



# CASE REPORT

## **Glycogenic Hepatopathy: A Complication of Type 1 Diabetes Mellitus**

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### **Introduction**

Glycogenic hepatopathy is an acquired glycogen storage disease seen in type 1 diabetes, particularly those that are not well controlled.<sup>1-3</sup> It causes elevated transaminase levels, hepatomegaly, and abdominal pain. It is less recognized than non-alcoholic steatohepatitis (NASH) which occurs more commonly in type 2 diabetes with metabolic syndrome, but is an important diagnosis to consider in the appropriate clinical setting.

### **Case Report**

A 25-year-old white female presented to the emergency department due to bilateral flank pain. The pain was present for two days and was progressing. It was stabbing in nature and did not radiate. The patient had associated nausea and vomiting. She also noted that the pain was similar to symptoms she had one month prior when she was treated for pyelonephritis.

The patient's past medical history was significant for uncontrolled type 1 diabetes mellitus diagnosed at age 12, hypothyroidism, and chronically elevated transaminase levels of undefined etiology. Additionally, she recently was treated with ceftriaxone and ciprofloxacin for pyelonephritis. Her medications included glargine insulin, insulins aspart, and levothyroxine. She reported smoking one-half pack of cigarettes per day, occasional marijuana use, and rare alcohol use. She had no knowledge of any family history of liver disease. Her

review of symptoms was negative, notably for dysuria, fever, or chills.

The patient was afebrile with normal vital signs. Her physical exam was benign other than mild costovertebral angle tenderness bilaterally. Initial labs showed a normal complete blood count, electrolytes, and kidney function. Transaminase levels were abnormal with a serum aspartate aminotransferase (AST) level of 870 units/L (normal < 37), an alanine aminotransferase (ALT) level of 272 units/L (< 65), and an alkaline phosphatase level of 262 units/L (< 136). The international normalized ratio was 0.9, the bilirubin level was 0.2 mg/dL (0.2 - 1.2), and albumin concentration was 3.2 gm/dL (3.4 - 4.5). Urinalysis showed trace leukocyte esterase activity, 3+ glucose, and 1+ bacteria. A urine drug screen was negative and acetaminophen and alcohol were not detected in the serum. Hemoglobin A1c was 11.0%.

Computed tomography (CT) revealed an enlarged liver with attenuation measured at 82 Hounsfield units (HU; normal for the liver is 40 - 60; Figure 1). Based on imaging results, hemochromatosis, hemosiderosis, or other heavy metal deposition was considered. Comparison was made to a CT scan done eight years previously which had similar findings and recommendations.

Review of the patient's prior hospitalizations revealed elevated transaminase levels dating back 11 years. Serologies for

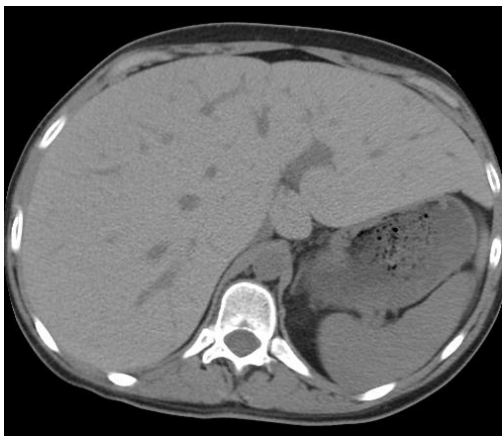


Figure 1. CT of the abdomen. The liver is enlarged and has increased attenuation at 82 Hounsfield units.

human immunodeficiency virus and viral hepatitis were negative over this time frame, but no other workup had been done. During the current hospitalization, the transaminase levels trended up over the first several days and a workup was initiated to determine the

cause of the elevation with the following results: ferritin level, 78 ng/ml (normal 7 - 283), percent saturation, 17% (11 - 46), total iron binding capacity, 322 mcg/dl (250 - 450), alpha-1-antitrypsin level, 94 mg/dl (90 - 200), ceruloplasmin level 20.7 mg/dl, (16 - 45), and absence of anti-nuclear, anti-smooth muscle, tissue transglutaminase, and endomysial antibodies.

The patient's transaminase levels peaked on day four of hospitalization with an AST level of 2,386 units/L and ALT level of 784 units/L. This was the highest they had been at any point in the past. A liver biopsy (Figure 2) showed pale cytoplasm on H&E stain, no evidence of fibrosis on trichrome stain, markedly positive glycogen staining on a periodic acid-Schiff stain (PAS), and washout of the PAS stain after addition of diastase (an enzyme that digests pure glycogen). These findings were consistent with glycogenic hepatopathy.

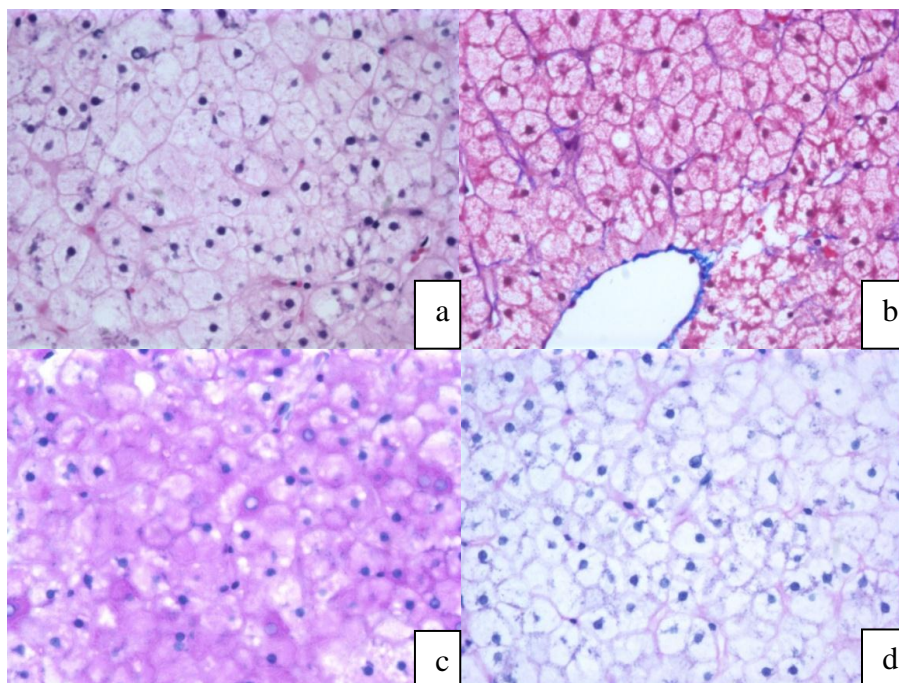


Figure 2. (a) H&E shows pale cytoplasm. (b) Trichrome shows no fibrosis. (c) PAS is positive for glycogen. (d) PAS washed out after diastase.

## Pathophysiology

Glycogenic hepatopathy (GH) is characterized by abnormal glycogen accumulation in the liver. It is an acquired disease seen in type 1 diabetes, generally patients with poor glycemic control.<sup>1-3</sup> It originally was described by Mauriac in 1930, after the discovery of insulin therapy for type 1 diabetes.<sup>4</sup> In children, it is a syndrome of hepatomegaly, growth impairment, and cushingoid features. In adults, it is seen as isolated liver disease without the other syndromic features.<sup>3</sup>

The classic presentation of GH is a triad of hepatomegaly, abdominal pain, and elevated serum transaminases, but not all of these features are required. CT scanning generally shows increased liver attenuation.<sup>5</sup> Definitive diagnosis is made by biopsy which shows glycogen accumulation within hepatocytes. Generally, fibrosis is minimal.

The glycogen accumulation seen in GH is dependent on high levels of both serum glucose and insulin at different times.<sup>1,3</sup> High serum glucose levels allow passive diffusion of glucose into hepatocytes where glucose is converted to glucose-1-phosphate by glucokinase and is trapped in the cell. Glucose-1-phosphate is converted to glycogen by glycogen synthase. Glycogen synthase is activated by dephosphorylation by glycogen synthase phosphatase. The concentration of this enzyme is maintained by insulin and its activity depends on glucose. In patients with poorly controlled type 1 diabetes who administer a large insulin bolus, hepatocytes will have a large amount of glucose-1-phosphate which will be converted to glycogen due to the activity of glycogen synthase. Glycogenic hepatopathy does not occur in all patients with poorly controlled type 1 diabetes. The development of GH is dependent on defects in regulatory proteins in susceptible patients (type 1 diabetes), which are clinically insignificant in the rest of the population.<sup>3</sup>

## Treatment and Prognosis

Treatment of GH is limited to more rigorous blood glucose control. Tight management of glucose and insulin levels can lead to complete resolution of the clinical, laboratory, and histologic findings.<sup>6-8</sup> Glycogenic hepatopathy rarely progresses to fibrosis. In the largest case series investigating histology, 2 of 14 patients had only mild fibrosis, while the remaining 12 patients had none.<sup>9</sup> This contrasts with NASH which is seen more commonly in type 2 diabetes with metabolic syndrome and has a much higher rate of fibrosis and cirrhosis (37% of patients had cirrhosis in one study).<sup>10</sup>

## Discussion

Some interesting aspects of GH are illustrated by this case. First, after admission, the transaminase levels trended up for the first four days. This may have been iatrogenic as she was given high doses of insulin to control her blood sugars. If true, it demonstrates the importance of high insulin levels for progression of this disease and may illustrate why GH was not described until after the discovery of insulin therapy. Additionally, this patient was known to have elevated transaminase levels for years, but on liver biopsy had no fibrosis, illustrating the typical lack of progression to fibrosis and cirrhosis in GH.

Our patient was informed that improvement in the control of her diabetes would reverse her liver disease. Three months after discharge, her hemoglobin A1c was 10.3%, down from 11.0% when she was hospitalized. Six months after discharge, her AST and ALT levels were 116 units/L and 87 units/L respectively, much lower than during her hospitalization.

## Conclusion

Glycogenic hepatopathy is an acquired disorder of glycogen accumulation within

hepatocytes seen exclusively in persons with poorly controlled type 1 diabetes, typically presenting as elevated transaminase levels, hepatomegaly, and abdominal pain. In contrast to NASH, GH less commonly progresses to fibrosis and cirrhosis.

### References

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Definitive diagnosis is made by liver biopsy, but an empiric trial of improved glucose control can be considered prior to biopsy in suspected cases. Treatment of GH is limited to improving glycemic control.

*Keywords:* liver diseases, glycogen storage, disease, diabetes mellitus, hepatomegaly