Case Report

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# Improvement of liver function and glycemic control with Combination of DPP-4 inhibitors and GLP-1 agonists in type II diabetes mellitus patients with non-alcoholic steatohepatitis

## Abstract

Non-alcoholic steatohepatitis (NASH), the aggressive form of non-alcoholic fatty liver disease (NAFLD), can lead to cirrhosis and hepatocellular carcinoma if left without appropriate management. It has been contributing to increasingly devastating mortality and morbidity in a substantial proportion of the human population. Studies on novel therapeutic agents targeting various molecular structures will open up new horizons for doctors dealing with NASH. Of these agents, the combined use of glucagon-like peptide 1 receptor agonist (GLP-1 receptor agonist) and dipeptidyl peptidase-4 inhibitor (DDP-4 inhibitor) showed promising clinical benefits in diabetic patients with NASH in our study. Our study involves a case of a 23-year-old female who presented with a new-onset type 2 DM, poor glycemic control, and NASH. We found improvement in liver function while getting optimal glycemic control without adverse clinical outcomes. We suggest that DDP-4 inhibitors and GLP-1 receptor agonists could be used together in diabetic patients with NASH while bringing this finding to your attention to have further studies for the advancement in medicine.

**Keywords:** non-alcoholic steatohepatitis, type II diabetes mellitus, DDP-4 inhibitor, GLP-1 receptor agonist, glycemic control, diabetes complication, fatty liver

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**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; DKA, diabetic ketoacidosis; NASH, non-alcoholic steatohepatitis; DDP-4 inhibitor, dipeptidyl peptidase-4 inhibitor; GLP-1 receptor agonist, glucagon-like peptide-1 receptor agonist; DM, diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; NAFL, non-alcoholic fatty liver; HbA1c, hemoglobin A1C

## Introduction

The prevalence of non-alcoholic fatty liver disease (NAFLD) in type 2 diabetes mellitus has been estimated to be around 60%.[1] Nonalcoholic fatty liver disease (NAFLD) encompasses a wide spectrum of clinical and histopathological conditions, ranging from simple steatosis [*i.e.*, nonalcoholic fatty liver (NAFL)] to liver injury [*i.e.*, nonalcoholic steatohepatitis (NASH), the aggressive form of NAFLD that can lead to cirrhosis and hepatocellular carcinoma].[2,3] The pathophysiology of NAFLD is not yet fully elucidated; however, it is widely believed that insulin resistance (IR) may play a critical role in the pathogenesis of the disease.[4] For type 2 DM patients with NAFLD, it is important to manage insulin resistance to prevent the progression of NAFL to NASH. Glucagon-like peptide-1 (GLP-1) agonists represent a novel class of antidiabetic drugs. They mimic the action of endogenous GLP-1, a gastrointestinal hormone of the incretin class of proteins that is secreted from Langerhans cells in response to nutrient ingestion.[5] This hormone has several metabolic effects, including the stimulation of glucose-dependent insulin secretion, inhibition of glucagon release, induction of pancreatic β-cell proliferation, and delay of gastric emptying.[6] While native GLP-1 is rapidly degraded by the enzyme dipeptidy1 peptidase-4 (otherwise known as DPP-4), GLP-1 agonists have increased resistance to DPP-4, thus prolonging the half-life time.[7] DDP-4 inhibitors inhibit the actions of enzyme DDP-4. GLP-1 agonists are Albiglutide, Dulaglutide, Exenatide, Liraglutide, Lixisenatide, and Semaglutide. DDP-4 inhibitors are Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, and Alogliptin. Here, we used these two agents: GLP-1 agonist and DPP-4 inhibitor together, and got optimal glycemic control and improvement in liver function.

## Case report

A 23-year old moderately overweight woman presented with new-onset type 2 diabetes mellitus, which initially manifested as gestational diabetes mellitus. She had been taking metformin ER 1000mg for her glycemic control. She has a family history of DM type 2 and hypertension. She had no known history of chronic alcohol abuse. Physical examination showed overweight and mild hepatomegaly. Ultrasound abdomen revealed a fatty liver. She had no history of viral hepatitis. She was tested negative for biliary cirrhosis and autoimmune hepatitis (negative antimitochondrial antibodies and anti-smooth muscle antibody). She presented with a finger-stick glucose of 552mg/dl and hemoglobin A1C(HbA1c) level of 14.9%, which indicated a poorly controlled type 2 DM. Her liver function tests showed alkaline phosphatase: 203U/l (high), AST 146 U/l (high) and ALT: 159 U/l (high). Her urine albumin/creatinine ratio was high

at 73.2 mg/g**.** C peptide level was normal. Otherwise, her lab findings were insignificant. Initially, the patient was hospitalized for a high blood sugar of 552mg % and treated with insulin coverage. DKA was excluded from negative acetones and normal acid-base balance. She was discharged home with long-acting insulin glargine.

On the follow-up visit, the patient refused to continue insulin therapy, and therefore we started DPP-4 inhibitors in addition to metformin. However, her type 2 DM was still poorly controlled. Therefore a GLP-1 agonist was added to her regimen for better glycemic control and weight loss. Three months after the combination treatment of DPP-4 inhibitor and GLP-1 agonist, her HbA1c level returned to normal range along with her normal liver function test and normal renal function.

During her subsequent visits, we observed that there had been a significant improvement in her HbA1c and liver function tests (Table 1). This indicated that we successfully controlled her type 2 DM and managed NASH by administering the combination of metformin, DPP-4 inhibitors, and GLP-1 agonists.

**Table 1** Hemoglobin A1c and liver function tests

| Date | 10/2018 | 11/2018 | 12/2018 | 02/2019 |
|---|---|---|---|---|
| *Diabetic treatment | Metformin Oral 1000mg | Exenatide Subcutaneous 2mg Weekly<br>Alogliptin Oral 25mg OD**<br>Metformin Oral 500mg OD** | Dulaglutide Subcutaneous 1.5mg Weekly<br>Sitagliptin Oral 50mg OD**<br>Metformin Oral 1000mg BID*** | Dulaglutide Subcutaneous 1.5mg Weekly<br>Sitagliptin Oral 25mg OD**<br>Metformin Oral 1000mg OD** |
| HbA1c (%) | 14.9 | 12 | Nil | 6 |
| Alkaline Phosphatase (U/L) | 203 | 137 | 109 | 102 |
| AST (U/L) | 146 | 92 | 70 | 41 |
| ALT (U/L) | 159 | 66 | 55 | 54 |

*Treatment was started at the start of the particular month and the test results were received at the end of this particular month. ** 24hourly, *** 12hourly

## Discussion

All patients with NAFLD might not have type 2 DM. It is estimated that over half of patients with type 2 DM have NAFLD. Since the liver is the major organ in glucose metabolism, it is important to have a normal liver function and architecture in patients with DM. In this case, we added GLP-1 agonist and DDP-4 inhibitor to her metformin treatment based on her glycemic control, body weight, and her choice. Following modifications in her management, her HbA1c level dropped from 14.9 to 6 over 4 months. Incidentally we found that her liver function test went back to normal. The benefit of using GLP-1 agonists together with the DDP-4 inhibitors is that it gave significant glycemic control and improved liver function in our case while we closely monitor her renal function.

## Conclusion

GLP-1 agonists act on GLP-1 receptors and stimulate glucose-dependent insulin secretion, inhibit glucagon release, induce pancreatic β-cell proliferation, and delay gastric emptying. But it cannot be destroyed by DDP-4. The theory behind utilizing a GLP-1 agonist with a DPP-4 inhibitor is that the combo will support the viability by giving the additional incretins (via the GLP-1 agonist) and enhance the impact of the endogenous in cretins (using the DPP-4 inhibitor).[8] To date, no drug treatment has been approved by Food and Drug Administration for NAFLD. In summary, our case has shown significant improvements in HbA1c level and liver function test. Thus, the synergistic effect of DPP-4 inhibitors and GLP-1 receptor agonists has a potential role in treating uncontrolled type 2 DM patients with NASH. Further studies are needed to validate those clinical findings.

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## Conflicts of interest

Author declares that there are no conflicts of interest.

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