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Insulin

Updated: April 26, 2018.

OVERVIEW

Introduction

Insulin is a pancreatic hormone that plays an essential role in regulation of blood glucose as well as lipid and carbohydrate metabolism. Both natural and recombinant forms of insulin are used therapeutically to treat type 1 diabetes. While insulin itself is not hepatotoxic and has not been linked to serum enzyme elevations or instances of clinically apparent liver injury, high doses including overdoses of insulin and glucose can result in hepatic glycogenosis and serum aminotransferase elevations.

Background

Insulin (in' su lin) is a polypeptide hormone produced by pancreatic islet β cells that is primarily responsible for regulation of blood glucose and storage of carbohydrates and lipids. Type 1 diabetes is due to inadequate production of insulin caused by destruction and loss of insulin producing pancreatic islet β cells. Type 2 diabetes is due to relative insulin resistance. Initial forms of insulin were isolated from pancreas tissue harvested from swine and cattle, and thus referred to as pork and beef insulins. More recently, human insulins have been produced by recombinant techniques. Since its first use in the 1930s, insulin has been the mainstay of therapy of type 1 diabetes. Insulin is also used in patients with type 2 diabetes that is refractory to lifestyle interventions (diet, physical activity, weight loss) and use of oral hypoglycemic agents. Multiple formulations of insulin are available including short-acting (regular), rapid-acting (aspart, glulisine, lispro) and medium- or long-acting (NPH, glargine, detemir) forms generically and under brand names such as Apidra, Basaglar, Humalog, Humulin, Lantus, Levemir, Novolin, Novolog and Tresiba. Commercial combination products with several forms of insulin or insulin with other agents are also available. Insulin can be given intravenously, intramuscularly and subcutaneously and the dose and frequency of administration varies by formulation and the individual being treated. Adverse events from insulin are largely due to hypoglycemia. Insulin therapy often results in weight gain. Local injection reactions (lipoatrophy) and hypersensitivity reactions are uncommon, particularly with newer recombinant forms of insulin.

Hepatotoxicity

Insulin in typical therapeutic doses is not associated with serum enzyme elevations or with episodes of clinically apparent liver injury. However, use of insulin in poorly controlled type 1 diabetes can result in a clinical syndrome known as glycogenosis or glycogenic hepatopathy, marked by varying degrees of hepatomegaly, abdominal pain and serum aminotransferase elevations. Serum ALT and AST levels range from normal to 20 to 30 times the upper limit or normal. Alkaline phosphatase and bilirubin levels are minimally increased or normal. Serum glucose and hemoglobin A1c levels are invariably elevated, and the liver and metabolic

abnormalities resolve rapidly with better glycemic control. A severe form of glycogenosis associated with hepatomegaly, growth retardation, delayed puberty and Cushingoid facies in children is known as Mauriac syndrome. Glycogenosis with serum enzyme elevations can also occur in patients with insulin overdose during treatment with high doses of intravenous glucose (Case 1). Glycogenosis has also been reported in patients recieving short-term, high-dose corticosteroids..

The diagnosis of glycogenosis can be confirmed by liver biopsy which typically shows slightly swollen hepatocytes with pale cytoplasm and accentuated cell membranes, which with periodic acid Schiff (PAS) staining demonstrates intracytoplasmic accumulation of glycogen. Imaging by CT usually shows an enlarged and hyper-dense liver in contrast to hepatic steatosis which generally causes a hypo-dense pattern. The condition can be relapsing, accompanying repeated episodes of hyperglycemia, but it does not appear to result in chronic liver injury, fibrosis or cirrhosis. Thus, the serum enzyme elevations are due to the combination of marked hyperglycemia and intermittent or high levels of insulin and not to intrinsic hepatotoxicity or an idiosyncratic reaction to insulin. The syndrome occurs most commonly in children or young adults with poorly controlled type 1 diabetes.

Likelihood score: A[H] (known cause of liver injury, but only when administered in high or intermittent doses and in the presence of hyperglycemia).

Mechanism of Liver Injury

Insulin acts to increase uptake of glucose in the liver, decreasing gluconeogenesis and promoting glycogen synthesis. Thus, the hyperglycemia in the presence of high doses of insulin cause excessive production and storage of glycogen in the liver. Glycogenosis can cause serum enzyme elevations, but does not seem to injure hepatocytes and is not associated with permanent liver damage or fibrosis. Glycogenosis reverses rapidly when insulin and glucose are discontinued. Glycogenosis can also result from hyperglycemia caused by high doses of corticosteroids.

Outcome and Management

The liver injury associated with insulin use or overdose is likely due to glycogenosis rather than inherent injury from insulin, and reverses rapidly when insulin and glucose are discontinued.

Drug Class: Hormonal Agents; Antidiabetic Agents

CASE REPORT

Case 1. Hepatic glycogenosis developing after overdose of insulin and high doses of intravenous glucose.

[Modified from: Tsujimoto T, Takano M, Nishiofuku M, Yoshiji H, Matsumura Y, Kuriyama S, Uemura M, 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: 469-73. PubMed Citation]

A 41 year old man with poorly controlled type 2 diabetes took an overdose of insulin (~180 units) and was admitted to hospital in coma with severe hypoglycemia (glucose 9 mg/dL). He was given continuous infusions of glucose, but hypoglycemia persisted for 36 hours. On day 3 after admission he developed upper abdominal pain and was found to have tender hepatomegaly and marked elevations in serum enzymes with ALT 1024 U/L, AST 1064 U/L, LDH 1751 U/L, alkaline phosphatase 202 U/L, GGT 181 U/L and total bilirubin 2.3 mg/dL. His serum enzymes had been normal on admission immediately after the overdose (Table). Abdominal CT scanning demonstrated marked hepatomegaly and increased attenuation (hyper-dense liver compared to spleen and kidneys). A liver biopsy showed glycogenosis with minimal cellular infiltration and no necrosis, mild steatosis

and no fibrosis. The presence of glycogen was documented by PAS staining with and without diastase. Doses of glucose were decreased and he was switched to oral intake only. Serum enzymes improved rapidly and were normal 2 weeks later. Repeat CT scanning showed a decrease in liver size and in hepatic attenuation. Repeat liver biopsy showed slight ballooning of hepatocytes and minimal residual intracytoplasmic glycogen accumulation.

Key Points

Medication:	Insulin glargine overdose treated with glucose infusions
Pattern:	Hepatocellular (R=~16.5)
Severity:	1+ (enzyme elevations without jaundice)
Latency:	3 days
Recovery:	2 weeks
Other medications:	Voglibose (alpha glucosidase inhibitor)

Laboratory Values

Time After Overdose (days)	Therapy	**ALT** (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
1	iv Glucose [326 g]	23	125	0.4	Coma
2	iv Glucose [811 g]	18			
3	iv Glucose [926 g]	1064	202	2.3	Abdominal Pain
4	iv Glucose [531 g]	708			
5	iv Glucose [200 g]	274			Liver biopsy (1)
6	iv Glucose [52 g]	214			
7	Oral intake only	135			
10		41			
14		24			
18		16			
21		19			Liver biopsy (2)
Standard Normal Values		**<40**	**<130**	**<1.2**	

Comment

The sudden onset of hepatomegaly with abdominal pain and marked serum aminotransferase elevations within days of starting glucose infusions after an overdose of insulin is typical of acute glycogenosis and dramatically demonstrates how rapidly the condition can develop and how rapidly it resolves. The clinical features resemble those of the hepatic glycogenosis that occurs in poorly controlled type 1 diabetes when insulin is being administered at a time that significant hyperglycemia is present. The diagnosis can be made based upon the clinical history and the finding of a hyper-dense liver by CT scanning. However, similar serum enzyme elevations can occur due to shock or ischemia and some degree of liver test abnormalities are common in patients with diabetes and fatty liver. The histologic findings of slightly swollen hepatocytes with pale cytoplasm and accentuation of plasma membranes suggests glycogenosis, which can be proven by PAS staining with and without diastase (an enzyme that digests glycogen demonstrating that the PAS-positive granules are composed of glycogen). Thus, insulin is not the direct cause of the liver abnormalities, but does allow for the excess circulating glucose to be taken up by hepatocytes producing amounts of intracytoplasmic glycogen that cause hepatocyte swelling, liver enlargement and release of hepatic enzymes.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Insulin – Generic, Lantus, Humulin®

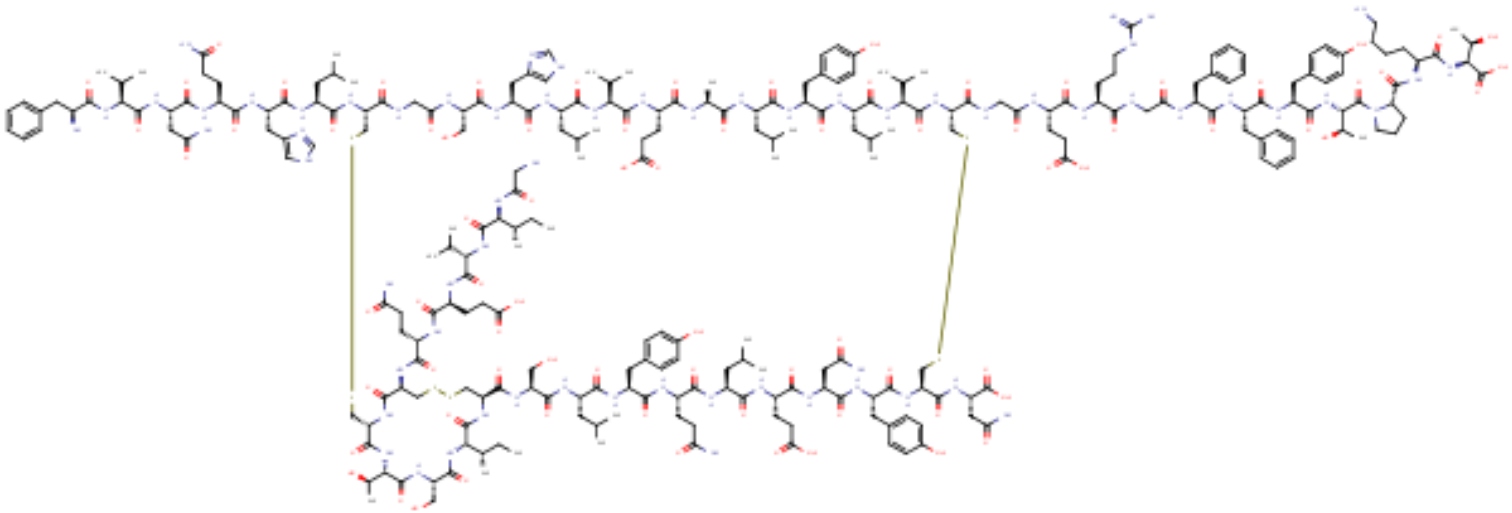
DRUG CLASS

Hormonal Agents; Antidiabetic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Insulin	11061-68-0	C257-H383-N65-O77-S6	

ANNOTATED BIBLIOGRAPHY

References updated: 26 April 2018

Zimmerman HJ. Hepatic injury from the treatment of infectious and parasitic diseases. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 589-637.

(Expert review of liver injury due to medications published in 1999; does not discuss insulin).

Kleiner DE. Histopathological evaluation of drug-induced liver disease. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd edition. Amsterdam: Elsevier, 2013, pp. 241-63.

(Multi-authored text book on drug induced liver injury discusses the histologic features of glycogenosis that can occur in type 1 diabetes and in patients receiving high doses of corticosteroids).

Powers AC, D'Alessio D. Endocrine pancreas and pharmacotherapy of diabetes mellitus and hypoglycemia. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1237-73.

(Textbook of pharmacology and therapeutics).

Mauriac P. Gros ventre, hepatomegalie, troubles de las croissance chez les enfants diabetiques traits depuis plusieurs annes par l'insuline. Gaz Hebd Med Bordeaux 1930; 26: 402-10. Not in PubMed

(Initial description of "Mauriac syndrome" occurring in children with type 1 diabetes on insulin therapy and marked by hepatomegaly, cushingoid features, growth retardation, delay in puberty and hepatic glycogenosis).

Goodman JI. Hepatomegaly and diabetes mellitus. Ann Intern Med 1953; 39: 1077-87. PubMed PMID: 13105180.

(Among 459 diabetic patients examined carefully by percussion, 9% with stable diabetes had hepatomegaly compared to 60% with uncontrolled diabetes and 100% with ketoacidosis, usually ascribed to fatty liver or cirrhosis).

Kaminer Y, Robbins DR. Attempted suicide by insulin overdose in insulin-dependent diabetic adolescents. Pediatrics 1988; 81: 526-8. PubMed PMID: 3281128.

(13- and 16-year old girls with insulin dependent diabetes attempted suicide with overdoses of insulin [150 and 600 units] and recovered with conservative management; no mention of liver test abnormalities).

Chatila R, West AB. Hepatomegaly and abnormal liver tests due to glycogenosis in adults with diabetes. Medicine (Baltimore) 1996; 75: 327-33. PubMed PMID: 8982149.

(Clinical descriptions of 8 adults and 3 children with poorly controlled diabetes and hepatic glycogenosis manifested by hepatomegaly [7 patients, 3 with tenderness] and serum ALT [45-910 U/L] and Alk P [1-10 times ULN] elevations, but normal bilirubin levels, liver biopsies showing glycogenosis, resolving rapidly with diabetes control).

Shimizu H, Ohtani KI, Kudoh T, Tsuchiya T, Takahashi H, Sato N, Iriuchijima T, et al. Possible liver damage by biosynthetic human insulin. Diabetes Obes Metab 1999; 1: 179-80. PubMed PMID: 11220297.

(Two patients, ages 53 and 51 years with type 2 diabetes developed liver test abnormalities shortly after starting a recombinant human insulin produced in yeast [Penfill] [ALT 330 U/L and 213 U/L], which fell to normal on stopping and did not increase on switching to an E. coli derived recombinant insulin [Humacart R]).

Munns CF, McCrossin RB, Thomsett MJ, Batch J. Hepatic glycogenosis: reversible hepatomegaly in type 1 diabetes. J Paediatr Child Health 2000; 36: 449-52. PubMed PMID: 11036799.

(Three adolescents with poorly controlled type 1 diabetes presented with hepato-splenomegaly and elevations in ALT [135, 147 and 316 U/L] and HgA1c [12.2-14.1], but normal bilirubin and Alk P, all 3 children improving rapidly with better glycemic control).

Jolliet P, Leverve X, Pichard C. Acute hepatic steatosis complicating massive insulin overdose and excessive glucose administration. Intensive Care Med 2001; 27: 313-6. PubMed PMID: 11280657.

(48 year old woman who injected 2000 IU of insulin in a suicide attempt and was admitted to a hospital in coma, developed abdominal pain and ALT elevations by day 3 of intravenous glucose infusions [ALT rising from normal to 610 U/L, Alk P 178 U/L, and bilirubin 8.7 mg/dL], with rapid resolution on stopping glucose infusions; assumed to be fatty liver, but without histologic confirmation).

von Mach MA, Meyer S, Omogbehin B, Kann PH, Weilemann LS. Epidemiological assessment of 160 cases of insulin overdose recorded in a regional poisons unit. Int J Clin Pharmacol Ther 2004; 42: 277-80. PubMed PMID: 15176650.

(Among 160 cases of insulin overdose, 89% were of suicidal intent, 5% accidental; full recovery occurred in 95%, 2.7% died, 2.7% had residual neurological deficits).

Tsujimoto T, Takano M, Nishiofuku M, Yoshiji H, Matsumura Y, Kuriyama S, Uemura M, 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: 469-73. PubMed PMID: 16679704.

(A 41 year old man with type 2 diabetes developed marked serum ALT and AST elevations 2-3 days after admission for hypoglycemia due to an overdose of insulin glargine [180 units] and while receiving intravenous glucose [ALT rising from 23 to 1024 U/L, ALK P 125 to 202 U/L, bilirubin 0.4 to 2.3 mg/dL], liver biopsy showing glycogenosis, abnormalities resolving within 1-2 weeks: Case 1).

Torbenson M, Chen YY, Brunt E, Cummings OW, Gottfried M, Jakate S, Liu YC, Yeh MM, Ferrell L. Glycogenic hepatopathy: an underrecognized hepatic complication of diabetes mellitus. Am J Surg Pathol 2006; 30: 508-13. PubMed PMID: 16625098.

(Among 14 cases of hepatic glycogenosis, all had diabetes and poor glycemic control, ages 8-34 years, ALT levels varying [normal to 1544 U/L], Alk P mildly elevated in 6, hepatomegaly, abdominal pain and nausea in most, biopsies showing cytoplasmic glycogen and minimal fat, responding to glycemic control).

Mahesh S, Karp RJ, Castells S, Quintos JB. Mauriac syndrome in a 3-year-old boy. Endocr Pract 2007; 13: 63-6. PubMed PMID: 17360304.

(A 3 year old boy with poorly controlled type 1 diabetes presented with protuberant abdomen, growth impairment, hepatomegaly and liver test abnormalities [ALT 146 U/L, HgA1c 14.2%], and liver, growth and metabolic features improved with better glycemic control).

Cuthbertson DJ, Brennan G, Walsh S, Henry E. Hepatic glycogenosis: abnormal liver function tests in Type 1 diabetes. Diabet Med 2007; 24: 322-3. PubMed PMID: 17305792.

(A 19 year old woman on insulin for type 1 diabetes developed ketoacidosis and was found to have hepatomegaly and abnormal liver tests [bilirubin 0.4 mg/dL, ALT 205 U/L, Alk P 132 U/L, HgA1c 12.2%], biopsy showing glycogenosis).

Sayuk GS, Elwing JE, Lisker-Melman M. Hepatic glycogenosis: an underrecognized source of abnormal liver function tests? Dig Dis Sci 2007; 52: 936-8. PubMed PMID: 17342391.

(Two patients, ages 19 and 36 years, with type 1 diabetes on insulin with persistently abnormal liver tests [bilirubin normal, ALT 33-49 and 366-844 U/L, Alk P 137-147 and 326-428 U/L, HbA1c 8.1%-9.5%] were found to have glycogenosis on liver biopsy).

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; 22: 325-8. PubMed PMID: 18413182.

(A 16 year old boy on insulin for type 1 diabetes developed hepatomegaly and abnormal liver tests [bilirubin 0.8 mg/dL, ALT 58 U/L, GGT 91 U/L, HbA1c 11%] and glycogenosis and steatosis on liver biopsy, resolving with better glycemic control).

Guclu M, Ersoy C, Imamoglu S. Suicide attempt of a physician with 3600 units of insulin and rapid onset acute hepatitis. Intern Med J 2009; 39: e5-7. PubMed PMID: 20233236.

(A 29 year old man with type 1 diabetes admitted for an insulin overdose [3600 units] developed sudden ALT and AST elevations 5 days after admission and starting glucose infusions [ALT rising from normal to 1010 U/L], resolving within a week of stopping glucose].

van den Brand M, Elving LD, Drenth JP, van Krieken JH. Glycogenic hepatopathy: a rare cause of elevated serum transaminases in diabetes mellitus. Neth J Med 2009; 67: 394-6. PubMed PMID: 20009116.

(A 29 year old woman on insulin for type 1 diabetes developed hepatomegaly and fluctuating serum ALT levels [peak values ~1500 U/L] with glycogenosis on liver biopsy and improvement with better glycemic control).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury including 4 due to troglitazone, but none were attributed to insulin or other antidiabetic medications).

Sweetser S, Kraichely RE. The bright liver of glycogenic hepatopathy. Hepatology 2010; 51: 711-2. PubMed PMID: 19957373.

(A 27 year old man with poorly controlled type 1 diabetes developed abdominal pain, hepatomegaly and abnormal liver tests [bilirubin 1.7 mg/dL, ALT 2549 U/L, Alk P 529 U/L, HgA1c 15%], with an enlarged and hyper-dense liver on CT and glycogenosis without fat or fibrosis on liver biopsy, resolving within 3 months with better glycemic control).

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. PubMed PMID: 21781150.

(A 26 year old man with type 1 diabetes developed marked abdominal pain and liver test abnormalities [ALT rising from 11 to 520 U/L, Alk P 98 to 203, bilirubin 0.7 to 1.0 mg/dL] 3 days after starting intravenous glucose for hypoglycemia caused by subcutaneous injection of 10 cartridges of glargine insulin, ultimately requiring surgical removal of cartridges).

Imtiaz KE, Healy C, Sharif S, Drake I, Awan F, Riley J, Karlson F. Glycogenic hepatopathy in type 1 diabetes: an underrecognized condition. Diabetes Care 2013; 36: e6-7. PubMed PMID: 23264308.

(A 19 year old woman with type 1 diabetes and poor glycemic control was found to have tender hepatomegaly during treatment of ketoacidosis [bilirubin not given, ALT 199 U/L, Alk P 139 U/L, HbA1c 14.6%], biopsy showing glycogenosis without fat or fibrosis).

Cha JH, Ra SH, Park YM, Ji YK, Lee JH, Park SY, Baik SK, et al. Three cases of glycogenic hepatopathy mimicking acute and relapsing hepatitis in type I diabetes mellitus. Clin Mol Hepatol 2013; 19: 421-5. PubMed PMID: 24459648.

(Three patients with type 1 diabetes, ages 20-26 years, were referred for evaluation of liver test abnormalities [ALT 169, 213 and 346 U/L, Alk P 346, 189 and 132 U/L, bilirubin 0.5, 0.5 and 0.2 mg/dL, HgA1c 13.8%, 12.9% and 13.6%], liver biopsies showing glycogenosis, liver tests improving, but fluctuating during follow up).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none were attributed to insulin or other antidiabetic medications).

Dias J, Martins S, Carvalho S, Marques O, Antunes A. Mauriac syndrome still exists. Endocrinol Nutr 2013; 60: 245-8. PubMed PMID: 23540612.

(Among 91 children with type 1 diabetes followed in a Portuguese pediatric endocrine clinic between 2005 and 2011, 6 had Mauriac syndrome, ages 13-17 years with known diabetes for 4-14 years, all had elevations in HbA1c, 5 had cushingoid features and delayed puberty, 5 hepatomegaly and ALT elevations [64 to 684 U/L]; and in follow up, improved glycemic control was difficult to achieve and clinical improvement varied).

Fitzpatrick E, Cotoi C, Quaglia A, Sakellariou S, Ford-Adams ME, Hadzic N. Hepatopathy of Mauriac syndrome: a retrospective review from a tertiary liver centre. Arch Dis Child 2014; 99: 354-7. PubMed PMID: 24412980.

(Retrospective survey from a large pediatric center in London identified 31 children with suspected Mauriac syndrome over a 10 year period, average age 15 years, 48% boys, mean ALT 76 U/L, and liver biopsies in 19 children showed glycogenosis is all).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, the most common implicated agents being nimesulide [n=53: 30%], cyproterone [n=18] and nitrofurantoin [n=17]; no case was attributed to insulin or other antidiabetic medications).

Giordano S, Martocchia A, Toussan L, Stefanelli M, Pastore F, Devito A, Risicato MG, et al. Diagnosis of hepatic glycogenosis in poorly controlled type 1 diabetes mellitus. World J Diabetes 2014; 5: 882-8. PubMed PMID: 25512791.

(Review of the pathophysiology, clinical features, diagnosis and management of hepatic glycogenosis).

Martin J, Tomlinson P. Hepatic complications in poorly controlled type 1 diabetes mellitus: a case report. N Z Med J 2014; 127: 95-7. PubMed PMID: 24806252.

(13 year old boy with poorly controlled type 1 diabetes developed rising serum aminotransferase levels shortly after an episode of diabetic ketoacidosis, biopsy showing glycogenic hepatopathy, perhaps complicated by ischemic hepatitis).

Parmar N, Atiq M, Austin L, Miller RA, Smyrk T, Ahmed K. Glycogenic hepatopathy: thinking outside the box. Case Rep Gastroenterol 2015; 9: 221-6. PubMed PMID: 26269698.

(21 year old woman with poorly controlled type 1 diabetes [HbA1c 13.3%] developed tender hepatomegaly [ALT 590 U/L, AST 3161 U/L, bilirubin and Alk P normal] and ultrasound suggested fatty liver, but biopsy showed glycogenosis and better control of diabetes was followed by fall of serum enzymes to normal).

Irani NR, Venugopal K, Kontorinis N, Lee M, Sinniah R, Bates TR. Glycogenic hepatopathy is an under-recognised cause of hepatomegaly and elevated liver transaminases in type 1 diabetes mellitus. Intern Med J 2015; 45: 777-9. PubMed PMID: 26134697.

(19 year old man with poorly controlled type 1 diabetes developed nausea and tender hepatomegaly [bilirubin 0.6 mg/dL, ALT 345 rising to 1180 U/L, Alk P 145 U/L, INR 1.0], biopsy showing glycogenosis, and symptoms and enzymes improving with better diabetic control).

Jung IA, Cho WK, Jeon YJ, Kim SH, Cho KS, Park SH, Jung MH, Suh BK. Hepatic glycogenosis in type 1 diabetes mellitus mimicking Mauriac syndrome. Korean J Pediatr 2015; 58: 234-7. PubMed PMID: 26213553.

(16 year old girl with poorly controlled diabetes presented with hepatomegaly, liver test abnormalities, cushingoid features, growth retardation and delayed puberty [ALT 459 U/L, GGT 430 U/L, HbA1c 14.3%], and glycogenosis on liver biopsy, and subsequently responded to better glycemic control with resolution of liver abnormalities followed by menarche and normal menses).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 4 were attributed to an antidiabetic agent [2 metformin, 1 sitagliptin, 1 glibenclamide], but none were attributed to insulin).

Julián MT, Alonso N, Ojanguren I, Pizarro E, Ballestar E, Puig-Domingo M. Hepatic glycogenosis: An underdiagnosed complication of diabetes mellitus? World J Diabetes 2015; 6: 321-5. PubMed PMID: 25789113.

(Review of the definition, pathogenesis, and clinical and histological features of glycogenosis).

Ikarashi Y, Kogiso T, Hashimoto E, Yamamoto K, Kodama K, Taniai M, Torii N, et al. Four cases of type 1 diabetes mellitus showing sharp serum transaminase increases and hepatomegaly due to glycogenic hepatopathy. Hepatol Res 2017; 47 (3): E201-E209. PubMed PMID: 27027269.

(Four patients with poorly controlled type 1 diabetes, ages 19-29 years, developed marked increases in serum ALT [216-956 U/L] and AST [469-2763 U/L] and hepatomegaly with liver biopsies showing glycogenosis; in follow up, serum enzyme elevations improved with better glycemic control, but often worsened again with subsequent episodes of hyperglycemia).

Deemer KS, Alvarez GF. A rare case of persistent lactic acidosis in the ICU: glycogenic hepatopathy and Mauriac syndrome. Case Rep Crit Care 2016; 2016: 6072909. PubMed PMID: 27699071.

(18 year old woman with poorly controlled type 1 diabetes [HbA1c 11.3%] receiving intravenous glucose and insulin developed hepatomegaly and lactic acidemia [bilirubin 0.2 mg/dL, ALT 36 U/L, Alk P 120 U/L], liver biopsy showing glycogenosis, lactate levels decreasing with better diabetic control).

Umpaichitra V. Unusual glycogenic hepatopathy causing abnormal liver enzymes in a morbidly obese adolescent with well-controlled type 2 diabetes: resolved after A1c was normalized by metformin. Clin Obes 2016; 6: 281-4. PubMed PMID: 27400632.

(15 year old boy with severe obesity [BMI 44] and diabetes but not on insulin had raised serum ALT levels [330 rising to 467 U/L], while bilirubin and Alk P were normal and liver biopsy showed glycogenosis; enzymes improving with metformin therapy).

Satyarengga M, Zubatov Y, Frances S, Narayanswami G, Galindo RJ. Glycogenic hepatopathy: a complication of uncontrolled diabetes. AACE Clin Case Rep 2017; 3: e255-e259. PubMed PMID: 28868358.

(18 year old man with poorly controlled type 1 diabetes developed marked hepatomegaly [bilirubin normal, peak ALT 1049 U/L, AST 3725 U/L, glucose 1,162 mg/dL, lactate 2.4 mmol/L], biopsy showing glycogenosis and enzymes improving with better diabetic control).

Chandel A, Scarpato B, Camacho J, McFarland M, Mok S. Glycogenic hepatopathy: resolution with minimal glucose control. Case Reports Hepatol 2017; 2017: 7651387. PubMed PMID: 28529811.

(12 year old girl with poorly controlled type 1 diabetes developed tender hepatomegaly [bilirubin 0.2 mg/dL, ALT 356 U/L, Alk P 158 U/L], biopsy showing glycogenosis and aminotransferase levels improving with better control of diabtes).

Sherigar JM, Castro J, Yin YM, Guss D, Mohanty SR. Glycogenic hepatopathy: a narrative review. World J Hepatol 2018; 10: 172-85. PubMed Citation (Review of the incidence, pathogenesis, clinical features, histology, diagnosis and management of glycogenic hepatopathy, mentions that imaging by ultrasound resembles changes of nonalcoholic fatty liver disease [NAFLD], but the two conditions differ by CT, glycogenosis yielding a dense and NAFLD a bright liver image).