Combination of synbiotic and sitagliptin in nonalcoholic fatty liver disease: Is it better than sitagliptin alone?

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Non-alcoholic fatty liver disease (NAFLD) has a wide spectrum ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis. NAFLD is a liver manifestation of metabolic syndrome. The prevalence of metabolic syndrome in NAFLD patients is about 40%. Metabolic comorbidities such as central obesity, dyslipidemia, hypertriglyceridemia, hypertension, and type 2 diabetes are associated with NAFLD. With increasing prevalence of obesity and metabolic syndrome, NAFLD has become the major cause of liver disease worldwide, with prevalence of 20% to 30%. The rising global burden of NAFLD is a serious health problem because NAFLD may progress to liver failure, cirrhosis, and hepatocellular carcinoma.

Various treatment strategies for NAFLD/NASH have been investigated actively. It is known that insulin resistance is a major mechanism in the progression of NAFLD. Thus, insulin sensitizers for NAFLD has gathered much attention. For example, thiazolidinediones can improve steatosis and blood aminotransferase levels in many randomized controlled trials, although they could not improve the extent of fibrosis. Recently, new anti-diabetic drugs that can influence glucagon-like peptide-1 (GLP-1) pathway have been developed. They are expected to have the capacity to attenuate hepatic steatosis. Armstrong et al. have reported that liraglutide, a GLP-1 analogue, can lead to histological resolution of NASH. Effects of dipeptidyl peptidase-4 (DPP-4) inhibitors, another category of anti-diabetic drugs related to GLP-1 pathway, on NAFLD have also been studied. Early trials have reported that DDP-4 inhibitors are associated with significant decrease of liver enzyme levels in patients with type 2 diabetes and NAFLD. However, recent randomized controlled trials have shown that DDP-4 inhibitors could not improve histologic features of NASH or biochemical hepatic parameters. Meanwhile, modulation of gut microbiota using probiotic and/or synbiotic has been suggested as another treatment option for NAFLD patients. Gut microbiota may participate in NAFLD progression through obesity promotion, endogenous ethanol production, and generation of inflammatory response. A meta-analysis has reported that probiotics could improve liver enzyme, total cholesterol, and insulin resistance. Another randomized controlled pilot study has also suggested that synbiotic supplementation has beneficial effect on...
liver enzyme and insulin resistance biomarker.\textsuperscript{15} However, probiotic and synbiotic therapies have limitation in that clinical studies using human subjects are sparse and data regarding histologic benefits are lacking.

In the current issue, Sayari et al.\textsuperscript{16} conducted a randomized, double-blind, controlled trial to evaluate the effect of a combination of sitagliptin, an anti-diabetic drug by inhibiting DPP-4, with synbiotic compared to sitagliptin alone in NAFLD patients with obesity (body mass index 25 or more) and impaired fasting blood glucose. Sixty-eight patients were assigned to the sitagliptin plus synbiotic group and seventy patients were assigned to the sitagliptin alone group. Their study showed that the combination of sitagliptin with synbiotic improved aspartate aminotransferase (P=0.018) and metabolic parameters, including fasting blood glucose (P<0.001), cholesterol (P<0.029), and low-density lipoprotein (P<0.001) levels more than sitagliptin therapy alone. The study of Sayari et al. revealed significant effects of synbiotic therapy on NAFLD patients through a randomized placebo-controlled trial.\textsuperscript{16} Although gut microbiota-related mechanisms involved in the development of NAFLD have been elucidated and many experimental studies have been reported, clinical studies are insufficient. Thus, their study adds to accumulating therapeutic evidence of gut microbiota-targeted therapy.

However, their study has severe limitations. First, it did not perform liver biopsy before or after treatment. Besides, image assessments such as ultrasonography or magnetic resonance imaging were not performed for the assessment of treatment response. Thus, their trial could not provide any information regarding improvement in hepatic fat change, inflammation, or fibrosis. Instead, their trial demonstrated that serum aspartate aminotransferase level, but not serum alanine aminotransferase level, was significantly improved compared to that in the placebo group. However, serum alanine aminotransferase level has been shown to be more associated with liver damage in NAFLD than serum aspartate aminotransferase level. Thus, efficacy of such therapy for liver damage remains unclear. Second, their study compared effects of combination therapy with synbiotic plus sitagliptin vs. sitagliptin monotherapy. However, there was no comparison with synbiotic monotherapy or non-treatment placebo. Thus, separate effects of each therapy could not be analyzed completely. To evaluate the efficacy of synbiotic alone or sitagliptin alone, comparing each therapy separately might be helpful. Third, their follow-up period was relatively short. Thus, further studies with longer follow-up might be needed to evaluate the long-term effect of synbiotic plus sitagliptin therapy. Lastly, measurement of additional parameters of insulin resistance such as homeostasis model assessment of insulin resistance might be useful for evaluating treatment response because pathogenesis of NAFLD is strongly associated with insulin resistance.

Pharmacological therapies on NAFLD are still in their infancy. Their study suggests that synbiotic might be beneficial for NAFLD, especially for those with metabolic comorbidities. Further studies with longer treatment duration using larger scale of participants are needed to verify the biochemical and histological efficacy of synbiotic therapy on NAFLD patients.

Conflicts of Interest
The author has no conflicts to disclose.

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