Elevated Liver Function Tests in Type 2 Diabetes

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Liver function tests (LFTs) are commonly used in clinical practice to screen for liver disease, monitor the progression of known disease, and monitor the effects of potentially hepatotoxic drugs.

The most common LFTs include the serum aminotransferases, alkaline phosphatase, bilirubin, albumin, and prothrombin time. Aminotransferases, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), measure the concentration of intracellular hepatic enzymes that have leaked into the circulation and serve as a marker of hepatocyte injury. Alkaline phosphatase (AP), γ-glutamyl transpeptidase (GGT), and bilirubin act as markers of biliary function and cholestasis. Albumin and prothrombin reflect liver synthetic function.

The aminotransferases AST and ALT are normally < 30–40 units/l. Elevations of aminotransferases greater than eight times the upper limit of normal reflect either acute viral hepatitis, ischemic hepatitis, or drug- or toxin-induced liver injury. Much more common than patients with acute hepatitis, however, are patients with chronic mild elevation of aminotransferases, or AST and ALT < 250 units/l for > 6 months.

Chronic mild elevation of transaminases are frequently found in type 2 diabetic patients. This article will provide a review of the pathology, incidence, causes, and drug therapy related to type 2 diabetic patients with elevated LFTs.

Theories Behind LFT Elevation in Diabetes

The liver helps maintain normal blood glucose concentration in the fasting and postprandial states. Loss of insulin effect on the liver leads to glycogenolysis and an increase in hepatic glucose production. Abnormalities of triglyceride storage and lipolysis in insulin-sensitive tissues such as the liver are an early manifestation of conditions characterized by insulin resistance and are detectable earlier than fasting hyperglycemia. The precise genetic, environmental, and metabolic factors and sequence of events that lead to the underlying insulin resistance, however, is not fully understood.[1]

In animal models, chronic hyperinsulinemia is found to predispose the liver to relative resistance to insulin. This is characterized by a failure of insulin to signal an increase in insulin receptor substrate-2. Upregulation of sterol regulatory element-binding protein 1c (SREBP-1c) also occurs, leading to increased lipogenesis.[2] Despite downregulation of the insulin receptor substrate-2–mediated insulin signaling pathway in insulin-resistant states, the up-regulation of SREBP-1c and subsequent simulation of de novo lipogenesis in the liver leads to increased intracellular availability of triglycerides, promoting fatty liver. This also increases VLDL assembly and secretion.[1] Thus, hyperinsulinemia might directly lead to hepatic insulin resistance with associated fatty changes.

The excess in free fatty acids found in the insulin-resistant state is known to be directly toxic to hepatocytes. Putative mechanisms include cell membrane disruption at high concentration, mitochondrial dysfunction, toxin formation, and activation and inhibition of key steps in the regulation of metabolism.[3] Other potential explanations for elevated transaminases in insulin-resistant states include oxidant stress from reactive lipid peroxidation, peroxisomal beta-oxidation, and recruited inflammatory cells. The insulin-resistant state is also characterized by an increase in proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), which may also contribute to hepatocellular injury. In preliminary studies, an increased frequency of specific TNF-α–promoter polymorphism was found in nonalcoholic steatohepatitis (NASH) patients, suggesting a possible genetic link or predisposition to fatty liver found in insulin-resistant states.[4]

The above theories all attribute elevated transaminitis to direct hepatocyte injury. It is also hypothesized that elevation in ALT, a gluconeogenic enzyme whose gene transcription is suppressed by insulin, could indicate an impairment in insulin signaling rather than purely hepatocyte injury.[5]

IN BRIEF

Individuals with type 2 diabetes have a higher incidence of liver function test abnormalities than individuals who do not have diabetes. Mild chronic elevations of transaminases often reflect underlying insulin resistance. Elevation of transaminases within three times the upper limits of normal is not a contraindication for starting oral antidiabetic or lipid-modifying therapy. In contrast, antidiabetic agents have generally been shown to decrease alanine aminotransferase levels as tighter blood glucose levels are achieved.

Can Elevated LFTs Predict the Development of Diabetes?

GGT is a nonspecific marker that is known to rise in patients with type 2 diabetes. In epidemiological studies, it has a positive association with alcohol intake, cigarette smoking, coronary heart disease, BMI, systolic blood pressure, serum triglyceride, heart rate, uric acid, and hematocrit. It has an inverse association with physical activity level.[6] Because GGT increases in diabetes, and increases as BMI increases, it has been proposed as another marker of insulin resistance.

To determine whether elevated GGT could predict the development of type 2 diabetes, a prospective cohort study of 7,458 nondiabetic men aged 40–59 years was conducted for 12 years.[7] Mean serum GGT at the start of the study was significantly higher in the 194 men who developed type 2 diabetes than in the rest of the cohort who did not develop diabetes (20.9 vs. 15.3 units/l, $P < 0.0001$). The association was independent of serum glucose and BMI. However, when GGT was added to a model for predicting the development of type 2 diabetes, it did not improve the power of BMI and glucose for predicting the development of type 2 diabetes.

Ohlson et al.[8] found elevated ALT in nondiabetic Swedish men to be a risk factor for type 2 diabetes, independent of obesity, body fat distribution, plasma glucose, lipid, AST, bilirubin concentrations, and family history of diabetes. With similar results, Vozaroza et al.[9] followed 451 nondiabetic Pima Indians for an average of 6.9 years to determine whether hepatic enzyme elevations could be linked to the development of type 2 diabetes. At baseline, ALT, AST, and GGT were related to percent body fat. After adjustment for age, sex, body fat, whole body insulin sensitivity, and acute insulin response, only elevated ALT at baseline was associated with an increase in hepatic glucose output. Prospectively, increasing ALT concentrations were associated with a decline in hepatic insulin sensitivity and risk of type 2 dia-betes. The authors concluded that higher ALT is a risk factor for type 2 diabetes and indicates a potential role of increased hepatic gluconeogenesis and/or inflammation in the pathogenesis of type 2 diabetes.

Incidence of Elevated LFTs in Diabetes

Salmela et al.[10] studied the prevalence of abnormal LFTs and their relationship to clinical findings in 175 unselected diabetic outpatients in Finland. One hundred and eighteen patients were classified as having type 2 diabetes and 57 as having type 1 diabetes. Of those with type 2 diabetes, 33 patients used insulin in addition to diet and oral hypoglycemic drugs including sulfonylurea and metformin. None of the patients had known chronic liver disease, and none had clinically significant diabetic nephropathy. Hemoglobin A_{1c} (A1C) averaged $11.2 \pm 2.4\%$.

LFTs measured included albumin, total bilirubin, AST, ALT, AP, GGT, and serum concentrations of cholic acid and chenodeoxycholic acid. Fifty-seven percent of the 175 diabetic outpatients (100 subjects) had at least one abnormal LFT; 27% (48 subjects) had at least two abnormal tests. The type 2 diabetic patients more frequently had elevated ALT (22.9 vs. 5.3%) and GGT (23.7 vs. 10.5%) levels than those with type 1 diabetes. On the other hand, patients with type 1 diabetes more frequently had elevated bilirubin levels (21.1 vs. 10.2%). However, increases in LFTs were rarely more than twice the upper limit of normal.

Multivariate analysis showed BMI > 25 kg/m^2 and poor diabetic control (fasting blood glucose > 216 mg/dl) were the most significant clinical variables associated with elevated ALT and GGT. Elevated ALT was also associated with onset of diabetes within the past 4 years, mature onset of diabetes (35–51 years), and use of diet or sulfonylurea.

To investigate the reliability of LFTs in assessing histological changes, Salmela et al.[10] looked at 72 consecutive diabetic inpatients with hepatomegaly or abnormal LFTs who were awaiting liver biopsy. Sixty-eight of the patients had type 2 diabetes; four had type 1 diabetes. All of the patients had hepatomegaly or abnormal LFTs. They had normal blood counts, serum electrolytes, and renal function. None had decompensated heart failure. Only 5 gave a history of social drinking; the other 67 patients were classified as abstainers.

Of the 72 patients who underwent liver biopsy, all 4 with type 1 diabetes had normal liver histology, but only 5 of the 68 with type 2 diabetes had normal liver histology. The most commonly elevated LFT in the nine patients with normal histology included bilirubin and AP. ALT was less frequently elevated, and GGT was not elevated at all.

Of the 63 patients with abnormal liver histology, 48 had fatty liver or steatosis with nonspecific inflammatory changes, whereas 14 had evidence of fibrosis. GGT and ALT were most commonly elevated. As histology worsened (steatosis to inflammation to fibrosis), there was no significant difference in mean values of ALT and GGT. Therefore, although abnormal LFT results are common in diabetes, especially in overweight type 2 diabetic patients, they are not reliable in predicting histological changes in the liver.

In a larger study, Erbey et al.[11] analyzed 18,825 noninstitutionalized patients within the United States with an oversampling of African Americans and Mexican Americans. Of the total sample, 4.1% had elevated ALT, and 6.7% had type 2 diabetes. Of those with type 2 diabetes, the prevalence of elevated ALT was 7.8%, compared to a 3.8% prevalence in those without diabetes. The prevalence of ALT elevation greater than three times normal was not significantly different between the nondiabetic and diabetic patients (0.4 vs. 0.7%). Those who were overweight (BMI 25–30 kg/m^2) and obese (BMI > 30 kg/m^2) were more likely to have elevated ALT. There was a 10.6% prevalence in obese diabetic patients versus a 6.6% prevalence in obese nondiabetic patients.

Nonalcoholic Fatty Liver Disease

The most common cause of elevated LFTs in type 2 diabetic patients is nonalcoholic fatty liver disease (NAFLD). NAFLD is a clinicopathological condition representing a spectrum of histological findings from hepatic steatosis or fat accumulation in hepatocytes without inflammation, to hepatic steatosis with a necroinflammatory component that may or may not have fibrosis, or NASH.

NAFLD is defined by the absence of or minimal alcohol consumption, liver biopsy showing macrovesicular steatosis with or without necro-inflammatory activity, and exclusion of other forms of liver disease. Although the pathogenesis is still unclear, it is characterized by accumulation of triglycerides within the hepatocytes. Insulin resistance is thought to play an important role in the triglyceride accumulation. Excess intracellular fatty acids, oxidant stress, ATP depletion, and mitochondrial dysfunction all contribute to hepatocyte injury and inflammation followed by fibrosis.[3]

Not surprisingly, the most common laboratory abnormality in patients with NAFLD is mild to moderate elevation of serum aminotransferases. As in the histological study of diabetic patients with abnormal LFTs by Salmela et al.,[10] level of transaminase elevation in NAFLD does not predict severity of liver histology.[12]

NAFLD in Nondiabetic Patients

NAFLD is replacing alcohol and viral hepatitis as the most common etiology of chronically elevated LFTs in the United States in both diabetic and non-diabetic individuals.[3] Of those patients with NAFLD, 60–95% are obese, 28–55% have type 2 diabetes, and 20–92% have hyperlipidemia.

In a prospective study of 1,124 adults who were referred for evaluation of chronically elevated LFTs, 81 were determined to have unknown etiology based on the absence of serum markers for infectious (including hepatitis B and C), metabolic (thyroid-stimulating hormone), autoimmune (serum protein electrophoresis, antinuclear antibody, antimitochondri-al antibody, anti–smooth muscle antibody), or hereditary causes of liver disease (α-1 antitrypsin, ceruloplasmin, iron, iron-binding capacity, or ferritin).[13] They had no history of alcohol or hepatotoxic drug use nor signs of chronic liver disease. Patients also had no evidence of sarcoid on chest X-ray. Of note, there is no mention in the article of evaluating unlikely but potential causes of transaminitis, such as muscle disorders, adrenal insufficiency, and celiac disease. Of the 81 "marker negative" patients with no identified etiology of elevated liver enzymes, 73 had abnormal histology, all with some degree of steatosis. In the patients without clear etiology of liver disease, the prevalence rate of steatosis and steatohepatitis was 50.6 and 32%, respectively.

In a similar study, 354 patients, both with and without diabetes, underwent liver biopsy to investigate abnormal LFTs. When patients with clinical or serological evidence of a specific diagnosis were excluded, 66% of the patients had evidence of steatosis and steatohepatitis on biopsy.[14]

Hepatitis C and Type 2 Diabetes

Hepatitis C virus (HCV), the leading cause of liver disease in the United States, is a known independent predictor of type 2 diabetes, the most common endocrine disease even in patients without cirrhosis.[15,16] HCV is known to have a higher prevalence within diabetic patients. When comparing 176 diabetic patients to 6,172 blood donors matched for recognized risk factors of acquiring HCV, there was a higher prevalence of HCV infection within the diabetic patients (11.5 vs. 2.5%, $P < 0.001$).[17] Of the diabetic patients with HCV, 72.3% had abnormally elevated LFTs, compared to 27.7% of diabetic patients without evidence of HCV ($P < 0.001$). This would suggest that any diabetic patient with elevated LFTs needs screening for HCV.

Statins in Type 2 Diabetic Patients With Elevated Transaminases

In the Heart Protection Study of 20,536 high-risk individuals with vascular dis-ease, including individuals with diabetes, the rates of elevated ALT level above twice the upper limit of normal were 1.8% in the simvastatin group and 1.6% in the placebo group. This was not a significant difference.[18] In the Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) trial,[19] only one patient in the pravastatin group and one patient in the placebo group had ALT or AST level above three times the upper limits of normal. None of the patients had rhabdomyolysis. Thirty-six patients in the pravastatin group had myalgias, compared to 32 patients in the placebo group.

High-dose statin therapy is associated with more frequent abnormalities of LFTs, although they are generally still relatively infrequent. In the Treating to New Targets (TNT) trial,[20] patients with clinical cardiovascular disease (CVD) were randomized to 10 or 80 mg of atorvastatin. The incidence of persistent elevation in ALT, AST, or both (defined as two consecutive measurements obtained 4–10 days apart that were more than three times the upper limit of the normal range) was 0.2 and 1.2%, respectively ($P < 0.001$).[20]

Because of large trials such as these, current recommendations from the American College of Physicians suggest that type 2 diabetic patients with other cardiovascular risk factors should take a statin for primary prevention of macrovascular complications. These patients do not need routine monitoring of LFTs while on statins unless they have baseline abnormalities in LFTs, myopathy, or are taking other drugs that could increase their risk of adverse events.[21]

For diabetic patients with baseline transaminases less than three times the upper limit of normal, it is not contraindicated to initiate, continue, or advance statin therapy as long as patients are carefully monitored.[22] The frequency of required monitoring in these patients is under debate. There is also a debate as to whether transaminase elevation in statin therapy even constitutes true hepa-

toxicity.[22] For diabetic patients over the age of 40 years, and certainly in the setting of multiple cardiovascular risk factors or known CVD, the potential risk of statin therapy from the perspective of hepatotoxicity is far outweighed by the proven benefit from CVD risk reduction.

Oral Antidiabetic Agents in Type 2 Diabetic Patients With Elevated Transaminases

The introduction of the insulin sensitizer troglitazone and subsequent cases of hepatotoxicity led Jick et al.[23] to investigate the baseline risk of liver disease in type 2 diabetic patients on oral agents other than thiazolidinediones.[23] Researchers identified 40,190 type 2 diabetic individuals within the U.K.-based General Practice Research Database who were treated with oral diabetic agents, including sulfonylureas, metformin, guar gum, and acarbose, between 1989 and 1996 and who had no known liver disease at the time oral therapy was begun. Of the total sample, 1.5% (or 605) were given a new diagnosis of liver disorder during the study period. Of those 605 cases, 249 (41.2%) were attributed to a predisposing condition, 186 (31%) were mild asymptomatic liver enzyme abnormalities that were not considered clinically relevant, and 113 (18.7%) had a specific nondrug etiology listed. The remaining 57 (8.7%) with clinically relevant liver disease and no identified predisposing condition or cause were attributed to other drugs, fatty liver, and unknown. Oral antidiabetic agents could not be ruled out in two cases, giving an incidence of 0.002/100 person-years.

The idiosyncratic hepatic reaction leading to hepatic failure and death in some patients on troglitazone before its removal from the market is not likely to be a class effect of the peroxisomal proliferator-activated receptor-gamma agonists.

Rajagopalan et al.[24] performed a retrospective analysis of claims data comparing the incidence of liver failure in people with type 2 diabetes on pioglitazone versus other oral antidiabetic agents. Patients were classified into treatment groups based on the antidiabetic therapy received on the date of their first antidiabetic pharmacy claim. Patients in the pioglitazone group were then matched to patients within the rosiglitazone, sulfonylurea, and metformin groups. Matched groups were similar in demographic and clinical characteristics. Patients evaluated included 4,458 matched pairs of pioglitazone-versus rosiglitazone-treated patients, 1,474 pairs of pioglitazone- versus sulfonylurea-treated patients, and 1,137 pairs of pioglitazone- versus metformin-treated patients. Over a 2-year period, patients on pioglitazone had no increased risk of liver failure or hepatitis beyond that of patients on the other antidiabetic agents.

In placebo-controlled, double-blind clinical trials with pioglitazone, the incidence of elevated ALT values greater than three times the upper limit of normal was virtually identical between patients on pioglitazone and those on placebo (0.26 vs. 0.25%). Enzyme elevations were reversible in all patients who developed elevated ALT on pioglitazone.[25]

Lebovitz et al.[26] studied more than 6,000 patients with type 2 diabetes in a double-blind clinical trial using various doses of rosiglitazone, placebo, and either glyburide, metformin, or insulin. Mean A1C levels at the start of the study were similar across all groups (8.5–9%). Measurement of liver enzymes occurred at screening, baseline, then every 4 weeks for the first 3 months of treatment and at 6- to 12-week intervals thereafter. Patients were excluded from the study if they had ALT, AST, or ALP greater than two and a half times the upper limit of normal at screening. This is consistent with current recommendations of when not to use rosiglitazone or pioglitazone.

Of those on rosiglitazone, ~ 3,800 were monitored for at least 6 months, 2,800 for at least 1 year, and 1,000 for at least 2 years. No evidence of hepatotoxic effects were observed in the 5,006 patients who took rosiglitazone. The percentage of patients who developed ALT greater than three times the upper limit of normal were 0.32% of the rosiglitazone group, 0.17% of the placebo group, and 0.40% for the group taking either sulfonylurea, metformin, or insulin. The respective incidence rates of 0.29, 0.59, and 0.64/100 person-years show no difference between treatment of rosiglitazone, placebo, and other antihyperglycemic agents and the development of ALT levels greater than three times the upper limit of normal.[26] Furthermore, of the 5.6% of the patients whose serum ALT values were between one and two and a half times the upper limit of normal at baseline, 66% of those treated with antihyperglycemic medicines normalized their ALTs, whereas only 38.7% of those treated with placebo normalized ALT levels.[26] This supports the important link among glycemic control, insulin resistance, and hepatic function and suggests that improved glycemic control and improvement in insulin resistance can reduce mild chronic elevation of transaminitis often found in diabetic patients.

The decrease in LFTs demonstrated with rosiglitazone and pioglitazone therapy in diabetic patients has also been shown in pilot studies using thiadolidinediones to treat NASH, a surrogate for insulin resistance. One study[27] placed 18 nondiabetic patients with NASH on pioglitazone, 30 mg daily, for 48 weeks. By the end of the study, serum ALT levels decreased in all patients and normalized in 72% of them. Serum ALT levels fell from an average of 99 units/L at baseline to 40 units/L at 48 weeks.

Another study[28] used rosiglitazone, 4 mg twice daily, for 48 weeks in the treatment of 30 patients with NASH, 50% of whom had either impaired glucose tolerance or diabetes. Of the 25 patients who completed the study, all had significant improvements in mean serum ALT levels, changing from a baseline of 104 units/l to 42 units/l at 48 weeks. At 72-week follow-up, after 24 weeks off

rosiglitazone, liver enzyme levels had increased to near pretreatment levels.

Conclusions

Individuals with type 2 diabetes have a higher incidence of LFT abnormalities than individuals who do not have diabetes. The most common abnormality is elevated ALT. Any diabetic patient found to have a mild chronic elevation of ALT, or elevation of ALT ≤ 250 units/l for > 6 months should have screening for treatable causes of chronic liver disease, particularly hepatitis B, hepatitis C, and hemochromatosis, which are found with increased incidence in type 2 diabetes. In patients for whom a directed medical history and physical examination do not raise suspicion of other causes of elevated LFTs, such as medications, alcohol, autoimmunity, metabolic etiology, or hereditary etiology, and for those who have no evidence of more serious liver disease, such elevations in bilirubin or prothrombin time or decreases in albumin, further diagnostic workup is probably not required.

Routine monitoring of LFTs in patients with type 2 diabetes should occur at the start of drug therapy and if patients develop symptoms raising concern about hepatic impairment. Beyond that, periodic screening will have to be based on clinical judgment, keeping in mind that elevation of transaminases does not always correlate with histological changes in the liver. Elevation of ALT within three times the upper limit of normal is not a contraindication for starting any oral antidiabetic or lipid-modifying therapy. In contrast, antidiabetic agents have generally been shown to decrease ALT levels as tighter blood glucose levels are achieved.

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