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CASE REPORT

# Statin-induced autoimmune hepatitis in patients with type 1 diabetes: A report of two cases and literature review

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## ABSTRACT

Statins are widely used medications for the treatment of hypercholesterolemia, as well as prevention of cardiovascular disease. We report two patients with type 1 diabetes who developed autoimmune hepatitis after the administration of statin. The first patient developed the marked elevation of liver enzymes 6 months into atorvastatin therapy. The second patient developed liver dysfunction 8 months after the initiation of rosuvastatin therapy. Liver biopsies in both patients showed either portal, interface and lobular hepatitis or a piece-meal necrosis with lymphocytes and plasma cell infiltration that were compatible with autoimmune hepatitis. Then, both patients were started on prednisolone, to which they responded well. Liver biopsy is to be considered for type 1 diabetes patients if there is no improvement of liver dysfunction after discontinuation of statins.

## INTRODUCTION

Statins are a widely prescribed class of medications for treating hypercholesterolemia and preventing cardiovascular disease. Furthermore, it is known that statins have immunomodulatory effects by the regulation of adhesion molecules, antigen-presenting cells and T cells[1]. Extensive investigation into these properties and their preventative effects on a variety of autoimmune diseases have been reported in numerous animal models, and more specifically, their efficacy has been well documented in, but not limited to, experimental autoimmune encephalomyelitis, collagen-induced arthritis and multiple low-dose streptozotocin-induced type 1 diabetes[2]. Although the research on statins is considerable, to date, there have been few reports associating statins with the development of autoimmune disorders. To the best of our knowledge, this article is the first to report patients with type 1 diabetes who developed autoimmune hepatitis (AIH) after the administration of statin.

## CASE REPORT

The first case was a 46-year-old Japanese male with type 1 diabetes. At 45 years-of-age, he developed diabetic ketoacidosis and was diagnosed with type 1 diabetes based on the presence of autoantibodies to glutamic acid decarboxylase, insulinoma-associated antigen-2 and insulin. One month later, the patient was started on atorvastatin therapy (10 mg/day) to treat hypercholesterolemia. Although his serum liver enzymes had been within the normal range, 6 months into the atorvastatin therapy, he developed markedly elevated levels of serum alanine aminotransferase (1,632 U/L) and aspartate aminotransferase (860 U/L). Even after discontinuing the statin therapy, the elevated levels of alanine aminotransferase and aspartate aminotransferase, and total bilirubin (5.1 mg/dL) remained persistent for 13 weeks. The viral hepatitis serologies, anti-mitochondrial antibody and anti-liver kidney-microsomal-1 antibody were negative, but an anti-nuclear antibody was positive (1:80). The patient's immunoglobulin G level was within the normal range (1,495 mg/dL). An abdominal ultrasound showed increased echogenicity of the liver. A subsequent liver biopsy showed lobular, portal and interface hepatitis with lymphocytes and plasma cell infiltration (Figure 1a). Using the revised scoring system of the International Autoimmune Hepatitis Group he scored 18 points (Table S1)[3]. Based on these findings, he was diagnosed with AIH and was started on prednisolone 50 mg/day. Four months later, tests showed that his liver function had normalized, allowing for the dose of

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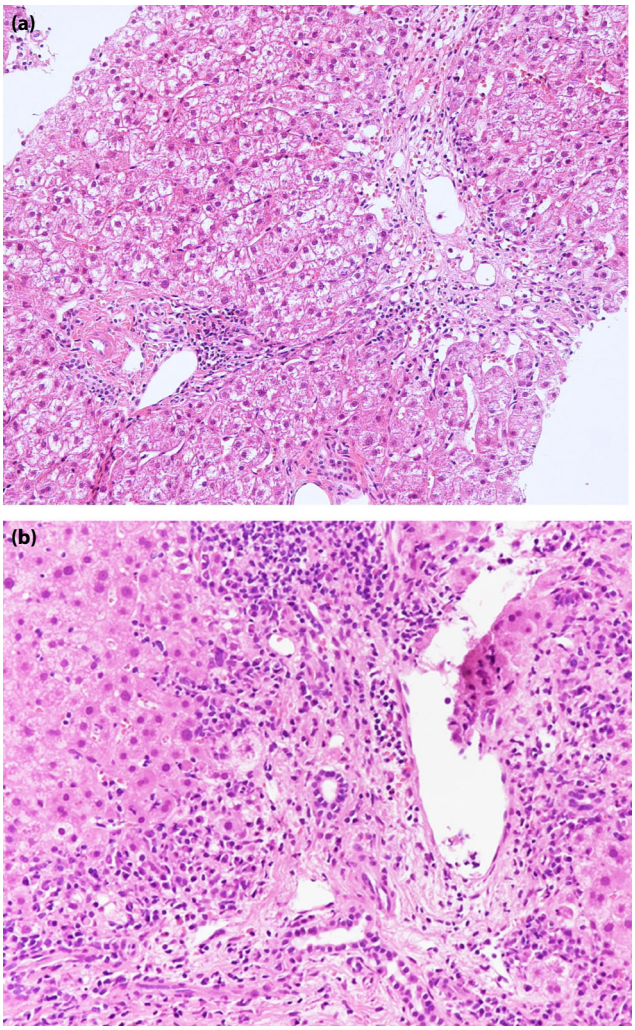


**Figure 1** | Photomicrographs of liver biopsy of (a) patient 1 and (b) patient 2 (hematoxylin–eosin staining; magnification: [a] ×100 and [b] ×200).

prednisolone to be tapered and finally maintained at 1 mg/day. HLA-DRB1-DQB1 typing showed the patient to be DRB1*09:01-DQB1*03:03 homozygote.

Our second case involved a 54-year-old Japanese man with slowly progressive type 1 diabetes diagnosed at the age of 51 years as a result of the presence of exhausted endogenous insulin secretion and glutamic acid decarboxylase autoantibodies. Two years later, he developed hypercholesterolemia, and rosuvastatin therapy (2.5 mg/day) was initiated. Although his serum liver enzymes had been perfectly normal, to begin with, 8 months into treatment, his aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase values increased to 606, 709 and 2,055 U/L, respectively. The viral hepatitis serologies, anti-mitochondrial antibody, liver kidney-microsomal-1 antibody and anti-nuclear antibody were negative, but his immunoglobulin G level was slightly elevated (1,857 mg/dL). We suspected drug-induced autoimmune hepatitis, and then referred him to the department of gastroenterology for further examination and treatment. An abdominal ultrasound showed hyperechogenic hepatic echostructure, and a liver biopsy showed a piece-meal necrosis (interface hepatitis) with lymphocytes and plasma cell infiltration (Figure 1b). The statin therapy was discontinued just before the liver biopsy. The revised International Autoimmune Hepatitis Group score was 13 points (Table S1). He was diagnosed as AIH and started on prednisolone 30 mg/day. Within 2 weeks, his liver function tests normalized. The dose of prednisolone was tapered and finally maintained at 5 mg/day. His HLA-DRB1-DQB1 haplotype was DRB1*04:01-DQB1*03:01 and DRB1*04:05-DQB1*04:01.

We obtained informed consent and received a consent form from both patients.

## DISCUSSION

Type 1 diabetes is frequently associated with other autoimmune diseases, but the coexistence of AIH and type 1 diabetes without autoimmune polyglandular syndrome has rarely been reported. In 1,212 patients with type 1 diabetes, Hughes *et al.* reported the prevalence of AIH to be only 0.2%[4], which is still higher than that in the general population (0.01–0.03%).[5–8] In sharp contrast, those with autoimmune thyroid disease showed a significantly higher rate of 27.3%[4]. Furthermore, they showed that patients with late-onset type 1 diabetes after the age of 30 years, similar to the present patients, have higher risks of developing additional autoimmune diseases.

Hero *et al.* reported that treatment with statin in primary prevention reduces, by 22–44%, the incidence of all-cause mortality, cardiovascular death, cardiovascular disease and stroke among patients with type 1 diabetes[9]. Due to such robust evidentiary data, the American Diabetes Association Standards of Medical Care in Diabetes recommends statin therapy in adult patients with type 1 diabetes[10]. Therefore, it is not unusual that treatment with statins has been so prevalent in patients with type 1 diabetes.

Although statins are generally considered to be safe, they might, on rare occasions, produce severe adverse reactions, including muscular and non-muscular complications, with the risk of severe statin-induced hepatotoxicity reported as being ≈0.001%[11]. Furthermore, drug-induced liver injury is sometimes difficult to distinguish from drug-induced AIH in its hepatic histology. However, interface hepatitis, portal and intra-acinar plasma cell infiltration, and hepatocyte rosette formation are findings that favored drug-induced AIH, whereas portal neutrophils and intracellular cholestasis are suggested as findings of drug-induced liver injury[12]. Since 1966, reports on Medline data search have shown just 14 previously reported cases of statin-induced AIH (Table 1). With the inclusion of the present two cases, they show a mild female predominance (males : females = 1:1.3). The mean age at diagnosis of AIH was 56.7 ± 11.0 years, and the majority of cases were diagnosed within 1 year of exposure to statins. Approximately half

**Table 1** | Clinical features of patients with autoimmune hepatitis triggered by statins

| No. | Age (years) | Sex | Statin | Time to hepatitis (months) | AIH score | HLA | Antibody | Other autoimmune disease | Reference |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 39 | M | Simvastatin | 22 | NA | NA | ASMA | None | *J Intern Med* 2001; 250: 249–254 |
| 2 | 63 | F | Simvastatin | 48 | NA | NA | ANA | None | *J Intern Med* 2001; 250: 249–254 |
| 3 | 58 | F | Atorvastatin | 7 | 19 | DR3, 4 | ANA | SLE | *Lupus* 2003; 12: 409–412 |
| 4 | 46 | F | Rosuvastatin | 2 | NA | NA | ASMA | None | *Eur J Gastroenterol Hepatol* 2005; 17: 589–590 |
| 5 | 68 | F | Pravastatin | 4 | 14 | DR1, 9 | ANA | None | *Kanzo* 2005; 46: 133–141 (in Japanese) |
| 6 | 62 | F | Pravastatin | 1 | 9 | DR4, 8 | ANA, AMA | None | *Kanzo* 2005; 46: 133–141 (in Japanese) |
| 7 | 50 | F | Atorvastatin | 19 | NA | NA | ANA | Chronic thyroiditis | *Ann Clin Biochem* 2005; 42: 402–404 |
| 8 | 47 | M | Atorvastatin | 4 | 17 | DR4,7 | ASMA | None | *J Clin Gastroenterol* 2006; 40: 757–761 |
| 9 | 51 | M | Atorvastatin | 4 | 14 | NA | ANA, ASMA | None | *J Clin Gastroenterol* 2006; 40: 757–761 |
| 10 | 57 | F | Simvastatin | 4 | 20 | DR4 | ANA, ASMA | Chronic thyroiditis | *J Clin Gastroenterol* 2006; 40: 757–761 |
| 11 | 67 | M | Fluvastatin | 4 | 11 | DR3, 3 | ANA | Chronic thyroiditis | *Liver Int* 2007; 27: 592 |
| 12 | 75 | F | Pravastatin | 96 | 13 | DR4 | ANA | None | *Kanzo* 2010; 51: 71–77 (in Japanese) |
| 13 | 76 | F | Simvastatin | Several years | NA | NA | ANA | Myositis | *Am J Ther* 2014; 21: e94–e96 |
| 14 | 47 | M | Rosuvastatin | 1.5 | NA | NA | Seronegative | None | *Gastroenterol Res* 2019; 12: 263–266 |
| 15 | 47 | M | Atorvastatin | 6 | 17 | DR9, 9 | ANA | T1D | Present patient |
| 16 | 54 | M | Rosuvastatin | 8 | 17 | DR4, 4 | Seronegative | T1D | Present patient |

AIH, autoimmune hepatitis; AIH score, International Autoimmune Hepatitis Group score; AMA, anti-mitochondrial antibody; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody; NA, not available; SLE, systemic lupus-like syndrome; T1D, type 1 diabetes.

of the patients had complications involving other autoimmune diseases. Human leukocyte antigen typing was available for nine of the 16 patients, all of whom were positive for DR3, 4 or 9, indicating that genetic background might be related to statin-induced AIH. To validate a potential link between genetic background and statin-induced AIH, further studies using a larger sample and different ethnic groups are necessary.

The exact mechanism of statin-induced AIH is unclear. Furthermore, we might consider a possibility that the coexistence of AIH and statin administration is just a coincidence, because AIH has been reported to occur in patients with type 1 diabetes, irrespective of use of statins. However, reports that statins upregulate the Toll-like receptors on activated dendritic cells and enhance the secretion of pro-inflammatory cytokines[13] could be indicative of an association with the etiology of statin-induced AIH[14]. Because it has been reported that the Toll-like receptors expression and activity, as well as the levels of pro-inflammatory cytokines, were increased in patients with type 1 diabetes[15], the presence of type 1 diabetes might increase the risk for developing AIH by statins in genetically susceptible individuals.

As diagnoses of AIH can only be achieved through a histological examination, the real number of statin-induced AIH cases could be much higher. Liver biopsy is to be considered for type 1 diabetes patients if there is no improvement of liver dysfunction after discontinuation of statins.

## DISCLOSURE

The authors declare no conflict of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** | Scores based on the revised scoring system for diagnosis of autoimmune hepatitis in the present cases.