

## Hepatic Glycogenosis in a Type 1 Diabetes Mellitus Patient with Ketoacidosis

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### Abstract

Hepatic glycogenosis, a rare disease characterized by hepatomegaly and elevated liver enzyme levels, is observed in patients with type 1 diabetes mellitus. We present a case of a 66-year-old woman with type 1 diabetes mellitus with poor glycemic control. She presented with impaired consciousness and findings of diabetic ketoacidosis (blood glucose level 1110 mg/dl; blood ketone bodies 10,926 µmol/l; pH 7.247). Hepatobiliary enzyme levels were elevated and CT showed hepatomegaly and elevated CT numbers in the hepatic parenchyma, from before and after hospitalization. A liver biopsy was performed and nuclear glycogen and ballooning in the hepatocytes were observed. Along with the stabilization of blood glucose levels, improvements in liver enzyme levels and hepatomegaly were observed. Appropriately adjusting the amount of insulin and continuing glycemic control should prevent future relapse of hepatic damage.

**Keywords:** Hepatic glycogenosis; Diabetic ketoacidosis; Hepatomegaly; Elevated liver enzyme level

### Case Report

A 66-year-old woman presented with impaired consciousness. Her past medical history was unremarkable. She had a family history of type 2 diabetes mellitus in her grandmother, grandfather, and cousin. She was living alone, working as a care worker, non-smoker, and her alcohol consumption was 350 ml/day of beer.

Around November X-24 (at the age of 43 years), the patient visited a nearby clinic with chief complaints of dry mouth, polydipsia, and polyuria. Her blood glucose level was 600 mg/dl, and the patient was diagnosed with diabetes mellitus. Treatment with oral sulfonylurea was started on an outpatient basis because the patient refused hospitalization. However, the patient lost 8 kg of body weight in six months, and insulin was started in March X-23 (at the age of 44 years). In X-22, the patient was referred to our hospital due to a high hemoglobin A1c (HbA1c) of 10.6% to 11.6% (National Glycohemoglobin Standardization Program), and she was subsequently diagnosed with type 1 diabetes mellitus, thereafter continuing with insulin treatment at our outpatient clinic. The patient was admitted to our hospital in August X-17 and May X for ketoacidosis. Peripheral neuropathy and simple retinopathy were observed as diabetic complications, along with stage 1 nephropathy.

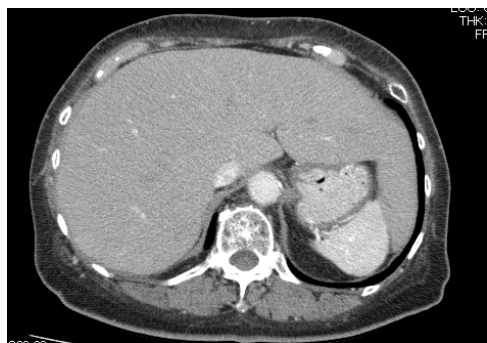
Around November 15, X, the patient presented with epigastric pain and vomiting. Upper gastrointestinal endoscopy on November 17 showed no abnormalities. Insulin aspart in the morning (6 units), at lunchtime (10 units), and in the evening (12 units), as well as glargine before bedtime (8 units), resulted in poor glycemic control with an HbA1c of 9.6% and a casual blood glucose level of 412 mg/dl. The urinary ketone level was 2<sup>+</sup>. During a regular outpatient check-up on December 4, hepatobiliary enzyme levels were elevated [aspartate transaminase (AST) 136 U/l, alanine transaminase (ALT) 127 U/l, alkaline phosphatase (ALP) 392 U/l, and lactate dehydrogenase (LDH) 326 U/l]. Contrast-enhanced computed tomography (CT) showed hepatomegaly and elevated CT numbers in the hepatic parenchyma (Figure 1).

While the blood glucose level was 242 mg/dl, the urinary ketone level was still 2<sup>+</sup>. The day after the check-up, the patient

### Introduction

Patients with diabetes mellitus often develop non-alcoholic steatohepatitis (NASH), and apart from NASH, hepatomegaly and elevated liver enzyme levels may occur when unstable glycemic control continues due to hyperglycemia caused by insulin deficiency, overdosing of insulin, and excessive glucose administration for hypoglycemia. Hepatomegaly and elevated liver enzyme levels are histological findings of hepatic glycogenosis, and they are often observed primarily in patients with type 1 diabetes mellitus, since they are prone to unstable glycemic control. We report the case of a patient with hepatomegaly and elevated liver enzyme levels, which coincided with the onset of severe diabetic ketoacidosis.

vomited once at night on December 5 and vomited again, twice, on December 7 at work. In the evening on December 7, a co-worker of the patient noticed the patient's finger tremors and incoherent speech, and the patient came to the emergency room of our hospital at around 7 PM. At the time of the check-up, the patient presented with findings of diabetic ketoacidosis (blood glucose level 1110 mg/dl; blood ketone bodies 10,926  $\mu\text{mol/l}$ ; pH 7.247), and she was immediately hospitalized on the same day.



**Figure 1** Contrast-enhanced CT image on December 4. Hepatomegaly (vertical diameter 19.45 cm) and elevated CT numbers in the hepatic parenchyma (66 to 114) are seen.

Conditions at visit: height 155 cm, body weight 50 Kg, body mass index (BMI) 20.8 kg/m<sup>2</sup>, blood pressure 82/39 mmHg, pulse rate 84 beats/min, respiratory rate 20 breaths/min, temperature 37.6°C, level of consciousness (restless), Japan Coma Scale Grade 1, Glasgow Coma Scale 14 out of 15 (eye opening 4, best verbal response 4, best motor response 6). No specific abnormalities in the head, neck, and chest areas were evident. Pressure pain was noted in the epigastric region. On

neurological examination, the pupil size was 3 mm/3 mm with a prompt response to light. No other neurological abnormalities were noted.

A markedly elevated blood glucose level (1110 mg/dl), high total blood ketone bodies (10,926  $\mu\text{mol/l}$ ), and urinary ketones (3<sup>+</sup>) were noted. Metabolic acidosis was observed, as shown by the venous blood gas results (pH 7.160 and BE-19.1 mmol/l). Compared to the results during the outpatient check-up on December 4, the patient had low Na levels (126 mEq/l), elevated K levels (5.5 mEq/l), and elevated hepatobiliary enzyme levels (AST 239 IU/l, ALT 169 IU/l, ALP 434 IU/l, LDH 508 IU/l,  $\gamma$ -GTP 383 IU/l). A slight increase in the inflammatory response (WBC 9030/mm<sup>3</sup>, CRP 0.59 mg/dl) was also observed (**Table 1**). There were no abnormal findings on plain chest X-rays, electrocardiograms, and head CT at that visit.

The patient was treated with fluid replacement and continuous insulin infusion in the intensive care unit (ICU) due to low blood pressure and a decreased level of consciousness. The patient received a total of 3.4 L of fluid replacement until the next morning, and after starting human insulin at 6 units/h, it was gradually decreased while monitoring the blood glucose levels. The blood glucose level decreased to 140 mg/dl by the morning of Day 2 of hospitalization, and the acidemia improved to pH 7.392. While continuous infusion of dopamine was temporarily administered for the low blood pressure, it was discontinued as dehydration was corrected, and the patient was transferred to the general ward on Day 4 of hospitalization. The patient still presented with a urinary ketone level of 2<sup>+</sup> at the time of transfer, but there was gradual improvement, and the patient tested negative on Day 5 of hospitalization. After waiting for food intake to stabilize, the patient transitioned to subcutaneous insulin.

**Table 1** Time courses of the hepatobiliary enzyme levels.

Hospitalization	2 months prior	3 weeks prior	3 days prior to	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 10	Day 12	Day 15	Day 18	Day 22	Day 29	Day 37
AST	26	49	136	239	222	379	188	106	78	86	74	53	44	45	50	29
ALT	14	28	127	169	133	194	156	112	78	72	58	43	36	31	37	20
ALP	203	219	392	434	301	388	451	451	470	473	450	394	346	344	292	237
LDH	235	249	326	508	337	454	305	293	298	285	334	241	253	227	210	193
ChE	213		212	192	136	160	183	167	155	168	168	154	147	173	181	185
$\gamma$ -GTP	30	37	289	383	291	370	394	355	315	314	289	235	190	169	123	84
Blood glucose	208	412	242	1110	134	153	174	72	61	54	40	49	69	44	105	55
Urinary ketones	-	2 <sup>+</sup>	2 <sup>+</sup>	3 <sup>+</sup>	3 <sup>+</sup>	2 <sup>+</sup>		-	-	-	-	-	-	-	-	-

Prior to hospitalization due to the ketoacidosis, liver enzyme levels were increasing; however, further elevation of predominantly AST was observed after hospitalization. Since AST (379 IU/l) and ALT (194 IU/l) increased by Day 3 of hospitalization, administration of ceftriaxone (CTRX), which is eliminated by hepatic metabolism and had been started in the ICU, was discontinued, and hepatoprotective drugs were started. To investigate the cause of the elevated liver enzyme levels, screening for hepatitis-causing viruses was performed. The test results did not show any acute viral infections, and the Epstein-Barr (EB) virus test suggested a previous infection pattern. Antinuclear antibody (ANA) and antimitochondrial antibody (AMA) tests were negative. Since the CT numbers in the hepatic parenchyma were elevated, ferritin and serum copper levels were measured to screen for hemochromatosis and Wilson's disease. There was only a slight elevation of ferritin and no drop in serum copper levels (Tables 2 and 3).

**Table 2** Laboratory test results at the time of immediate hospitalization (December 7).

Qualitative urinary test results		General blood test results		Creatine kinase (CK)	137 IU/l
Protein	(-)	White blood cell (WBC) count	9030/mm <sup>3</sup>	Total protein (TP)	6.5 g/dl
Glucose	(4 <sup>+</sup> )	Hb	11.9 g/dl	Albumin (Alb)	3.4 g/dl
Occult blood	(-)	Hematocrit (Ht)	38.7%	Urea nitrogen (BUN)	23.8 mg/dl
Ketones	(3)	Platelet (PLT) count	27.2 × 10 <sup>4</sup> /mm <sup>3</sup>	Creatinine (Cre)	0.94 mg/dl
Venous blood gas parameters		Biochemical test results		Estimated glomerular filtration rate (eGFR)	46 ml/min
pH	7.160	Total blood ketone bodies	10926 μmol/l	Sodium (Na)	126 mEq/l
pCO <sub>2</sub>	24.1 mmHg	AST	239 IU/l	Potassium (K)	5.5 mEq/l
pO <sub>2</sub>	46.3 mmHg	ALT	169 IU/l	Chlorine (Cl)	79 mEq/l
HC O <sub>3</sub> <sup>-</sup>	7.4 mmol/l	ALP	434 IU/l	Blood glucose	1110 mg/dl
Base excess (BE)	-19.1 mmol/l	LDH	508 IU/l	C-reactive protein (CRP)	0.59 mg/dl
		Cholinesterase (ChE)	192 IU/l		
		Gamma-glutamyltransferase (γ-GTP)	383 IU/l		
		Amylase (Amy)	42 IU/l		

		Total bilirubin (T-Bil)	1.1 mg/dl		
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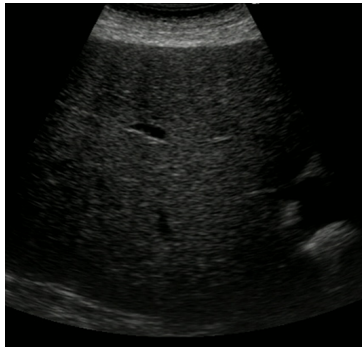
Hepatobiliary enzyme levels started to decrease along with the start of hepatoprotective drugs and improvements in the general conditions including blood glucose levels; however, a follow-up CT scan on Day 4 of hospitalization showed that the hepatomegaly was the same as that observed prior to hospitalization, with a higher liver parenchymal concentration (Figure 2). The echo-level of the liver was normal on abdominal ultrasound, and there was no increase in liver-kidney contrast (Figure 3).

**Table 3** Results of the detailed examinations related to the elevated liver enzyme levels.

Hepatitis immunoglobulin A (HA-IgM)	(-)	Antinuclear antibody (ANA)	< × 40
HA-IgM-signal-to-cutoff ratio (S/CO)	0.10	Antimitochondrial antibody (AMA)	< × 20
Hepatitis B surface (HBS) antigen	(-)	Ferritin	467.8 mg/ml
Hepatitis C virus (HCV) antibody	(-)	Copper	154 μg/dl
EB-EB nuclear antigen (EBNA)	80		
Epstein-Barr virus capsid antigen (EBVCA) IgM	< 10		
Cytomegalovirus (CMV) IgM enzyme immunoassay (EIA)	(-)		
CMV IgM index	0.28		

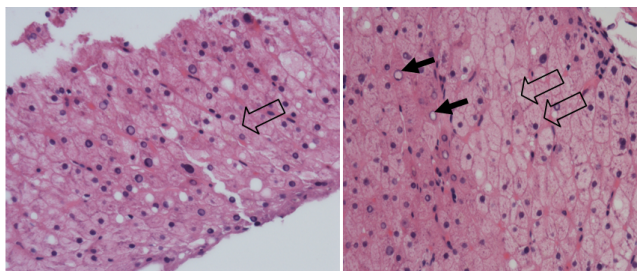


**Figure 2** Plain CT image on Day 4 of hospitalization. Hepatomegaly (liver vertical diameter 19.24 cm) remains. Hepatic parenchymal concentration is higher, with CT numbers of 80 to 121.



**Figure 3** Abdominal ultrasound examination. Normal echo-level of the liver. No increase in liver-kidney contrast.

A liver biopsy was performed on Day 11 of hospitalization, with no findings of iron deposition that suggested hemochromatosis. There was hardly any cluster of differentiation 8 (CD8)-positive T-cell infiltration as observed in viral hepatitis. However, nuclear glycogen, which suggests glycogen deposition in the hepatocytes, and ballooning, indicating steatosis, in the hepatocytes, were observed (**Figure 4**).



**Figure 4** Microscopy examination of the liver biopsy on Day 11 of hospitalization. Nuclear glycogen (←) and hepatocyte ballooning (↔) are observed.

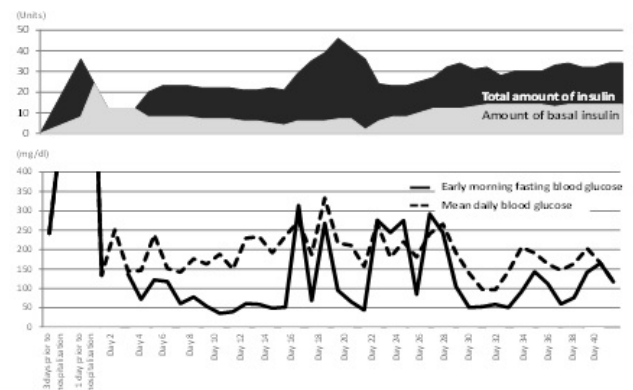
The follow-up CT scan on Day 29 of hospitalization showed that hepatomegaly had improved, and the CT numbers in the hepatic parenchyma had returned to the normal range (**Figure 5**).



**Figure 5** Liver (vertical diameter 14.8 cm) and improvement of the CT numbers in the hepatic parenchyma (50 to 93).

Despite the discontinuation of hepatoprotective drugs after the liver biopsy, liver enzyme levels continued to decrease, returning to a normal range on Day 37 of hospitalization.

Blood glucose levels were unstable even after transitioning to subcutaneous insulin (**Figure 6**).



**Figure 6** Changes in blood glucose.

Glargine, a long-acting insulin, was switched and adjusted to degludec, another long-acting insulin. However, early morning hypoglycemia of 40 to 60 mg/dl persisted when a long-acting insulin was injected once before bedtime as before hospitalization. When the amount of long-acting insulin was reduced, assuming that the insulin requirement at night was extremely low, it resulted in hyperglycemia due to deficiency in basal insulin during the day time. Now, when a long-acting insulin was injected before breakfast, hyperglycemia was observed from early morning throughout the day, because the dawn phenomenon could not be prevented. When a long-acting insulin was injected twice, once before breakfast and bedtime, while also injecting degludec before breakfast (11 units) and before bedtime (3 units) and eating a 100 to 150 kcal snack before bedtime, it resulted in no nighttime hypoglycemia, and the daytime fasting blood glucose level was also stable at 110 to 170 mg/dl. The patient was taught carbohydrate counting for ultra-rapid-acting insulin. Her blood glucose level stabilized when insulin aspart was used at a carbohydrate-to-insulin ratio of 8.3 g per unit in the morning and 25 g per unit both at lunchtime and in the evening. The patient was then discharged. Along with the stabilization of blood glucose levels, improvements in liver enzyme levels and hepatomegaly were observed.

## Discussion

Hepatic glycogenosis, also known as glycogenic hepatopathy, is one of the rare complications found mainly in patients with type 1 diabetes mellitus who have prolonged, poor glycemic control. It is defined as pathological glycogen storage in hepatocytes with hepatomegaly and elevated liver enzymes. In 1930, this disease was initially described as Mauriac syndrome, a rare complication found in children with type 1 diabetes



mellitus. It was characterized by hepatomegaly, liver glycogen deposition, growth impairment, and a Cushingoid appearance in cases of poorly controlled type 1 diabetes mellitus [1]. Today, liver glycogen deposition is known to be caused by prolonged, unstable glycemic control due to hyperglycemia caused by insulin deficiency, overdosing of insulin, and excessive glucose administration for hypoglycaemia [1]. While there are many reported cases of patients with type 1 diabetes mellitus, studies have been reported in patients with type 2 diabetes mellitus with poor glycemic control due to depleted endogenous insulin secretion and in patients with dumping syndrome, as well as with short-term, high-dose steroid administration [2,3]. The symptoms include abdominal pain, nausea, vomiting, and characterized by elevated liver enzyme levels and hepatomegaly. Hepatomegaly is reversibly improved with adequate glycemic control for 2 to 14 weeks [4-6].

Fat deposition in hepatocytes in non-alcoholic fatty liver disease (NAFLD) and NASH can also show hepatomegaly and elevated liver enzyme levels. However, the difference between liver fat deposition and liver glycogen deposition is that there is more liver fat deposition among patients with type 2 diabetes mellitus and more glycogen deposition among patients with type 1 diabetes mellitus. Improvement in liver fat deposition requires time even after improving glycemic control, and there is no full recovery. On the other hand, glycogen deposition improves rapidly with improvement in glycemic control. Furthermore, while liver fat deposition develops into cirrhosis, there are no such reports to date for glycogen deposition. There is also a difference in imaging findings [7,8].

It is difficult to differentiate between liver fat deposition and glycogen deposition by ultrasound examination, but CT examination is known to be effective. While there is an increase of 2.5 to 3 HU in the CT numbers with every 1% increase of liver glycogen deposition, the CT numbers decreases by 1 to 1.5 HU with a 1% increase of fat deposition [5]. However, since deposition of both fat and glycogen is possible, the densities in the liver vary according to this proportion [6]. When gradient dual-echo magnetic resonance imaging (MRI) was used for the diagnosis of liver glycogen deposition in a patient with new-onset, fulminant type 1 diabetes mellitus, it was reportedly effective in differentiating fat deposition [7]. Partial liver glycogen deposition has also been reported recently, and a study was successful in identifying the areas of deposition using CT and MRI [8].

Liver biopsy is the gold standard for diagnosing hepatic glycogenosis, and glycogen deposition in the hepatocytes can be seen as swelling of the hepatocytes, clear cytoplasm, and a sharp cellular membrane. Fat deposition is either absent or minimal, with basically no findings of inflammation, lobular necrosis, or fibrosis [5].

While the cause of liver glycogen deposition remains partially uncertain, it is thought to be related to the presence of high concentrations of glucose and insulin. During hyperglycemia, there is excessive insulin-independent glucose uptake into the hepatocytes mediated by glucose transporter-2 (GLUT-2), and it is rapidly converted to glucose-6-phosphate by glucokinase and trapped inside the hepatocytes. Glycogen synthase converts

glucose-6-phosphate into glycogen, and glycogen synthase is activated by a phosphatase. Since the activity of the phosphatase is dependent on the concentration of insulin and glucose, in the presence of high concentrations of glucose and insulin in the cytoplasm of the hepatocyte, glycogen synthesis is promoted, and liver glycogen deposition occurs. Recurrent ketoacidosis also becomes a risk factor in hepatic glycogenosis; however, this is caused by the continuous administration of intravenous insulin for hyperglycemia in the process of treatment [6,9].

Ueki et al. summarized the findings of 28 glycogenosis patients in Japan with a mean age of 28 years (age range 9 to 62 years) and 15 patients, over 50% of all patients, had type 1 diabetes mellitus. The size of the liver was over four fingerbreadths in 16 patients, and the time to develop hepatomegaly was a mean of 2.6 weeks, with a duration of 8.3 weeks. Four patients also had fat deposition. There was a wide range in blood glucose levels (49 to 1088 mg/dl), and the HbA1c for all patients was at least 10%. The elevated liver enzyme levels were predominantly AST, and elevation of CT numbers in the hepatic parenchyma was noted in three patients [10]. According to a study reported by Glushko et al. in 2017, of a total of 90 patients, 52 were women (58%), with a mean age of 20 years and a mean duration of disease of 10 years. In this study, 95% had type 1 diabetes mellitus, 3% had type 2 diabetes mellitus, 2% had dumping syndrome, glycemic control was poor, and the mean HbA1c was 12%. The mean liver enzyme levels were ALT 508 IU/l, AST 928 IU/l, ALP 326 IU/l, and Bil 5 mg/dl [1].

The patient in the present study was 66 years of age, much older than patients in previously reported studies. While the patient had a high blood glucose level (1110 mg/dl) at the time of hospitalization, HbA1c (9.6%) was lower than previously reported studies, suggesting that there was a very wide fluctuation in blood glucose levels. Although the elevated liver enzyme levels and hepatomegaly improved in the process of glycemic control, it was extremely difficult to achieve glycemic control in this case, as described in the course of events after hospitalization. Even though the trigger for hepatic glycogenosis is not yet known, appropriately adjusting the amount of insulin and continuing glycemic control should prevent future relapse of hepatic damage.

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