

Relieving hepatic steatosis: Another benefit of dipeptidyl peptidase-4 (DPP4) inhibitors

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Hepatic steatosis is strongly associated with type 2 diabetes (T2DM), both of which are common disorders resulting from obesity [1]. Compared to the general population, there is a higher risk for chronic liver disease and cirrhosis, arising from hepatic steatosis, in diabetic persons [2.3-fold increase of mortality in older onset (diagnosed after age 30) and 4.8-fold increase of mortality in younger onset (diagnosed before age 30)] [2]. Therefore, hepatic steatosis is a key issue in the treatment of T2DM. Furthermore in recent studies, dipeptidyl peptidase-4 (DPP4) inhibition has been suggested to ameliorate hepatic steatosis [3–5].

Oral delivery of glucose induces a greater insulin response than intravenous delivery, a phenomenon called “incretin effect”. This effect is mediated by so called “incretin hormones”, including glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP), two small peptides produced by enteroendocrine L cells and K cells, respectively [6]. One primary role of incretins is to promote postprandial insulin secretion. They increase insulin biosynthesis through a PDX-1-dependent pathway [7]. These incretins can be rapidly inactivated by DPP4 [8]. DPP4 inhibitors are a novel class of oral anti-diabetic drugs with several available in the market for the treatment of diabetes: sitagliptin (Januvia, marketed by Merck & Co., FDA approved 2006), vildagliptin (Galvus, marketed by Novartis, European Medicines Agency approved 2007), Saxagliptin (Onglyza,

marketed by Bristol-Myers Squibb and AstraZeneca, FDA approved 2009), linagliptin (Tradjenta, marketed by Eli Lilly Co and Boehringer Ingelheim), and alogliptin (Nesina, marketed by Takeda Pharmaceutical Co., FDA approved 2013). There are also two DPP4 inhibitors that were approved in Japan in 2012: anagliptin (trade name Suiny) and teneligliptin (trade name Tenelia). DPP4 inhibitors have shown mild effect on glycemia lowering, with a 0.4–0.8% lowering of HbA1c [9–11]. However, they are weight neutral, easy to use (oral delivery), and well-tolerated (especially with regards to hypoglycemia) and thus widely utilized in clinic. Both clinical trials and experimental evidence indicate DPP4 inhibitors are safe from a cardiovascular standpoint [12–15].

In a recent paper published in the June 2015 issue of *Diabetes*, DPP4 inhibition by MK0626, an analog of des-fluoro-sitagliptin (Merck Research Laboratories, West Point, PA), prevented western diet-induced hepatic steatosis and insulin resistance through hepatic lipid remodeling and modulation of hepatic mitochondrial function [3]. We showed that DPP4 inhibition improved liver insulin sensitivity and ameliorated hepatic diacylglycerol accumulation, independent of changes in body weight or adiposity. Triglyceride accumulation in the liver is a major cause of hepatic steatosis and hepatic triglyceride export, via very low density lipoprotein (VLDL), is an important mechanism utilized by the liver to eliminate excessive triglycerides [16]. Western diet resulted in a dramatic reduction in liver triglyceride secretion and MK0626 was shown to partially reverse this effect. VLDL export of triglyceride requires microsomal triglyceride transfer protein (MTTP) and Apolipoprotein B (apoB), both of which increased in MK0626-treated western diet-fed mice. We showed that DPP4 inhibition also reduced hepatic diacylglycerol and triglyceride accumulation by enhancing mitochondrial carbohydrate utilization. Hepatic mitochondrial function was significantly improved in MK0626-treated mice as evidenced by increased pyruvate dehydrogenase (PDH) activity and tricarboxylic acid (TCA) cycle flux. Western diet-induced reduction of sirtuin-1 (Sirt1), an important regulator of mitochondrial function [17], was completely prevented by DPP4 inhibition. Consistent with this,

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Sirt1-regulated genes (including PGC-1 α , CPT-1, TFAM and PPAR- α) increased in MKO626-treated mice. DPP4 inhibition also decreased incomplete palmitate oxidation, a marker of hepatic insulin resistance and mitochondrial dysfunction [18], in western diet-fed mice.

In summary, there are several recent studies suggesting a role of DPP4 inhibitors in improving diabetes-associated fatty liver disease. Both hepatic lipid remodeling and mitochondrial function modulation may perhaps be involved in this process. However, further studies are required to confirm the relieving effect of DPP4 on fatty liver disease. Effect of other DPP4 inhibitors need to be further examined. Although the improving effect of vildagliptin on hepatic steatosis has been observed in a human study with a total of 44 T2DM patients, this effect in humans needs to be confirmed in future studies with a larger sample size.

Keywords: Hepatic Steatosis, Dipeptidyl peptidase-4 inhibitors, DPP4

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Conflict of Interest

Authors declare no conflict of interest.

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