

# Glycogenic Hepatopathy

## An Underrecognized Hepatic Complication of Diabetes Mellitus

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**Abstract:** Reported are the clinical and pathologic features of glycogenic hepatopathy, a pathologic overloading of hepatocytes with glycogen that is associated with poorly controlled diabetes mellitus. Fourteen cases were studied by stains, including hematoxylin and eosin, trichrome, periodic acid–Schiff, and periodic acid–Schiff with diastase. Ultrastructural analysis was performed in 2 cases. Medical records were reviewed for clinical presentations, laboratory findings, and clinical outcomes. The individuals ranged from 8 to 25 years of age. All had type I diabetes mellitus with poor glycemic control. The clinical presentations included hepatomegaly, abdominal pain, and elevated transaminases (range, 50–1600 IU/L). The transaminases were dramatically elevated in 3 cases to greater than 10 times the upper limit of normal. All biopsies showed diffusely pale staining hepatocytes on hematoxylin and eosin stains, with excessive glycogen accumulation demonstrated by periodic acid–Schiff stains. Ultrastructural examination revealed marked glycogen accumulation in the cytoplasm and nuclei. Most cases showed no evidence for fatty liver disease: steatosis was absent in 12 of 14 cases, simple steatosis was seen in 1 of 14 cases, and mild steatohepatitis was present in 1 of 14 cases. Mallory hyaline was absent in all cases, acidophil bodies were only rarely seen, and inflammation was absent or minimally present. Fibrosis was typically absent, with only 2 cases demonstrating focal mild fibrosis. Three patients had adequate follow-up and demonstrated improvement of liver enzyme levels

with control of blood glucose. We conclude that glycogenic hepatopathy can cause hepatomegaly and significant transaminase elevations in individuals with type I diabetes mellitus. The pathology is distinct from steatohepatitis.

**Key Words:** glycogen, glycogenosis, diabetes mellitus, hepatomegaly, Mauriac syndrome

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Liver pathology in individuals with type II diabetes mellitus has been well characterized and ranges from minimal nonspecific inflammatory changes to nonalcoholic fatty liver disease (NAFLD).<sup>17</sup> NAFLD is a term that includes both simple fatty change as well as nonalcoholic steatohepatitis (NASH) and requires the clinical exclusion of excess alcohol use.<sup>5</sup> The histologic findings in NAFLD reflect dysregulation of fat and glucose metabolism coupled with other incompletely understood factors leading to hepatic inflammation.<sup>7</sup> Whereas liver biopsy specimens in type I patients with diabetes, like type II patients with diabetes, can show NAFLD,<sup>13</sup> biopsy specimens in type I patients with diabetes can also show a unique pathologic change that we have designated glycogenic hepatopathy (GH).

GH can present with different clinical signs and symptoms, the most dramatic being a syndrome first described by Mauriac of growth retardation, hepatomegaly, cushingoid features, and delayed puberty.<sup>14</sup> Whereas the Mauriac syndrome was first described 75 years ago, the histologic findings of GH remain under-recognized. We have encountered cases of GH that posed diagnostic challenges to clinicians and pathologists based on the relative lack of awareness of this entity. For example, 3 of the cases in this study were sent in consultation (to L.F., M.M.Y.) with an original diagnosis of glycogen storage disease. The aim of this study is to describe the clinical characteristics and pathologic features of GH to improve wider recognition of this lesion.

### METHODS

Institutional guidelines regarding human experimentation were followed. Fourteen liver biopsies with histologic features of GH were collected from the files of the participating institutions. Pertinent clinical and

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**TABLE 1** Histologic Findings on Liver Biopsies of Patients With Glycogenic Hepatopathy

Patient No.	Hepatocyte Swelling	Glycogenated Nuclei	Fatty Change†	Inflammatory Cell Infiltrate	Acidophil Bodies	Pericellular Fibrosis	Periportal Fibrosis	Giant Mitochondria	Additional Features
1	+++	+++	—	—	—	—	—	—	
2	+++	+++	—	+	—	—	+	—	EM confirmed glycogen
3	+++	+++	G1	+	+	+	—	+	Mild NASH
4	+++	++	—	—	—	—	—	—	
5	+++	+++	—	+	—	—	—	—	
6	+++	+++	G1	+	—	—	—	—	
7	+++	—	—	—	—	—	—	—	
8	+++	+++	—	+	—	—	—	—	
9	+++	+++	—	—	—	—	—	++	
10*	+++	++	—	—	—	—	—	++	EM confirmed glycogen
11	+++	++	—	—	—	—	—	+	
12	+++	+++	—	—	—	—	—	++	
13	+++	+++	—	+	—	—	—	+	
14	+++	+++	—	—	—	—	—	+	

—, not noted; +, mild degree or few in number; ++, moderate in degree or number; +++, severe or diffuse; many; EM, electron microscopy; NASH, nonalcoholic steatohepatitis.

\*Follow-up liver biopsy a few months later when patient's diabetes was stable showed normal histology.

†Grading for fatty change: —, 0 to < 5%; G1, 5%–33%; G2, 34%–66%; G3, > 66%.

laboratory data were collected corresponding as closely as possible to the time of liver biopsy. Hematoxylin and eosin, Masson trichrome, periodic acid–Schiff (PAS), and periodic acid–Schiff with diastase (PAS/D) stains were reviewed. Stains were performed using standard histologic techniques at the referring institution or the coauthor's institution. All cases were also reviewed and collated by two of the authors (Y.Y.C., L.F.). Biopsies were semi-quantitatively evaluated for the pathologic features listed in Table 1, using a scale from 0 (none) to +++ (severe and /or diffuse). Ultrastructural analysis by transmission electron microscopy using standard techniques for glycogen preservation was performed in 2 cases. The biopsies were also examined for features of steatohepatitis. Steatohepatitis was defined as the combi-

nation of steatosis, lobular inflammation, acidophilic bodies, and pericellular fibrosis. The biopsies were also searched for Mallory hyaline and mega-mitochondria. Ballooning of hepatocytes was not used as a criterion for steatohepatitis, as ballooning would potentially be obscured by the swollen, glycogen-laden hepatocytes.

## RESULTS

### Clinical and Laboratory Findings

The clinical manifestations of GH included hepatomegaly, abdominal pain, and other symptoms such as nausea and vomiting (Table 2). All individuals had elevated serum glucose levels. Other clinical findings included ketoacidosis and elevated hemoglobin A1c

**TABLE 2** Clinical and Laboratory Data in Glycogen Hepatopathy

Case No.	Age (yr)/ Sex	DM Type	Presentation	Hepatomegaly	Glucose (mg/dL)	HbA1c (%) (N < 6)	ALT/AST(U/L) (N < 36/ < 45)	Alkaline Phosphatase (U/L) (N < 142)
1	19/F	I	RUQ pain, KA	+ †	520	NA	83/97	80
2	12/M	I	RUQ pain, hepatomegaly, KA	+ †	635	13.5	47/49	182
3	22/F	I	RUQ pain, abnormal LTs	+	183	NA	77/48	62
4	8/M	I	Mauriac syndrome*	+	H	NA	H/H	NA
5	15/F	I	NA	NA	NA	NA	N/N	NA
6	22/M	I	RUQ pain, weight loss, KA	+ †	404	16	360/1100	251
7	25/M	I	Vomiting, hypoglycemia, ascites, abnormal LTs	NA	40	10.8	1128/1629	298
8	16/M	I	Nausea, vomiting, fatigue, KA, abnormal LTs	NA	H	NA	H/H	NA
9	20/M	I	Hepatomegaly	+	288	9.9	120/N	147
10	18/F	I	Abnormal LTs	NA	137	10.8	57/N	N
11	28/M	I	Abnormal LTs	NA	H	NA	1544/1099	384
12	34/M	I	Hepatomegaly	+	259	10.1	NA/N	N
13	16/M	I	Hepatomegaly and abnormal LTs	+	365	NA	1354–1413	476
14	23/F	I	Hepatomegaly, RUQ pain, nausea, SOB	+	NA	NA	224/255	307

RUQ, right upper quadrant; KA, ketoacidosis; LTs, liver tests; NA, not available; H, elevated level; N, normal; SOB, shortness of breath.

\*Growth retardation, delayed puberty, hepatomegaly, cushingoid features, and hypercholesterolemia.

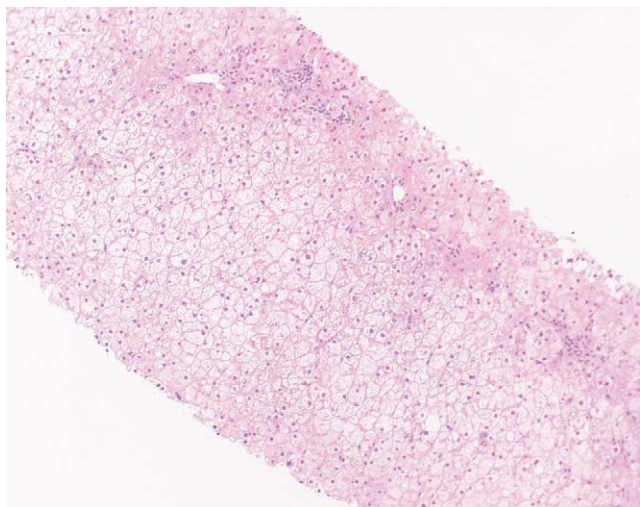
†Massive hepatomegaly.

levels, indicating poor long-term glycemic control. Rarely, hypoglycemia and ascites were present. The serum levels of alanine aminotransferase and aspartate aminotransferase levels varied significantly, from normal (1 of 14 cases, 7%) to marked elevations that were in some cases 10 times or greater than the upper limits of normal (3 of 14 cases, 21%). Modest serum alkaline phosphatase elevations were common.

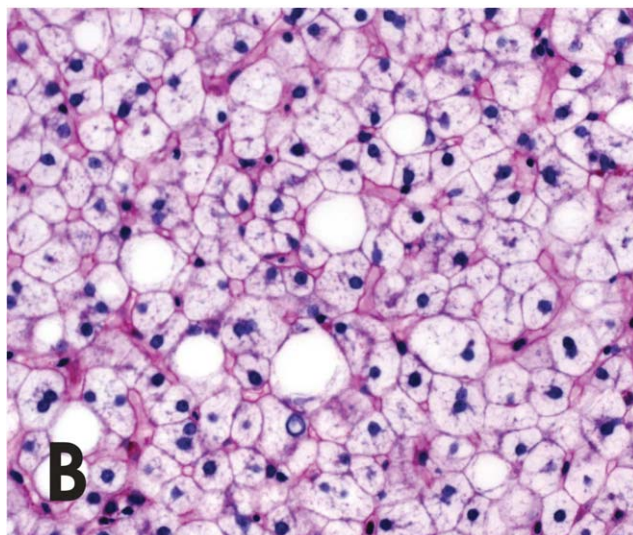
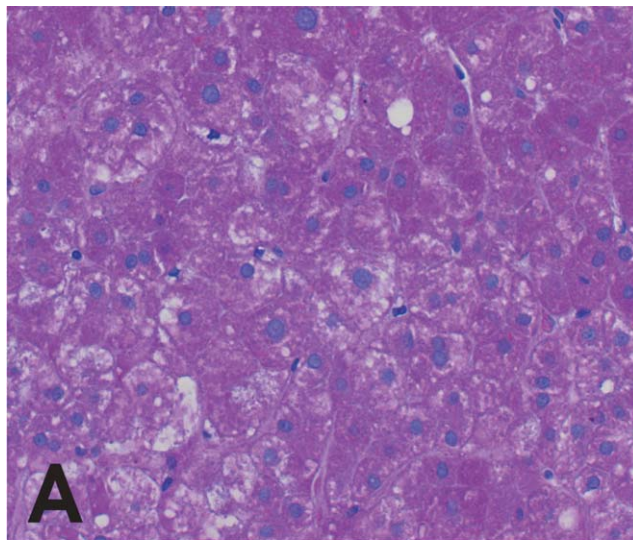
### Histologic Findings

Overall, the liver parenchyma and architecture were preserved (Fig. 1). The most striking finding was a diffuse hepatocellular change characterized by pale hepatocytes with cytoplasmic rarefaction and accentuation of the cell membranes (Fig. 1). Sinusoids often appeared compressed by the swollen hepatocytes. Numerous hepatocytes exhibited glycogenated nuclei. Abundant cytoplasmic glycogen deposits were demonstrated by PAS stains (Fig. 2A), which disappeared after digestion with diastase (Fig. 2B). The presence of glycogen accumulation in the cytoplasm (Fig. 3A) and in some nuclei was confirmed on ultrastructural examination in 2 cases, similar to previously reported findings.<sup>13</sup>

Steatosis was either absent (12 of 14 cases) or mild (2 of 14 cases). Only 1 case showed changes sufficient for a diagnosis of mild steatohepatitis. Overall, inflammation was absent (8 cases) or minimal (6 cases). Two cases showed mild fibrosis, one with periportal fibrosis and the other with pericellular fibrosis; the latter being the case with concurrent mild steatohepatitis. Acidophil bodies were rare. Giant mitochondria were commonly found (Fig. 3B).



**FIGURE 1.** The liver architecture is preserved. The hepatocytes are diffusely swollen with rarefaction of the cytoplasm and accentuation of the cell membranes. Sinusoids appear compressed by the swollen hepatocytes, imparting a paved or mosaic appearance to the liver parenchyma. Numerous hepatocytes exhibit glycogenated nuclei.



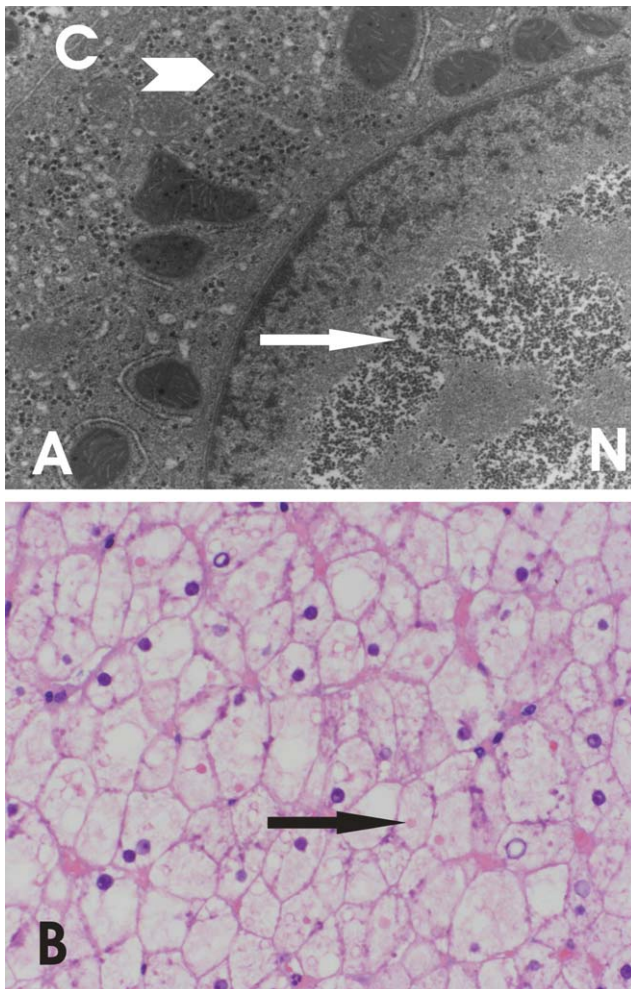
**FIGURE 2.** A, Abundant cytoplasmic glycogen deposits are demonstrated by a PAS stain. B, Diastase digestion removes the glycogen. Focal mild large droplet fatty change is also present in this example.

### Clinical Course

Three patients had adequate follow-up, and all showed improvement of transaminase levels and reduced hepatomegaly with control of blood glucose. One of these patients had a follow-up liver biopsy that demonstrated an essentially normal liver.

### DISCUSSION

Glycogen loading of the liver was first documented as a component of Mauriac's syndrome in 1930.<sup>14</sup> In this syndrome, glycogen loading, hepatomegaly, and abnormal liver enzymes are associated with other features, including growth retardation and/or dwarfism, delayed puberty, cushingoid features, and hypercholesterolemia.



**FIGURE 3.** A, Ultrastructural examination (case no. 2) revealed marked glycogen accumulation in the cytoplasm (C) in a rosette form (arrowhead) and nucleus (N) in a dispersed pattern (arrow). B, Giant mitochondria are seen as round, red to pink globules within the cytoplasm of the hepatocytes (arrow). Mild small droplet fat is also present in this case (case no. 12).

Over time, it has been recognized that glycogen loading can be present without the full spectrum of changes seen in the Mauriac syndrome.<sup>13</sup> This process has variably been referred to as hepatic glycogenosis,<sup>4</sup> liver glycogenosis,<sup>3</sup> liver glycogen storage,<sup>8,22</sup> and diabetes mellitus-associated glycogen storage hepatomegaly.<sup>18</sup> We recognize that any of these terms may be reasonable nomenclature for this lesion. However, we propose the term “glycogenic hepatopathy” for this pattern of glycogen-loading of the hepatocytes in the clinical setting of either hepatomegaly or elevated transaminase levels, as we suggest the term “glycogenic hepatopathy” better reflects the noninflammatory pathologic findings.

Our cases show similar clinical and histologic features to those described by others.<sup>3,4,8,16,18,19,22</sup> Based on our results and those of others (Table 3), individuals

with GH can be adults or children with marked or prolonged hyperglycemia who are treated with insulin, usually in the setting of type I diabetes mellitus. Most individuals had poor glycemic control and elevated liver transaminases. All individuals with available clinical history had hepatomegaly. Coincidental fatty change or NASH was uncommon (<20% in combined studies), and no evidence was noted for the development of significant fibrosis or cirrhosis as can be seen in NASH.

Glycogenic hepatopathy appears to be underrecognized by clinicians, radiologists, and pathologists, even though this entity has been described several times over the years in the medical literature. This may be due to both the rarity of this lesion as well as to the more common (and current) emphasis on fatty liver disease.<sup>6</sup> Glycogenic hepatopathy has not been reported in the pathology literature, which may further limit the exposure of pathologists to this entity. In addition, ultrasound does not distinguish fatty liver from glycogen overload,<sup>3,4,16,22</sup> so clinicians may assume that a patient with hepatomegaly has fatty liver if no biopsy is obtained.

The histology of GH demonstrates these key features: 1) marked glycogen accumulation leading to pale, swollen hepatocytes, 2) no or mild fatty change, 3) no or minimal inflammation, 4) no or minimal spotty lobular necrosis, and 5) intact architecture with no significant fibrosis. The key clinical features are hepatomegaly and elevated transaminases, which in some cases can be dramatically elevated. Even in those cases with marked transaminase elevations, there is no histologic evidence that the enzyme elevations are due to liver necrosis per se, and their elevation presumably reflects sufficient hepatocyte injury to cause enzyme “leakage” instead of cell death. We suspect a similar mechanism (marked accumulation of hepatocellular glycogen leading to enzyme leakage) explains the observations of transient elevations in liver transaminases following insulin loading to treat diabetic ketoacidosis.<sup>1,20</sup> In GH, liver transaminases typically return to normal with adequate control of blood sugar levels, even in those cases with marked enzyme elevations.<sup>3,4,16,19,21</sup> As seen in case no. 7 in this study, ascites can also rarely be part of the clinical presentation of GH. The underlying pathophysiology is unclear but may involve sinusoidal compression by the glycogen-laden hepatocytes. Ascites has been reported in the setting of GH previously,<sup>1,4</sup> and improved significantly with adequate control of blood sugar.

GH is also known to occur in one additional clinical setting: following short-term high-dose steroid therapy.<sup>11</sup> The clinical presentation of hepatomegaly and elevated transaminases elevations as well as the histologic findings are identical to that seen in the setting of diabetes mellitus and imply a common mechanism of glycogen trapping within hepatocytes. The ability of steroids to induce GH has been confirmed by animal studies.<sup>9</sup>

Mechanistically, GH results from excess accumulation of glycogen in hepatocytes, occurring when marked or prolonged hyperglycemia is treated with insulin.<sup>16</sup> Glucose in the sinusoidal blood is rapidly taken up by

**TABLE 3** Selected Summary of Representative Literature on Glycogenic Hepatopathy

Authors	Patients (N)	Adults/Children	DM Type I/II/Unknown	Insulin Treatment	Hepatomegaly	Increased AST/ALT
Evans et al <sup>8</sup>	4	1/3	4/0/0	4/4	4/4	NA
Olsson et al <sup>19</sup>	4	3/1	3/1/0	3/3	3/3	4/4
Nakamuta et al <sup>18</sup>	1	1/0	0/1/0	Not insulin dependent by report but on high doses of insulin	1/1	1/1
Chatila and West <sup>4</sup>	11	8/3	6/3/2	11/11	9/11	9/11
Munns et al <sup>16</sup>	3	0/3	3/0/0	3/3	3/3	3/3
Torres and Lopez <sup>22</sup>	1	1/0	1/0/0	1/1	1/1	1/1
Carcione et al <sup>3</sup>	2	0/2	2/0/0	2/2	2/2	2/2
Total	26	13/12	18/5/2	24/24	23/25	20/22

DM, diabetes mellitus; I, type I (juvenile); II, type II, adult-onset; AST/ALT, aspartate aminotransferase/alanine aminotransferase. NA, not available.

hepatocytes, and this is followed by rapid conversion of the glucose to glycogen, which is then trapped within the liver (Fig. 4). This is in contrast with the central role of insulin resistance and hyperinsulinemia as the cause of fat accumulation in hepatocytes in NAFLD.<sup>2</sup>

GH is not the only pathologic finding seen in type I diabetes mellitus. In a study of liver biopsy findings in 99 cases of hepatomegaly in diabetic children, Lorenz and Bärenwald found that most cases of hepatomegaly were related to glycogen accumulation, with moderate glycogen accumulation in 22% of cases and pronounced glycogen accumulation in 19% of cases.<sup>13</sup> Fatty liver appeared to explain the hepatomegaly in another 8% of individuals, although mild fatty change was seen in nearly half of the total number of cases overall. The differential for elevated liver enzymes in type I diabetes also includes drug effect as well as hepatosclerosis, in which dense fibrosis is deposited in the perisinusoidal spaces in a nonzonal fashion in the absence of NAFLD or GH.<sup>10</sup>

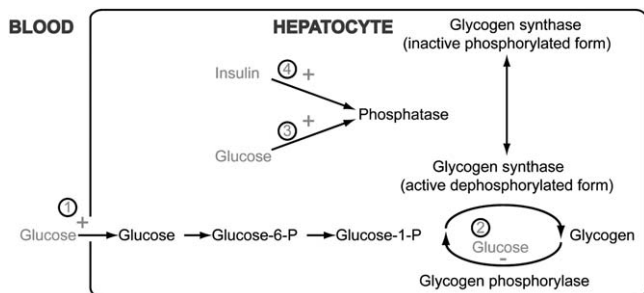
At the time of GH presentation, the clinical differential usually includes NAFLD, from which GH is histologically easily distinguished as discussed above. After histologic review, the differential diagnosis may also include the possibility of glycogen storage disease.<sup>12,15</sup> The hepatocytes in both entities are markedly swollen and filled with glycogen. While a subtle clue can be the

presence of greater cytoplasmic clumping of glycogen in glycogen storage disease, there can be significant histologic overlap. However, clinical parameters, such as the poorly controlled diabetes and response to diabetic control of GH, are key features to distinguish this entity from a glycogen storage disorder. Finally, microvesicular fatty change may also be in the histologic differential but can be distinguished by the strong PAS positivity of GH as well as the clinical setting.

In summary, GH most commonly occurs in individuals with type I diabetes mellitus and poorly controlled blood sugar. Clinically, the presentation varies but typically includes hepatomegaly and transaminase elevations. Histologically, GH manifests as large, swollen, glycogen-laden hepatocytes without significant fatty change, inflammation, lobular spotty necrosis, or fibrosis. The pathology is distinct from steatohepatitis.

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**FIGURE 4.** Pathogenesis of hepatocellular glycogen accumulation (modified from Munns et al<sup>16</sup>): Synergistic effects of hyperglycemia and insulin treatment in glycogenic hepatopathy in poorly controlled DM.

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