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

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Abbreviations:

BMP (Basic Metabolic Profile) CBC (Complete Blood Count) CT (Computed tomography) COVID 19 (Corona Virus Disease 2019) ED (emergency department) GLUT2 (glucose transporter 2) HbA1c (Hemoglobin A1c) HG (Hepatic glycogenosis) IV (intravenous) MRI (Magnetic resonance imaging) NAC (N acetyl cysteine) NAFLD (nonalcoholic fatty liver disease) T1DM (type 1 diabetes mellitus) T2DM (type 2 diabetes mellitus)
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 T1DM due to insulin overdose treated with oral glucose administration. **Clinical course:** An adolescent boy with T1DM on a basal bolus insulin regimen presented with abdominal discomfort, nausea, vomiting and hypoglycemia of few hours. His glucose was 71 mg/dl, AST 119 U/L and 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. Work up 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 58 mg/dl, AST 776 U/L, ALT 496 U/L, negative toxicology studies, and normal abdominal ultrasound. His serum insulin level was 249.7 mU/L and, c-peptide was <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. **Conclusions:** 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.

**Keywords:** Adolescent, Type 1 diabetes mellitus, Insulin overdose, Hepatic Glycogenesis
Introduction:

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 upon insulin and glucose levels are stabilized, and hepatic injury is reversible.

Most cases of HG occur in individuals with T1DM, while a small percent of cases occurs in those with type 2 diabetes mellitus (T2DM). 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 two episodes of acute hepatitis due to HG following insulin overdoses and repeated oral glucose administration to treat hypoglycemia.

**Case presentation:**

A 16-year-old male 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, non-bilious non bloody vomiting, and hypoglycemia for the past 8 hours. Most recent hemoglobin A1c (HbA1c) was 9.5%. The abdominal symptoms started in the late afternoon on 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 labs including pH (7.36), blood gas, complete blood count (CBC) with total white blood cell count 6100 cells/mm3, and basic metabolic profile (BMP) including bicarbonate 28 mEq/L, were normal. An extended respiratory viral panel and corona virus disease 2019 (COVID19) test were all negative. Testing for Epstein Barr virus and enterovirus were 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 prior to bed. Overnight, he had two additional episodes of hypoglycemia and was treated with juice (total carbohydrate 60 grams). The patient did not require IV dextrose to correct the hypoglycemia. Repeat laboratory values 12 hours after admission showed marked elevation in liver enzymes (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. Due to the rapid rise in transaminase levels, the patient was treated empirically with a 21 hour NAC (N-acetyl cysteine) 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 (Table 1).

He was discharged home after a prolonged hospitalization that included stay in behavioral health unit, due to 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) on 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 8/10 in intensity during the day, and symptoms worsened by late afternoon. He also had an episode of non-bilious non-bloody 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 CBC with total white blood cell count 3800/mm3, normal BMP (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 <0.1 ng/ml at the time of
hypoglycemia, consistent with excess exogenous insulin (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 (Table 3). His liver enzymes normalized within 2 months (Table 3).

With improved supervision of insulin administration, he 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 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 [7,8,9]. 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 type 1 diabetes [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 [7,14]. 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 (CT) 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 [Table 4] [13, 15, 16, 17]. All of the cases describe administration of large doses of IV dextrose over multiple days. Three reports describe development of hepatomegaly and hepatitis on the third day after insulin administration, and one case reported these symptoms on day 4. All 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 on the same day that he developed hypoglycemia, after treatment with multiple glucose tablets and juice. Our patient had poorly controlled type 1 diabetes, with chronic hyperglycemia and elevations in the HbA1c over the past few years. One possible explanation for the onset of abdominal symptoms prior to the detection and treatment of hypoglycemia is that baseline hyperglycemia led to glucose influx into 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 (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 (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.
Table 1. Glucose and liver enzymes during the first presentation

| Laboratory test | Reference range | 0 hour | 12 hours | 25 hours | 37 hours | 53 hours | Day 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     |
Table 2. Laboratory evaluation for causes of abdominal pain and hepatitis

| Variable                                                                 | Reference range | Results       |
|--------------------------------------------------------------------------|-----------------|---------------|
| Celiac panel: Total IgA                                                  | 63-484 mg/dl    | 102           |
| TTG IgA                                                                  | 0-20 units      | 4.2           |
| Cortisol (7.45 am)                                                       | 5.5-20 ug/dl    | 15.8 ug/dl    |
| Alpha 1 antitrypsin phenotype                                            | -               | PI*M1N        |
| Ferritin                                                                 | 22-322 ng/ml    | 20            |
| Ceruloplasmin                                                            | 20-60 mg/dl     | 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: 15-30mg/dl | Acetaminophen <10 ug/dl Salicylate: <2.5mg/dl |
| Urine Toxicology                                                         | --              | Negative      |
Table 3: Glucose and liver enzymes during the second presentation

| Laboratory test      | Reference range | 0 hour | 5 hours | 15 hours | 26 hours | Day 6 | 2 months |
|----------------------|-----------------|--------|---------|----------|----------|-------|----------|
| 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            | 0.8-3.85 ng/ml  | <0.10  |         |          |          |       |          |
| Total serum insulin  | 3-25 mU/L       | 249.7  |         |          |          |       | 19.5     |
Table 4. Case reports of hepatic glycogenosis following insulin overdose

| Reference year | Diabetes diagnosis | Age, gender | Insulin type and units | Presenting symptoms | Treatment prior to development of HG | Onset of symptoms |
|----------------|--------------------|-------------|------------------------|---------------------|-------------------------------------|------------------|
| 2001 [15]      | Non-diabetic       | 48 years, Female | 1000 units of long-acting insulin along with benzodiazepines and ASA | Coma with severe hypoglycemia, requiring intubation for 3 days | Boluses of 40% glucose, Continuous infusion of 20% glucose (1200-1400 g daily x 3 days). | On day 3, nausea, RUQ abdominal pain, hepatomegaly with worsening of liver enzymes |
| 2012 [16]      | Type 1             | 26 years, Male | 4800 units of glargine | Severe hypoglycemia | Parenteral 20% glucose, 10% glucose, oral fruit concentrate | On day 3, nausea, right sided abdominal pain and hepatomegaly, elevated liver enzymes, bilirubin elevation |
| 2006 [17]      | Type 2             | 41 years, Male | 180 units of glargine | Loss of consciousness | Parenteral glucose and hypercaloric feed. | Deranged hepatic function and hepatomegaly on day 3 |
| 2020 [13]      | Type 1             | 25 years, Male | 3600 units of insulin glargine and 2100 units of insulin lispro | Cold sweat, feeling groggy | Continuous 17.5% glucose infusion. About 900 g of glucose/day x 4 days | On day 4 with general fatigue, persistent right hypochondral pain, abdominal discomfort, and appetite loss, elevated liver enzymes |
| Our patient    | Type 1             | 16 years, Male | Unknown                | Severe hypoglycemia, abdominal pain, nausea | Multiple glucose tablets, juice | At admission, about 18 hours after the onset of |
hypoglycemia with pain abdomen, nausea, vomiting and elevated liver enzymes.

Data Availability: Data sharing is not applicable to this article because no data sets were generated or analyzed during the present study.
References:

1. Mauriac P Gros ventre, hepatomegalie, troubles de croissance chez les enfants diabetiques traites depuis plusieurs annee par l’insuline. Gaz Hebd Med Bordeaux 1930;26:402–4102.

2. Kim MS, Quintos JB. Mauriac syndrome: growth failure and type 1 diabetes mellitus. Pediatr Endocrinol Rev. 2008 Aug;5 Suppl 4:989-93. PMID: 18806715.

3. Abaci A, Bekem O, Unuvar T, Ozer E, Bober E, Arslan N, Ozturk Y, Buyukgebiz A. Hepatic glycogenosis: a rare cause of hepatomegaly in Type 1 diabetes mellitus. J Diabetes Complications. 2008 Sep-Oct;22(5):325-8. doi: 10.1016/j.diabcomp.2007.11.002. Epub 2008 Apr 16. PMID: 18413182.

4. Ikarashi Y, Kogiso T, Hashimoto E, Yamamoto K, Kodama K, Tanai M, Torii N, Takaie H, Uchigata Y, Tokushige K. Four cases of type 1 diabetes mellitus showing sharp serum transaminase increases and hepatomegaly due to glycogenic hepatopathy. Hepatol Res. 2017 Mar;47(3):E201-E209. doi:

5. Giordano S, Martocchia A, Tousson L, et al. Diagnosis of hepatic glycogenosis in poorly controlled type 1 diabetes mellitus. World J Diabetes. 2014;5(6):882-888. doi:10.4239/wjd.v5.i6.882

6. Bua J, Marchetti F, Faleschini E, Ventura A, Bussani R. Hepatic glycogenosis in an adolescent with diabetes. J Pediatr. 2010 Dec;157(6):1042. doi: 10.1016/j.jpeds.2010.06.018. Epub 2010 Jul 16. PMID: 20638077.

7. Sherigar JM, Castro J, Yin YM, Guss D, Mohanty SR. Glycogenic hepatopathy: A narrative review. World J Hepatol. 2018;10(2):172-185. doi:10.4254/wjh.v10.i2.172

8. Chatila R, West AB. Hepatomegaly and abnormal liver tests due to glycogenosis in adults with diabetes. Medicine (Baltimore). 1996 Nov;75(6):327-33. doi: 10.1097/00005792-199611000-00003. PMID: 8982149

9. Mukewar S, Sharma A, Lackore KA, Enders FT, Torbenson MS, Kamath PS, Roberts LR, Kudva YC. Clinical, Biochemical, and Histopathology Features of Patients With Glycogenic Hepatopathy. Clin Gastroenterol Hepatol. 2017 Jun;15(6):927-933.

10. Scapaticci S, D’Adamo E, Mohn A, Chiarelli F, Giannini C. Non-Alcoholic Fatty Liver Disease in Obese Youth With Insulin Resistance and Type 2 Diabetes. Front Endocrinol (Lausanne). 2021 Apr 6;12:639548. doi: 10.3389/fendo.2021.639548. PMID: 33889132; PMCID: PMC8056131.

11. Regnell SE, Lernmark A. Hepatic steatosis in type 1 diabetes. Rev Diabet Stud. 2011 Winter;8(4):454-67. doi: 10.1900/RDS.2011.8.4.454. Epub 2012 Feb 10. PMID: 22580727; PMCID: PMC3359690.

12. van den Brand M, Elving LD, Drent J, Van Krieken JH. Glycogenic hepatopathy: a rare cause of elevated serum transaminases in diabetes mellitus. Neth J Med. 2009 Dec;67(11):394-6. PMID: 20009116.

13. Fujisaki N, Kosai Y, Nojima T, Higaki T, Yamada T, Koga H, Gochi A, Naito H, Nakao A. Glycogenic hepatopathy following attempted suicide by long-acting insulin overdose in patient with type 1 diabetes. J Am Coll Emerg Physicians Open. 2020 May 25;1(5):1097-1100. doi: 10.1002/emp2.12093. PMID: 33145563; PMCID: PMC7593440.
14. Giordano S, Martocchia A, Toussan L, et al. Diagnosis of hepatic glycogenosis in poorly controlled type 1 diabetes mellitus. *World J Diabetes*. 2014;5(6):882-888. doi:10.4239/wjd.v5.i6.882

15. Jolliet P, Leverve X, Pichard C. Acute hepatic steatosis complicating massive insulin overdose and excessive glucose administration. *Intensive Care Med* 2001;27:313–6

16. Warriner D, Debono M, Gandhi RA, Chong E, Creagh F. Acute hepatic injury following treatment of a long-acting insulin analogue overdose necessitating urgent insulin depot excision. *Diabet Med* 2012;29:232–5.

17. Tsujimoto T, Takano M, Nishiofuku M, Yoshiji H, Matsumura Y, Kuriyama S et al. Rapid onset of glycogen storage hepatomegaly in a type-2 diabetic patient after a massive dose of long-acting insulin and large doses of glucose. *Intern Med* 2006; 45: 469–473.