Diagnosis of hepatic glycogenosis in poorly controlled type 1 diabetes mellitus

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Abstract
Hepatic glycogenosis (HG) in type 1 diabetes is a underrecognized complication. Mauriac firstly described the syndrome characterized by hepatomegaly with altered liver enzymes, growth impairment, delay puberty and Cushingoid features, during childhood. HG in adulthood is characterized by the liver disorder (with circulating aminotransferase increase) in the presence of poor glycemic control (elevation of glycated hemoglobin, HbA1c levels). The advances in the comprehension of the metabolic pathways driving to the hepatic glycogen deposition point out the role of glucose transporters and insulin mediated activations of glucokinase and glycogen synthase, with inhibition of glucose-6-phosphatase. The differential diagnosis of HG consists in the exclusion of causes of liver damage (infectious, metabolic, obstructive and autoimmune disease). The imaging study (ultrasonography and/or radiological examinations) gives information about the liver alterations (hepatomegaly), but the diagnosis needs to be confirmed by the liver biopsy. The main treatment of HG is the amelioration of glycemic control that is usually accompanied by the reversal of the liver disorder. In selected cases, more aggressive treatment options (transplantation) have been successfully reported.

INTRODUCTION
Primary glycogenosis or glycogen storage disease is a well known hereditary disease affecting liver and muscles, characterized by the presence of hepatomegaly, hypoglycemia, muscle weakness and growth delay. On the contrary, secondary glycogenosis (hepatic glycogenosis [HG]) is less described in the literature, but it may be frequently
observed and underrecognized in type 1 diabetes (T1D)\[10\]. Mauriac\[2\] firstly described the syndrome in 1930. The main features in prepuberal children are hepatomegaly with increased liver enzymes, growth impairment, delay puberty and Cushingoid features in poorly controlled T1D\[10\]. In young adults with T1D the syndrome is uncomplete, and, in fact, only hepatomegaly with increased liver enzymes are present. The latter alterations are often underrecognized or confused with fatty liver disease or non-alcoholic steatohepatitis (NASH), that is common in T2D\[12\]. In rare cases, glycogen storage hepatomegaly has been described also in T2D\[13\].

**PATHOPHYSIOLOGY**

As pointed out by Wasserman\[11\], 4 grams of glucose circulates in the blood (a small fraction of the body mass) and 100 grams of glycogen are present in the liver. In glucose homeostasis, the liver plays a significant role for synthesis, storage and redistribution of carbohydrates, with opposite effects during hyperglycemic (glucose uptake and glycogen synthesis) and hypoglycemic conditions (glycogenolysis and gluconeogenesis)\[3\].

The glucose transport into cells is mediated by fourteen members of membrane glucose transporter (GLUT) molecules, divided into three families (Classes 1 to 3). The expression of the GLUTs varies between different cellular subtypes in liver (hepatocytes, endothelial cells, Kupffer cells and cholangiocytes)\[14\].

The liver is not considered as an insulin-sensitive tissue, such as skeletal and cardiac muscle, brown and white adipose tissue and endothelial cells. In fact, the transport of glucose into the hepatocytes is mainly mediated by the GLUT2 (insulin-independent, low-affinity, high-capacity with a Km of 10-20 mmol/L), but hepatocytes also express lower levels of GLUT1, GLUT3, GLUT4 (insulin-dependent), GLUT8, GLUT9, GLUT10\[15,16\] (Figure 1).

After the entrance, glucose is available for the intracellular metabolism. Glucokinase is a phosphorylating enzyme, acting with not stringent substrate specificity for glucose (it is able to phosphorylate hexoses like mannose or fructose in addition to glucose), to produce glucose-6-phosphate (G6P)\[17\]. There are four mammalian isoenzymes (hexokinases I - IV or A-D), displaying extensive sequence identities\[18\]. Glucokinase (GCK, or hexokinase IV or D) has a low affinity for glucose (Km approximately equal to 6 mmol/L) and a rate of reaction with sigmoid dependence on intracellular glucose concentration (cooperativity), operating as an ultrasonic physiological glucose sensor in hepatocytes with non-limiting glucose transport. If blood glucose is below 5 mmol/L (90 mg/dL) there is no significant effect of GCK on G6P production and subsequent steps, ensuring that hepatic glycogen synthesis is only engaged when blood glucose levels are high.

In the human liver, expression of GCK is strictly dependent on the presence of insulin, and the sterol regulatory element binding protein (SREBP1c), a master regulator of lipogenic enzymes, has been proposed to be a mediator of insulin induction of GCK\[19\].

Moreover, the GCK activity is modulated by the GCK regulatory protein (GCKRP) that binds and inhibits GCK, competitively with respect to glucose\[20\]. GCK is localized to the nucleus of the hepatocyte, where it is retained by GCKRP, but moves into the cytosol when glucose levels increase.

The hydrolysis of G6P to glucose (the inverse reaction of GCK) is mediated by the enzyme glucose-6-phosphatase (G6Pase), and its deficiency causes the impaired glycogenolysis of one type of the genetic accumulation of glycogen in hepatocytes, previously described by Von Gierke [glycogen storage disease type I (GSD1a)]\[21,22\]. GSD1a has typical hypoglycemic events after a four to six hour fast (differentiating GDS1a from T1D), lactic acidosis, hypersplenism, and hyperuricemia\[3\].

The G6P is successively converted into G1P by phosphoglucomutase. Then, uridine diphosphate (UDP)-glucose pyrophosphorylase transforms G1P into UDP-glucose in the presence of uridine triphosphate, releasing inorganic pyrophosphate.

The G6P, after the phosphorylation by GCK, functions as an allosteric activator of the phosphorylated glycogen synthase (GS) for the glycogen synthesis\[24\]. Insulin significantly stimulates the glycogen synthesis in hepatocytes. Insulin binds the α-subunit of insulin receptor (IR) on the cellular surface of hepatocytes, inducing the dimerization of the αβ2 complex and the tyrosine kinase activity of the β-subunits. Then, the IR is auto-phosphorylated and the IR activation recruits and phosphorylates several substrates, including insulin receptor substrate 1-4. The downstream signaling proteins activates phosphotyrosine-3-kinase (PI3K) to protein kinase B (PKB, also known as Akt signaling cascade), a pathway controlled via a multistep process\[25\]. In particular, the activation of PI3K converts phosphatidylinositol (3,4)-bisphosphate to phosphatidylinositol (3,4,5)-trisphosphate (PIP3). The 3-phosphoinositide-dependent protein kinase 1 and 2 (PDK1 and PDK2) phosphorylate and activate PKB/Akt, allowing to bindPIP3 at the plasma membrane. The activation of PKB/Akt phosphorylates and inhibits glycogen synthase kinase 3 (GSK3). GSK3 is a negative regulator of GS, through the phosphorylation at COOH-terminal residues. The result of insulin signal transduction is the GS dephosphorylation that activates the enzyme and the glycogen production. The GS is the rate-limiting enzyme for glycogen synthesis and it catalyzes the addition of α,1,4-linked glucose units from UDP-glucose to a nascent glycogen chain\[26\]. The UDP-glucose is the glycosyl donor in the reaction catalyzed by GS. There are two GS isofoms: the muscle GS (encoded by GYS1 gene), and the liver isoform (encoded by GY2 gene)\[27\].

Glycogen is a branched polymer of glucose residues connected by α,1,4-glycosidic linkages formed by the enzyme GS and branchpoints formed via α,1,6-glycosidic linkages, introduced by the branching enzyme, occurring...
every 8-12 glucose units.

New glycogen synthesis begin near the plasma membrane, at the periphery of the hepatocyte. Then, glycogen deposits grow from the periphery towards the interior of the cell. Through this way of glycogen deposition, hepatocytes may store large amounts of glycogen.

Glycogen degradation takes place in the reverse order. Glycogen phosphorylase (GP) is the key enzyme in glycogenolysis, yielding G1P\(^ {28} \). When hepatocytes are depleted of glucose, the GP-mediated phosphorolysis of glycogen proceed from the interior to the exterior of the hepatocyte\(^ {29} \). Phosphorylase kinase stimulates GP and protein phosphatase 1 inhibits phosphorylase kinase and GP.

Besides stimulating the glycogen synthesis, insulin severely inhibits hepatic glucose output, suppressing gluconeogenesis and glycogenolysis, by inhibiting expression and activity of the key enzymes phosphoenolpyruvate carboxykinase (PEPCK) and G6Pase\(^ {30} \).

The inhibition of gluconeogenesis and glycogenolysis are IR-mediated PI3K and Akt dependent effects. Akt translocates into the nucleus, where it phosphorylates FOXO1 (a member of the O-class of forkhead/winged helix transcription factors), inhibiting PEPCK and G6Pase gene transcription\(^ {31} \). Moreover, Akt phosphorylates and inhibits CRTC2, cAMP response element binding protein-regulated transcription coactivator-2, also reducing hepatic gluconeogenesis\(^ {32} \).

Adolescent diabetic patients with their metabolic activity, dietary intake, and disease state (high frequency of ketoacidosis and increase in exogenous insulin) represents a high-risk subjects, with diabetes control often deteriorating\(^ {33} \).

In T1D patients with poor glycemic control, two
combined events are usually present, promoting hepatic glycogen deposition: hyperglycemia (as pointed out by increased blood glucose level and glycated hemoglobin, HbA1c) and consequent large amount of insulin (as demonstrated by elevated insulin dose as UI/kg of body weight/day). In hyperglycemia, glucose passively enters the hepatocytes by insulin-independent GLUT2, and it is rapidly phosphorylated, with inhibition of its release from hepatocytes[33]. The GCK convert the glucose into the G6P, with subsequent trapping in the hepatocyte. Then, an increased insulin administration promotes the polymerization of G6P in glycogen by GS, driving the consequent liver damage become evident with the blood release of aminotransferases.

Repealed ketoacidosis episodes in T1D increase the risk for hepatic glycogen overload, since diabetic ketoacidosis (a fatal complication of poor controlled diabetes) is usually treated with sustained levels of intravenous insulin (in the presence of high glucose blood concentrations).

## DIAGNOSIS

Nowadays Mauriac syndrome during childhood is uncommon especially with the advent of new insulin analogues and intensive insulin regimens. More frequently, patients affected are teenager or young adults and the diagnosis may be difficult[34]. During adulthood, the key symptoms are hepatomegaly, abdominal pain, and other symptoms such as nausea and vomiting. Laboratory findings are high levels of glucose, glycated hemoglobin (HbA1c, demonstrating a poor long-term glycemic control) and aminotransferases [aspartate and alanine, Aspartate-aminotransferase (AST) and Alanine-amino transferase (ALT), respectively] suggesting liver damage[35]. The range of AST/ALT values is from 47/48 to 4000/1900 UI/L (Table 1). The investigations include investigations for infectious diseases, metabolic and autoimmune liver tests to exclude all these possible combined etiologies, as well as liver biopsy.

### Table 1 Summary of hepatic glycogenosis in type 1 diabetes patients

| Ref. | Sex | Age (yr) | BMI | AST (U/L) | ALT (U/L) | HbA1c (%) | Insulin (U/kg) | Glucose (mg/dL) | US exam | CT scan | Biopsy |
|------|-----|---------|-----|-----------|-----------|-----------|---------------|----------------|----------|---------|--------|
| [51] | M   | 16      | 20  | 66        | 58        | 11.1      | 0.98          | 198            | X        | X       |        |
| [52] | F   | 17      | 138 | 164       | 12        |           |               |                | X        | X       |        |
| [54] | M   | 19      | 262 | 519       | 12.7      | X         | X             | X              | X        | X       |        |
| [55] | F   | 19      | 27  | 98        | 49        | 7.9       |               |                | X        | X       |        |
| [56] | F   | 19      | 23  | 800       | 12.2      | X         | X             | X              | X        | X       |        |
| [57] | F   | 3       | 300 | 350       | 9.5      | 1.5       | 522           |                | X        | No      |        |
| [58] | M   | 22      | 18.6| 1028      | 13.8      | X         | X             |                | X        | X       |        |
| [59] | F   | 20      | 21  | 1310      | 13.6      | X         | X             |                | X        | X       |        |
| [60] | M   | 13      |     | 1000      | 15.3      | X         | X             |                | X        | X       |        |
| [61] | F   | 20      | 249 | 383       | 13.3      | X         | X             |                | X        | X       |        |
| [54] | F   | 13      |     | 113       | 8.8      | 890       | X             |                | X        | X       |        |
| [63] | F   | 13      |     | 83        | 97        | 520       | X             |                | X        | X       |        |
| [64] | M   | 47      | 49  | 13.5      | 635       | X         | X             |                | X        | X       |        |
| [65] | F   | 22      | 48  |           | 183       | X         | X             |                | X        | X       |        |
| [66] | M   | 8       |     | H         | H         |           | X             |                | X        | X       |        |
| [67] | F   | 15      |     | N         | N         |           | X             |                | X        | X       |        |
| [68] | M   | 22      | 360 | 1100      | 16.0      | 404       | X             |                | X        | X       |        |
| [69] | M   | 12     | 1128| 1629      | 10.8      |           | X             |                | X        | X       |        |
| [70] | M   | 16      |     | H         | H         |           | X             |                | X        | X       |        |
| [71] | M   | 120     | N   | 9.9       | 288       | X         | X             |                | X        | X       |        |
| [72] | F   | 18      | 57  | N         | 10.8      | 137       | X             |                | X        | X       |        |
| [73] | M   | 1544    | 1099|           | H         | X         | X             |                | X        | X       |        |
| [74] | M   | 14     | 10  |           | 259       | X         | X             |                | X        | X       |        |
| [75] | M   | 16      | 1354| 1413      | 365       | X         | X             |                | X        | X       |        |
| [76] | F   | 23      | 224 | 255       |           | X         | X             |                | X        | X       |        |
| [77] | F   | 19      | 199 | 14.6      |           | X         | X             |                | X        | X       |        |

*Recent ketoacidosis; *Magnetic resonance imaging. H: High level; N: Normal levels; M: Male; F: Female; BMI: Body mass index; AST: Aspartate-amino transferase; ALT: Alanine-amino transferase; HbA1c: Glycated hemoglobin; US: Ultrasound; CT: Computed tomography.
cases and make the differential diagnosis. The ultrasound examination of the liver is a simple and useful procedure to have information about the dimension and the characteristics of the liver tissue. In few cases, T1D patients were submitted to an abdomen computed tomography scan. Unfortunately, HG cannot be clinically distinguished from non-alcoholic fatty liver disease or non-alcoholic steatohepatitis (NASH) by history, physical examination or ultrasound: the gold standard examination is the liver biopsy. The preparation of the tissue is very important for the identification of the glycogen in tissue sections. The Carnoy’s solution is rapid acting, gives good nuclear preservation, retains glycogen and dissolves lipids. The cytoplasmic swelling due to glycogen can be quickly demonstrated by the staining with Best’s carmine or periodic acid-Schiff (PAS) with and without diastase since the slides treated with diastase, that digest the glycogen, lack the PAS positive staining. The main histological features of HG are marked glycogen accumulation leading to pale swollen hepatocyte, no or mild fatty change, no or minimal inflammation, no or minimal spotty lobular necrosis, and intact architecture with no significant fibrosis. Best’s carmine is another common used stain for glycogen, that appears bright red in sections. On the contrary, in hematoxylin & eosin sections, pale hepatocytes loose their glycogen during tissue preparation and may give a hint to hepatic glycosgenosis (Figure 2).

Navigator-gated and gradient-echo shimmed point-resolved spectroscopy with proton hydrogen$^1$ (1H) magnetic resonance (MR) has been recently proposed to quantify liver glycogen concentrations in vivo, even if this measurement is more challenging than just lipid quantification. In previous studies, an MR technique was used with (1-13C) glucose to measure changes in net hepatic glycogen concentration in normal and diabetic subjects.

To our best knowledge, in only one study the authors investigated the liver by the means of the MR imaging, with anatomical purposes.

Whereas it is well known that glycogen storage diseases, particularly type I, develop hepatic adenoma that potentially progress into hepatocellular carcinoma (HCC), to our best knowledge no data have been published about the association of diabetic glycosgenosis and the progression of carcinogenesis to HCC.

**TREATMENT**

The more the T1D patients (and their caregivers) obtain a good glycemic control, the more HG is expected to be minimal.

The Diabetes Control and Complication Trial (DCCT) is a well-known multicenter randomized trial that compared intensive with conventional therapy in insulin-dependent diabetes mellitus, demonstrating a prevention of diabetic complications. The percentage of adolescent (13-18 years old) was 9%-19% of 1441 patients, with a 2.6-8.9 years of disease duration, a starting insulin dose of 0.62-0.72 U/kg of body weight/day and an insulin dose after 5 year of 0.46-1.10 U/kg of body weight/day.

As it has been described in the literature, the mean insulin dose in T1D patients with HG was significantly higher than in DCCT trial (1.33 U/kg), having been treated with supra-physiologic doses of insulin (Table 1).

Repeated ketoacidosis episodes in T1D significantly increase the risk for hepatic glycosgen overload, since diabetic ketoacidosis (a fatal complication of poor controlled diabetes) is usually treated with sustained levels of intravenous insulin (in the presence of high glucose blood concentrations). As matter of fact, a high percentage of the HG cases described in the literature presented diabetic ketoacidosis, with a frequency of about 40% (14/35 cases), confirming the association of sustained insulin treatment and the development of HG.

With a significant difference from NASH, HG is completely reversible with a good metabolic control. Adequate management of glucose and insulin levels can result in complete remission of clinical, laboratory and histological abnormalities. Continuous subcutaneous insulin infusion should be considered as an option because the insulin requirements usually come down with improved
glycemic control[41]. In severe and rare cases, pancreatic transplantation has been reported to be effective[42].

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