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Case Report

Case Report

Acute Hepatitis due to Hepatic Glycogenosis After Insulin Overdose and Oral Glucose Administration in an Adolescent

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Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; ED, emergency department; GLUT2, glucose transporter 2; HG, hepatic glycogenosis; IV, intravenous; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; T1DM, type 1 diabetes mellitus.

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Abstract

Background: Hepatic glycogenosis (HG) has been reported after intravenous (IV) dextrose administration to treat insulin overdose. We describe a case of HG in a patient with type 1 diabetes mellitus (T1DM) due to insulin overdose treated with oral glucose administration.

Case Presentation: An adolescent boy withT1DM on a basal bolus insulin regimen presented with abdominal discomfort, nausea, vomiting, and hypoglycemia of a few hours. His glucose was 71 mg/dL, aspartate transaminase (AST) 119 U/L, and alanine transaminase (ALT) 65 U/L. Hypoglycemia was treated with juice, and 12 hours later AST and ALT were 979 U/L and 700 U/L, respectively. Workup for infectious, autoimmune, metabolic, and toxic causes of hepatitis was negative. The transaminases improved by the next day and normalized within 3 weeks. Two weeks after discharge the patient returned with hypoglycemia, nausea, and right-sided abdominal pain of 13 hours. Hypoglycemia persisted despite multiple courses of glucose tablets and juice. Laboratory studies showed glucose of 58 mg/dL, AST of 776 U/L, ALT of 496 U/L, negative toxicology studies, and normal abdominal ultrasound. His serum insulin level was 249.7 mU/L and, C-peptide was less than 0.1 ng/mL, consistent with insulin overdose. He received IV fluids with dextrose, and insulin was held. Transaminases improved by the following day. Repeat serum insulin while on home regimen was normal.

Conclusion: Along with other diagnoses, HG should be considered in patients treated with insulin who present with hypoglycemia and acute hepatitis. HG can occur in cases of insulin overdose treated with repeated oral glucose administration.

Key Words: adolescent, type 1 diabetes mellitus, insulin overdose, hepatic glycogenesis

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Pierre Mauriac first described hepatic glycogenosis (HG) in 1930, a syndrome in children with poorly controlled type 1 diabetes mellitus (T1DM) characterized by glycogen accumulation in the liver causing hepatomegaly, growth failure, round facies, and delayed puberty [1, 2]. This constellation of symptoms is also referred to as Mauriac syndrome, liver glycogenosis, liver glycogen storage, diabetes mellitus-associated glycogen storage hepatomegaly, and glycogenic hepatopathy [3, 4].

HG occurs when insulin levels are elevated in the presence of high levels of glucose and is typically seen in those with wide fluctuations in glucose and insulin levels. Hyperglycemia leads to increased glucose entry into the hepatocytes, and excess insulin promotes conversion of the glucose into glycogen. Liver injury is mediated by increased glucose uptake, glycogenesis, and inhibition of gluconeogenesis [4], and pathologic glycogen accumulation leads to elevated hepatic transaminases [5]. HG can also occur with isolated liver involvement, without the full phenotype of growth delay and hepatomegaly and has been reported in individuals across the lifespan [6]. Excess glycogenesis reverses rapidly once insulin and glucose levels are stabilized, and hepatic injury is reversible.

Most cases of HG occur in individuals with T1DM, while a small percentage of cases occurs in those with type 2 diabetes mellitus. HG has also been reported in the setting of dumping syndrome following gastrostomy and in cases of hyperglycemia following high-dose glucocorticoid therapy [4, 5], as frequent hypoglycemia and its correction with glucose administration contributes to the pathogenesis.

Transient hepatitis secondary to HG has been reported after intravenous (IV) dextrose administration to treat insulin overdose in adults. We describe an adolescent male with T1DM who developed 2 episodes of acute hepatitis due to HG following insulin overdoses and repeated oral glucose administration to treat hypoglycemia.

Case Presentation

A 16-year-old boy with T1DM for 7 years treated with a basal bolus insulin regimen presented in the evening to an emergency department (ED) of a tertiary care hospital with complaints of abdominal discomfort, nausea, nonbilious nonbloody vomiting, and hypoglycemia for the past 8 hours. Most recent glycated hemoglobin A_{1c} was 9.5%. The abdominal symptoms started in the late afternoon the day of presentation. His blood sugar was in the 40-mg/dL range and was treated with oral glucose tablets. He described taking his usual insulin doses earlier in the day, and denied taking any other medications, substances, or excess insulin. His medications included glargine insulin each night, lispro insulin with meals, sertraline 100 mg daily, guanfacine 1 mg in the morning and 3 mg at night, and melatonin 3 mg nightly as needed. On examination, he was alert, afebrile, with stable vital signs and an exam notable for epigastric and right upper-quadrant tenderness. His initial laboratory workup showed elevated liver enzymes (Table 1) and hypoglycemia. Additional laboratory values including pH (7.36), blood gas, complete blood count with total white blood cell count 6100 cells/mm^3, and basic metabolic profile, including bicarbonate 28 mEq/L, were normal. An extended respiratory viral panel and COVID-19 test were all negative. Testing for Epstein-Barr virus and enterovirus was also negative. Urinalysis was negative for ketones. Chest and abdominal plain films were unremarkable. The hypoglycemia was treated with juice, and he was admitted to the hospital for monitoring. He ate dinner and 2 snacks before bed. Overnight, he had 2 additional episodes of hypoglycemia and was treated with juice (total carbohydrate 60 g). The patient did not require IV dextrose to correct the hypoglycemia. Repeat laboratory values 12 hours after admission showed marked elevation in liver enzymes (see Table 1). Given concern for an undisclosed ingestion, infection, or other cause of hepatitis, additional laboratory studies were obtained (Table 2). An abdominal ultrasound showed normal liver size and texture, and Doppler ultrasound of the liver vasculature was also normal. He had normal thyroid function. Owing to the rapid rise in transaminase levels, the patient was treated empirically with a 21-hour NAC (*N*-acetylcysteine) protocol for presumed ingestion, as per the recommendation of the poison control team. Transaminases began to trend down by 25 hours after admission and normalized by 3 weeks (see Table 1).

The patient was discharged home after a prolonged hospitalization that included a stay in a behavioral health unit

Table 1. Glucose and liver enzymes during the first presentation

Laboratory test	Reference range	0 h	12 h	25 h	37 h	53 h	D 22
Glucose, mg/dL	67-99	71	219	262	287	212	89
AST, U/L	13-38	119	979	377	166	78	20
ALT, U/L	8-36	65	700	627	475	336	28

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase.

Table 2. Laboratory evaluation for causes of abdominal pain and hepatitis

Variable	Reference range	Results
Celiac panel: total IgA, mg/dL	63-484	102
TTG IgA, units	0-20	4.2
Cortisol (7:45 AM), µg/dL	5.5-20	15.8
Alpha 1 antitrypsin phenotype	–	PI*M1N
Ferritin, ng/mL	22-322	20
Ceruloplasmin, mg/dL	20-60	34
Acute hepatitis panel (hepatitis A antibody, IgM; hepatitis B core antibody, IgM; hepatitis B surface antigen; hepatitis C virus antibody)	–	Negative
Autoimmune hepatitis panel: actin Ab IgG, anti-LKM Ab, anti-smooth muscle actin Ab, ANA	Negative	Negative
Toxicology (ethchlorvynol and phenothiazine, acetaminophen, salicylate, imipramine/desipramine, GC and MS)	Acetaminophen: 11-20 mg/dL Salicylate: 15-30 mg/dL	Acetaminophen < 10 µg/dL Salicylate: < 2.5 mg/dL
Urine toxicology	–	Negative

Abbreviations: Ab, antibody; ANA, antinuclear antibodies; GC, gas chromatography; Ig, immunoglobulin; LKM, liver kidney microsome; MS, mass spectrometry; TTG, tissue transglutaminase.

Table 3. Glucose and liver enzymes during the second presentation

Laboratory test	Reference range	0 h	5 h	15 h	26 h	D 6	2 mo
Glucose, mg/dL	67-99	58	42	143	259	245	356
AST, U/L	13-38	776	955	441	229	40	13
ALT, U/L	8-36	496	747	546	444	101	12
C peptide, ng/mL	0.8-3.85		< 0.10				
Total serum insulin, mU/L	3-25		249.7			19.5	

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase.

because of concern of medication overdose, despite repeated denials. He did not have any hypoglycemia during the admission. Two weeks after his discharge home (30 days after the initial admission), the patient returned to the ED with complaints of nausea, vomiting, abdominal pain, and hypoglycemia. The patient was found to have hypoglycemia (40 mg/dL) the morning of admission, when his school nurse checked his blood sugar before breakfast. He did not receive prandial insulin with breakfast or lunch. He consumed more than 20 glucose tablets and servings of juice (4 ounces) to maintain blood glucose above 70 mg/dL. He developed nausea and right-sided abdominal pain of 8 out of 10 in intensity during the day, and symptoms worsened by late afternoon. He also had an episode of nonbilious, nonbloody emesis. He was brought to the ED about 13 hours after the detection of hypoglycemia. He did not have fever, sick contacts, or recent travel, and denied ingestion of any medications or substances. In the ED, examination was unremarkable except for right upper-quadrant abdominal tenderness. Laboratory evaluation showed elevated liver enzymes (Table 3) and hypoglycemia. He had a normal complete blood count with total white blood cell count 3800/mm^3, normal basic metabolic profile (bicarbonate, 24 mEq/L), negative urine ketones, and negative COVID-19 testing. His insulin level was 250 mU/L with a C-peptide level of less than 0.1 ng/mL at the time of hypoglycemia, consistent with excess exogenous insulin (see Table 3). As his serum glucose levels improved, his IV fluids were weaned and then discontinued 22 hours after presentation. The abdominal pain and nausea subsided over 3 days. He resumed his home insulin regimen and did not have further hypoglycemia. Repeat serum insulin when he was receiving his home insulin regimen was 19.5 mU/L (see Table 3). His liver enzymes normalized within 2 months (see Table 3).

With improved supervision of insulin administration, the patient did not have further episodes of hypoglycemia episodes or elevated liver enzymes. He continued to deny insulin overdose.

Discussion

We describe HG that occurred after insulin overdose and solely oral glucose treatment of hypoglycemia, without classic features of Mauriac syndrome. Unlike previous case reports of HG in adults treated for insulin overdose with prolonged IV dextrose administration (Table 4), our

Table 4. Case reports of hepatic glycogenosis following insulin overdose

Reference y	Diabetes diagnosis	Age, y; sex	Insulin type and units	Presenting symptoms	Treatment before development of HG	Onset of symptoms
2001 [14]	Nondiabetic	48, female	1000 units of long-acting insulin along with benzodiazepines and ASA	Coma with severe hypoglycemia, requiring intubation for 3 d	Boluses of 40% glucose, continuous infusion of 20% glucose (1200-1400 g daily × 3 d)	On d 3, nausea, RUQ abdominal pain, hepatomegaly with worsening of liver enzymes
2012 [15]	Type 1	26, male	4800 units of glargine	Severe hypoglycemia	Parenteral 20% glucose, 10% glucose, oral fruit concentrate	On d 3, nausea, right-sided abdominal pain and hepatomegaly, elevated liver enzymes, bilirubin elevation
2006 [16]	Type 2	41, male	180 units of glargine	Loss of consciousness	Parenteral glucose and hypercaloric feed	Deranged hepatic function and hepatomegaly on d 3
2020 [13]	Type 1	25, male	3600 units of insulin glargine and 2100 units of insulin lispro	Cold sweat, feeling groggy	Continuous 17.5% glucose infusion. ~ 900 g of glucose/d × 4 d	On d 4 with general fatigue, persistent right hypochondral pain, abdominal discomfort, appetite loss, elevated liver enzymes
Our patient	Type 1	16, male	Unknown	Severe hypoglycemia, abdominal pain, nausea	Multiple glucose tablets, juice	At admission, ~ 18 h after onset of hypoglycemia with pain abdomen, nausea, vomiting, elevated liver enzymes

Abbreviations: ASA, acetylsalicylic acid; RUQ, right upper quadrant.

patient developed HG following insulin overdose managed with repeated courses of oral glucose administration.

During his second episode, our patient developed hypoglycemia during the school day and was treated repeatedly with glucose tablets and juice. HG may present with nausea, vomiting, abdominal pain, and hepatomegaly with elevated transaminases [5] due to increased glycogen synthesis and deposition in the setting of excess insulin and glucose levels. Increased serum glucose leads to increased glucose entry into the hepatocyte through insulin-independent facilitated diffusion via glucose transporter 2 (GLUT2). The excess insulin promotes conversion of this glucose into glycogen and inhibits glycogenolysis, leading to glycogen deposition. The rapid glycogen deposition causes elevation of liver enzymes, and the sudden increase in liver size with stretching of the liver capsule triggers the abdominal pain [7]. Though hepatomegaly is characteristic of HG in more than 90% of cases, it can occur without hepatomegaly [7-9]. Our patient did not have hepatomegaly on exam or by imaging.

It is essential to distinguish HG from nonalcoholic fatty liver disease (NAFLD). NAFLD is characterized by triglyceride deposition in hepatocytes due to factors other than alcohol intake and can also present with hepatomegaly and elevated transaminases. Obesity is a driving factor in NAFLD development, and it has been reported in children and adolescents with obesity [10]. NAFLD has also been described in children with T1DM [11]. NAFLD is associated with mild, persistent elevation of liver enzymes [6, 12] and can progress to fibrosis and cirrhosis, while the hepatomegaly and elevated liver enzymes of HG are transient and complete resolution occurs with improvement of glycemic control.

Demonstration of glycogen deposition in hepatocytes by liver biopsy is the gold standard for the diagnosis of HG [6]. The characteristic histologic finding in HG is ballooned hepatocytes with intracytoplasmic glycogen deposition [13]. Other histological features include no or minimal fatty change, portal inflammation, nor necrosis or fibrosis with intact architect of the liver parenchyma [5, 7]. In contrast, liver biopsy in NAFLD typically shows macrovesicular steatosis and mild lobular and portal inflammation and fibrosis of varying degrees [7]. Ultrasound does not help in distinguishing HG from NAFLD as both conditions lead to increased echogenicity of the liver [13]. Computed tomography of the liver demonstrates high density in HG and low density in NAFLD. Magnetic resonance imaging (MRI) shows low density on T2-weighted images for HG. Gradient dual-echo MRI is more helpful in distinguishing between the glycogen and fat deposition by demonstrating low intensity in phase and high intensity out of phase with HG [13].

We identified 4 case reports in the literature that describe HG in adults following insulin overdose and subsequent IV dextrose administration to manage the profound and prolonged hypoglycemia (see Table 4) [13-16]. All of the cases describe administration of large doses of IV dextrose over multiple days. Three reports describe development of hepatomegaly and hepatitis the third day after insulin administration, and one case reported these symptoms on day 4. All patients had a dramatic recovery of liver enzymes after stabilization of glucose levels.

In contrast, during his initial presentation, our patient's hypoglycemia was detected after the development of abdominal symptoms, and during the second admission, he presented with hepatitis the same day that he developed hypoglycemia, after treatment with multiple glucose tablets and juice. Our patient had poorly controlled T1DM, with chronic hyperglycemia and elevations in the glycated hemoglobin A_{1c} over the past few years. One possible explanation for the onset of abdominal symptoms before the detection and treatment of hypoglycemia is that baseline hyperglycemia led to glucose influx into the liver cells via GLUT2 channels with trapping of glucose-6-phosphate in hepatocytes after phosphorylation by glucokinase. The addition of supraphysiological doses of insulin could have promoted glycogenesis from trapped glucose-6-phosphate, leading to HG [7]. Glucose administration to treat hypoglycemia would have further enhanced glycogenesis in the setting of high insulin, with worsening of abdominal symptoms.

Our patient did not acknowledge excess insulin administration, though his markedly elevated plasma insulin and undetectable C-peptide at the time of hypoglycemia (see Table 1) and the return of plasma insulin to a normal level while receiving his typical doses suggested exogenous insulin administration. Infections, ingestions, and metabolic and autoimmune disease were ruled out with various laboratory studies (see Table 2). Two episodes with dramatic recovery of the liver enzymes with improved glycemic control and unremarkable liver ultrasound favors a diagnosis of HG, though he did not have a liver biopsy or MRI performed. Along with other diagnoses, HG should be considered in patients treated with insulin who present with hypoglycemia and acute hepatitis, as HG can develop after repeated administration of oral glucose for treatment of hypoglycemia.

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