Acute Liver Injury Induced by Sitagliptin: Report of Two Cases and Review of Literature

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Abstract
We present two cases of acute liver injury associated with sitagliptin. The first case was a 58-year-old male with a history of poorly controlled type 2 diabetes mellitus and hyperlipidemia. Sitagliptin was added for better control of diabetes. After initiation of sitagliptin, the patient’s serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels increased gradually over a period of six months. The second case was a 44-year-old female with type 2 diabetes mellitus, and she experienced a more than ten-fold elevation in ALT and AST levels after starting sitagliptin therapy. Both patients did not have any history of alcohol abuse, acetaminophen use, or chronic liver disease. In the literature review, the reported magnitude of liver enzyme derangement with sitagliptin is generally mild and transient (two-fold upper limit of normal). We believed that the acute derangement of ALT and AST in our patients was due to sitagliptin since the ALT and AST normalized shortly after sitagliptin was discontinued and remained at baseline after resuming all other medications. Further research is needed to understand the mechanism of dipeptidyl peptidase 4 (DPP-4) inhibitors associated liver injury.

Categories: Endocrinology/Diabetes/Metabolism, Internal Medicine
Keywords: sitagliptin, drug-induced liver injury, side effects, type 2 diabetes mellitus

Introduction
Diabetes mellitus is either type 1, caused by inherited and/or acquired deficiency in the production of insulin, or type 2, caused by a resistance to the effectiveness of insulin. Sitagliptin is a dipeptidyl-peptidase-4 (DPP-4) inhibitor, an oral antihyperglycemic agent. It blocks the degradation of incretin and enhances incretin levels, which stimulate insulin secretion and decreases glucagon production. Sitagliptin is effective in lowering glycosylated hemoglobin (Hb A1C) and improves fasting and postprandial glucose levels [1]. DPP-4 inhibitors have a favorable safety profile in clinical trials. Further investigation is needed as rare side effects arise in post-marketing surveillance. Some important but rare side effects of DPP-4 inhibitors are a potential risk for pancreatitis and thyroid cancer [2]. In clinical practice, a drug-induced liver injury is not a common side effect in patients taking DPP-4 inhibitors. We reported two cases of drug-induced hepatic injury caused by sitagliptin.

Case Presentation
The first case was a 58-year-old male with poorly controlled type 2 diabetes mellitus and hyperlipidemia who experienced a six-fold increase in his serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels from baseline. The patient had been taking...
pravastatin and ezetimibe for a few years for hyperlipidemia. Sitagliptin was recently added to
the patient’s medical regimen for better control of his diabetes. After initiating sitagliptin, the
patient’s ALT and AST increased gradually over a period of six months. Work up was done to
find the possible cause of the abnormal liver function tests (LFTs). Hepatitis serologies were
negative. An abdominal sonogram was also negative for gallstones. In the absence of any
pathological cause, a diagnosis of drug-induced liver injury was made. All medications were
discontinued and LFTs were done on regular follow-up visits. After discontinuing sitagliptin,
pravastatin, and ezetimibe, the patient’s ALT and AST returned to baseline levels. Resumption
of pravastatin and ezetimibe was not associated with the elevation in ALT and AST levels.
When we rechallenged the patient with sitagliptin, we observed a five-fold increase in the
levels of serum ALT and AST from the baseline that became normal after discontinuation of
sitagliptin. The second case was a 44-year-old female with type 2 diabetes who experienced a
more than ten-fold elevation in ALT and AST levels after six months of sitagliptin therapy.
Further workup revealed a negative hepatitis B-surface antigen with a normal liver sonogram.
The patient’s ALT and AST levels returned to normal after discontinuing sitagliptin,
pioglitazone, and rosuvastatin. Resumption of pioglitazone and rosuvastatin was not associated
with elevation in ALT and AST levels. The patient refused the rechallenge with sitagliptin.

Discussion
The efficacy and safety of sitagliptin have been well documented in clinical trials of patients
with type 2 diabetes, either as a monotherapy or in combination with other oral hypoglycemic
agents. A review of the literature identified only two case reports of elevated hepatic
transaminases associated with sitagliptin [3-4]. However, clinical trials of sitagliptin
monotherapy or in combination with other oral hypoglycemic agents have demonstrated no
change or a slight decrease in AST or ALT levels from the baseline with sitagliptin treatment [5].

Raz et al. studied the safety and efficacy of 100 mg and 200 mg doses of sitagliptin as
monotherapy versus placebo and found no meaningful change from the baseline in AST or ALT
levels between the treatment groups [5]. Nauck et al. conducted a study to compare the effect of
sitagliptin 100 mg and metformin, or glipizide and metformin. The researchers found a slight
mean decrease in ALT in the sitagliptin group versus a slight increase in ALT in the glipizide
group, which was not statistically significant [6].

We present two cases of acute liver injury caused by sitagliptin. Other causes of elevated liver
enzymes, such as acute viral hepatitis, nonalcoholic steatohepatitis, autoimmune hepatitis, or
the consumption of alcohol and hepatotoxic drugs were ruled out. Also important were the
observed disappearance of symptoms and the return of elevated liver enzymes to baseline after
discontinuation of the sitagliptin. DPP-4 is expressed in the liver and, in fact, DPP-4 has been
implicated in the pathogenesis of several chronic liver diseases [7]. For these reasons, DPP-4
inhibition has been proposed as beneficial in chronic liver diseases [8]. Further research is
needed to explore the possible underlying mechanism of DPP-4 inhibitors associated liver
injury. While reviewing the literature, we also found one case report of potential linagliptin and
vildaglptin induced liver toxicity [9-10]. This suggests that liver toxicity might be a class effect
of DPP-4 inhibitors. Discontinuation of the offending agent will bring about a dramatic
improvement in symptoms and prevent adverse outcomes [11].

Conclusions
Drugs are an important cause of acute liver injury. Physicians should take a detailed and
thorough history of drug intake in any patient presenting with abnormal liver function tests.
When a diabetic patient using sitagliptin presents with unexplained elevated liver enzymes,
then drug-induced hepatic injury should be suspected. We recommend that all patients
receiving sitagliptin should have their liver function assessed periodically. Sitagliptin

administration should be stopped immediately at the onset of abnormal liver function if no other obvious cause for the abnormal liver function is present.

**Additional Information**

**Disclosures**

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**References**