

HEPATOMEGALY AND ELEVATED AMINOTRANSFERASES IN A PATIENT WITH POORLY REGULATED DIABETES

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SUMMARY – Elevated liver function tests, right upper quadrant abdominal pain, and hepatomegaly occurring in a diabetic patient treated with high doses of insulin may point to the presence of pathologic glycogen accumulation in the liver parenchymal cells. The condition was first described in children, however, studies performed in adults have shown a condition that is similar in many aspects. A case is presented of a 41-year-old female diabetic patient with abnormal liver tests and hepatomegaly. Abdominal ultrasound confirmed liver enlargement without any signs of fatty liver. Liver biopsy revealed a picture compatible with glycogenosis. As excessive hepatic glycogen deposition occurred at an adult age and without a related family history, while the patient presented with normal mental and motor development, the diagnoses of Mauriac syndrome and hereditary were ruled out. The condition was attributed to insulin hyperdosage. The patient was recommended improved glycemic control, more appropriate diet and physical exercise. On follow-up visit 3 months of discharge from the hospital, significant hepatomegaly regression was demonstrated by palpation and ultrasonography, and was accompanied by normalization of serum aminotransferases, blood glucose and glycosylated hemoglobin. Elevated serum aminotransferases and alkaline phosphatase with hepatomegaly as a consequence of hepatocellular glycogen accumulation can occur in diabetic patients of any age who are treated with high doses of insulin, and should therefore be included in the differential diagnosis.

Key words: *Hepatomegaly – etiology; Glycogen storage disease – etiology; Insulin – adverse effects; Diabetes mellitus, insulin-dependent – complications; Case report*

Introduction

The liver plays a central role in the regulation of glucose metabolism, and its normal functioning is essential for glucose homeostasis. The liver uses glucose as fuel, and also has the ability to store it as glycogen and to synthesize it from noncarbohydrate precursors. The role of the liver in glucose homeostasis offers a clue to the pathogenesis of glucose intolerance in liver diseases, but the mechanisms of liver disease in diabetes mellitus remain unclear. Excessive glycogen accumulation is observed in up to 80% of diabetic patients¹. Studies performed in animals with

recently induced diabetes have shown that glycogen synthesis in the liver is mildly impaired due to defective activation of glycogen synthase. On the other hand, in patients with long-standing diabetes, glycogen accumulation is seen, postulating that long-standing insulin deficiency may actually facilitate synthase activity, which together with enhanced gluconeogenesis may account for the excessive accumulation of glycogen in diabetes². Connection between the type of diabetes and accumulation of glycogen or fat in hepatocytes has not yet been found³. The exact mechanisms of cytoplasmic and nuclear glycogen deposition in hepatocytes are unclear. Glycogen is actually synthesized in the nucleus and can be found in 60%-75% of diabetic patients^{4,5}. It is also seen in sepsis, tuberculosis, some patients with autoimmune chronic hepatitis, Wilson's disease, and cirrhosis³. During periods of hyperglycemia, glucose freely enters the hepatocytes driving glycogen

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synthesis, which is augmented further by insulin administration to supraphysiologic levels. Excessive cytoplasmic glycogen deposition in diabetes mellitus may be related to intermittent episodes of hyperglycemia and hypoglycemia, and the use of excessive insulin. Histologically, throughout the lobule the hepatocytes appear pale and fluffy with clearly defined cell boundaries. Ultrastructural examination reveals cytoplasmic glycogen in clumps displacing organelles to the periphery of the cells, or pronounced nuclear glycogenosis, and there is little if any steatosis⁶. The typical biochemical findings are mildly to moderately elevated aminotransferases, with or without mild elevations of alkaline phosphatase. Liver synthetic function is usually normal. Patients showing excessive glycogen deposition may complain of abdominal pain and have obstructive symptoms such as early satiety, nausea, and vomiting. Ascites has rarely been reported. All these abnormalities may improve with sustained glucose control⁶.

Case Report

A 41-year-old female patient with insulin dependent diabetes mellitus was admitted to our hospital for evaluation of elevated serum aminotransferases. Her medical history included hepatitis A in childhood and diabetes mellitus in her grandmother. Nine years before, the patient was diagnosed with diabetes mellitus and was treated with higher doses of intermediate-acting insulin, 24 IU at 8 a.m. and 11 p.m. For the last 3 years, the patient had repeatedly had elevated serum aminotransferase values. She denied

alcohol consumption. On admission, the patient appeared to be in a good clinical state with increased appetite. Physical examination revealed a liver enlarged by 2 cm in the mediosagittal line and mild edema of both legs. Laboratory findings showed slightly elevated levels of aspartate transaminase (33 IU/ml), alanine transaminase (41 IU/ml), alkaline phosphatase (107 IU/ml), gamma-glutamyl transpeptidase (60 IU/ml), blood glucose (13.6 mmol/L), and glycosylated hemoglobin (HbA_{1c}, 8.5%). Ultrasound (US) examination confirmed liver enlargement with minimal amounts of ascites. Needle biopsy of the liver was performed for diagnostic evaluation of elevated aminotransferases. Histologic analysis showed no major changes in the structure of liver tissue. On hematoxylin – eosin (HE) stained histologic slides, ballooning of liver cells and hepatocytomegaly with pronounced nuclear glycogenosis were the predominant changes. When stained with periodic acid-Schiff (PAS)-diastasis, only a small number of hepatocytes were PAS positive for glycogen, while most of the hepatocytes had bright, transparent watery cells as the result of hydrolyzation of the glycogen by diastasis. According to elevated aminotransferases, positive US finding of hepatomegaly and review of the literature, we concluded that this glycogen accumulation was a complication of high dose insulin therapy in the poorly regulated insulin dependent diabetes mellitus. We recommended improved glycemic control, including short-acting insulin 6+8+4 IU 30 minutes before each meal, intermediate-acting insulin 6 IU at 8 a.m., and 10 IU at 11 p.m., with controlled dietary and exercise regime, which should have led to the

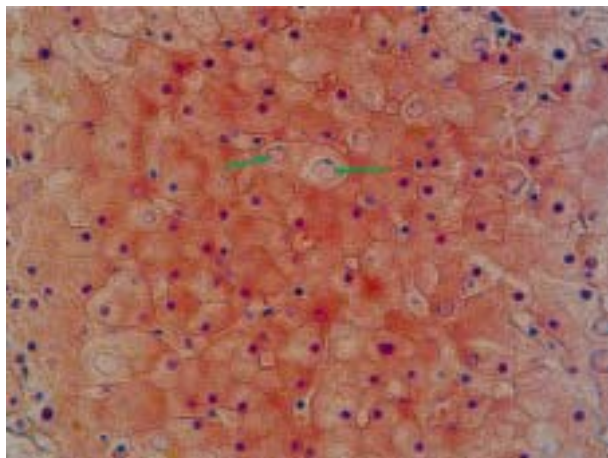


Fig. 1. Liver biopsy; HE, 400 x: Distended hepatocytes with pronounced nuclear glycogenosis (Arrows).

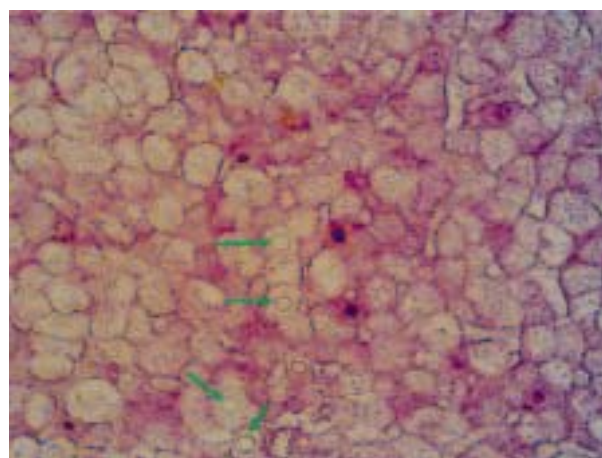


Fig. 2. Liver biopsy, PAS-D, 400 x: Nuclei digested by diastasis (Arrows).

resolution of hepatomegaly and elevated serum liver transaminase concentrations. On follow-up examination 3 months upon discharge from the hospital, there was significant regression of hepatomegaly on palpation and US, accompanied by normalization of serum aminotransferases, blood glucose and HbA_{1c} (6.9%).

Discussion

Abnormal liver tests, right upper quadrant abdominal pain, and hepatomegaly occurring in a diabetic patient may point to the presence of fat or glycogen accumulation in the liver parenchymal cells. First cases of unstable diabetes mellitus with marked hepatomegaly and pronounced elevations of serum aminotransferases and alkaline phosphatase as a consequence of hepatocellular glycogen accumulation were described in pediatric patients⁷⁻⁹. In adults, there have been 20 cases of Japanese diabetics with marked hepatomegaly reported in the literature, in whom vigorous treatment of diabetic ketoacidosis with insulin seemed to be a trigger for liver enlargement. It mostly occurred in patients with insulin dependent diabetes mellitus, however, cases of non-insulin dependent diabetes mellitus with glycogen storage hepatomegaly have also been reported¹⁰. Chatila and West⁶ as well as Olsson *et al.*¹¹ have shown that hepatomegaly due to glycogenosis in adults with diabetes is similar in all aspects to the condition seen in children. When hepatomegaly due to cytoplasmic glycogen deposition is accompanied by cushingoid features, growth retardation and delayed puberty, a diagnosis of Mauriac syndrome can be made^{12,13}.

Glycogenoses are diseases with excessive and/or abnormal glycogen deposition in tissues with various forms affecting different enzymes or structures. Most of them affect the liver, usually in infancy or early childhood, with hypoglycemia, massive hepatomegaly, poor physical growth, a tendency to increased fat deposition, particularly in the cheeks, and biochemical abnormalities¹⁴. In this case report of a 41-year-old female diabetic patient with abnormal liver tests and hepatomegaly, US confirmed enlargement of the liver without signs of fatty liver; liver biopsy revealed a picture compatible with glycogenosis. As excessive hepatic glycogen deposition in our case appeared in adulthood, without related family history, and the patient presented with normal mental and motor development, the diagnoses of Mauriac syndrome and hereditary glycogenoses were not considered. The condition was rather attributed to the poorly regulated diabetes and insulin hyperdosage. Leg edema present in our patient has also

been described as part of the clinical picture in the study by Olsson *et al.*¹¹.

Another major cause of hepatomegaly in patients with diabetes is steatosis. Hepatic fat accumulation is a common complication of diabetes, with a reported frequency of 40%-70%⁵. In type 1 diabetes, fat accumulation is indicative of a poor diabetic control and is rarely seen if glycemia is well controlled. On the other hand, type 2 diabetes may have a 70% incidence of liver steatosis regardless of blood glucose control. This is a function of the body habitus and state of insulin resistance rather than glycemic control. The distinction between steatosis and glycogenosis is important. Steatosis may progress to fibrosis and cirrhosis; glycogenosis does not but reflects the need of better diabetic control. US findings cannot distinguish between these two conditions; histology, on the other hand, is definitive. In glycogenosis secondary to diabetes mellitus, liver enzyme abnormalities are unreliable in predicting the presence or the extent of glycogen accumulation. In general, there is no correlation between the degree of biochemical alterations and the severity of histologic findings¹³. With improved glycemic control, resolution of the symptoms can occur as early as one month of admission, as described by Nakamuta *et al.*¹⁰.

Conclusion

Elevated serum aminotransferases and alkaline phosphatase with hepatomegaly as a consequence of hepatocellular glycogen accumulation can be seen in diabetics of any age treated with high doses of insulin, and should therefore be included in the differential diagnosis. Resolution of the symptoms and liver test normalization can be achieved with improved glycemic control.

References

1. STONE BE, Van THIEL DH. Diabetes mellitus and the liver. *Semin Liver Dis* 1985;5:8-28.
2. FERRANNINI E, LANFRANCHI A, ROHNER-JEANRENAUD F, MANFREDINI G, VANDEWERVE G. Influence of long-term diabetes on liver glycogen metabolism in rat. *Metabolism* 1990;39:1082-8.
3. LEVINTHAL GN, TAVILLAS. Liver disease and diabetes mellitus. *Clin Diabetes* 1999;17: <http://journal.diabetes.org/clinicaldiabetes/v17n21999/pg73.htm>
4. KAUTZSCH E. Leberbefunde bei Diabetes mellitus. *Med Monatsschr* 1963;17:229-34.
5. ROBBERS H, STOHPFELDT P, KRUGER C. Differential Diagnose der diabetischen und alkoholischen Fettleber: Unterschlungen in

- 171 Diabetikern und 100 Patienten mit Alkoholabusus. Dtsch Med Wochenschr 1968;93:112-3.
6. CHATILA R, WEST AB. Hepatomegaly and abnormal liver tests due to glycogenesis in adults with diabetes. *Medicine (Baltimore)* 1996;75:327-33.
7. LORENZ G, BARENWALD G. Histologic and electron-microscopic liver changes in diabetic children. *Acta Hepatogastroenterol* 1979;26:435-8.
8. MUNNS CF, McCROSSIN RB, THOMSETT MJ, BATCH J. Hepatic glycogenesis: reversible hepatomegaly in type 1 diabetes. *J Paediatr Child Health* 2000;36:449-52.
9. MARANGIELLO R, GIORGETTI R. A case of glycogenesis in a patient with insulin dependent diabetes. *Minerva Pediatr* 1996;48:279-81.
10. NAKAMUTA M, OHASHI M, GOTO K, TANABEY, HIROSHIGE K, NAWATA H. Diabetes mellitus-associated glycogen storage hepatomegaly: report of a case and review of the Japanese literature. *Fukuoka Igaku Zasshi* 1993;84:354-8.
11. OLSSON R, WESSLAU C, WILLIAM-OLSSON T, ZETTERGREN L. Elevated aminotransferases and alkaline phosphatase in unstable diabetes mellitus without ketoacidosis or hypoglycemia. *J Clin Gastroenterol* 1989;11:541-5.
12. LORENZ G. Biopsical liver changes in Mauriac syndrome. *Zentralbl Allg Pathol* 1981;125:364-8.
13. Van STEENBERGEN W, LANCKMANS S. Liver disturbances in obesity and diabetes mellitus. *Int J Obes Relat Metab Disord* 1995;19 (Suppl 3):27-36.
14. SHERLOCKS, DOOLEY J. The glycogenoses. In: *Diseases of the liver and biliary system*. 10th ed. Oxford: Blackwell Science, 1997:436-7.

Sažetak

HEPATOMEGALIJA I POVIŠENE AMINOTRANSFERAZE U BOLESNICE S LOŠE REGULIRANOM ŠEĆERNOM BOLEŠĆU

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Pojava povišenih jetrenih enzima, bolova u desnom gornjem abdominalnom kvadrantu i hepatomegalije u bolesnika sa šećernom bolešću liječenih visokim dozama inzulina može ukazivati na patološko nakupljanje glikogena u stanicama jetrenog parenhima. Ovo je stanje prvotno opisano u djece, a kasnije studije provedene na odraslima pokazale su jednaku kliničku sliku. Prikazan je slučaj 41-godišnje žene oboljele od šećerne bolesti s poremećenim jetrenim nalazima i hepatomegalijom, kod koje je ultrazvuk potvrdio povećanje jetre bez znakova steatoze, a biopsijom je postavljena dijagnoza glikogenoze. S obzirom na to da je izrazito nakupljanje glikogena u ovom slučaju nastupilo u odrasloj dobi, bez pozitivne obiteljske anamneze, a bolesnica je imala uredan psihički i tjelesni razvoj, iz diferencijalne dijagnoze se je mogao isključiti Mauriacov sindrom i nasljedna glikogenoza. Uzrok ovoga stanja u ove bolesnice bilo je liječenje osnovne bolesti visokim dozama inzulina. Stoga joj je preporučena poboljšana kontrola glikemije praćena ispravnom dijetom i tjelesnom aktivnošću. Na kontrolnom pregledu nakon tri mjeseca došlo je do regresije hepatomegalije potvrđene palpacijom i ultrazvukom, te do normaliziranja serumskih aminotransferaza, glukoze u krvi i glikoziliranog hemoglobina. Povišene aminotransferaze i alkalna fosfataza uz hepatomegaliju mogu se naći kod bolesnika dijabetičara liječenih visokim dozama inzulina, kao posljedica nakupljanja glikogena u jetrenim stanicama, pa ovo stanje treba uključiti u diferencijalnu dijagnozu.

Ključne riječi: *Hepatomegalija – etiologija; Bolest pohrane glikogena – etiologija; Inzulin – štetni učinci; Dijabetes melitus, ovisan o inzulinu – komplikacije; Prikaz slučaja*