parfait B, Vidaud M, et al. High glucose and hyperinsulinemia stimulate connective tissue growth factor expression: a potential mechanism involved in progression to fibrosis in nonalcoholic steatohepatitis. Hepatology 2001;34(4 Pt 1):738-44.
8. Baumeier C, Schluter L, Saussenthaler S, Laeger T, Rodiger M, Alaze SA, et al. Elevated hepatic DPP4 activity promotes insulin resistance and non-alcoholic fatty liver disease. Mol Metab 2017;6:1254-63.
9. Itou M, Kawaguchi T, Taniguchi E, Sata M. Dipeptidyl peptidase-4: a key player in chronic liver disease. World J Gastroenterol 2013;19:2298-306.
10. Miyazaki M, Kato M, Tanaka K, Tanaka M, Kohjima M, Nakamura K, et al. Increased hepatic expression of dipeptidyl peptidase-4 in non-alcoholic fatty liver disease and its association with insulin resistance and glucose metabolism. Mol Med Rep 2012;5:729-33.

11. Nguyen G, Park SY, Do DV, Choi DH, Cho EH. Gemigliptin alleviates succinate-induced hepatic stellate cell activation by ameliorating mitochondrial dysfunction. Endocrinol Metab (Seoul) 2022;37:918-28.
12. Kim KS, Lee BW. Beneficial effect of anti-diabetic drugs for nonalcoholic fatty liver disease. Clin Mol Hepatol 2020;26:430-43.
13. Chiang DJ, Pritchard MT, Nagy LE. Obesity, diabetes mellitus, and liver fibrosis. Am J Physiol Gastrointest Liver Physiol 2011;300:G697-702.