Original Study

Liver Function Tests in Type 2 Diabetes Mellitus Patients with and without Oral Hypoglycemic Agents and Statin Intake

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Abstract

Background: Type 2 diabetes (T2DM) is often associated with liver function abnormalities, covering the entire spectrum from asymptomatic transamnitis to cirrhosis. The oral drugs used in diabetes are also associated with hepatic insult. *Aims:* Here we have tried to assess the prevalence the liver function test abnormality in type 2 diabetes mellitus patients with special reference to intake of oral hypoglycemic agents (OHA) and statins. *Methods:* We selected 101 patients of Type 2 Diabetes mellitus (T2DM). Among those diabetic patients 50 were on oral hypoglycemic drugs (OHA) and statins for at least last 6 months. Another 51 age and sex matched patients were diabetic but not on these drugs. The patients were screened for any existing liver disease by biochemical tests. *Results and analysis:* Our results showed that the prevalence of elevated liver enzymes and bilirubin is more in Diabetic patient than normal values but the oral hypoglycemic drugs and statins had no added effect. Altogether 70 patients (69.3%) had at least one liver function test abnormality. In our study, 4.95% of the patients had elevated bilirubin (>2.5 mg/dL). 24.75% of the study patients had ALT levels above normal (40 U/L) although high values (>100 U/L) were present only in 5 (4.95%). High AST levels (>40) was found in 34.65% cases. Mean alkaline phosphatase levels in 2 groups were similar (213.96 ± 46.2 vs. 222.75 ± 42.52 U/L). Serum proteins, INR and alkaline phosphatase did not also show any association with drug intake in our study. *Conclusion:* Thus screening for liver function abnormalities can be a useful test in diabetic population to prevent future complications.

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Keywords

hepatotoxicity, transaminase, insulin resistance, blood glucose, glitazones, statin

Introduction

Individuals with type 2 diabetes have a higher incidence of liver function test abnormalities than non diabetics[1, 2]. Mild chronic elevations of transaminases often reflect underlying insulin resistance [2]. The excess free fatty acid found in the insulin-resistant states is directly toxic to hepatocytes. Putative mechanisms include liver cell membrane disruption at high concentration of fatty acids, mitochondrial dysfunction, toxin formation, and activation and inhibition of key steps in hepatic metabolism[1]. Several oral hypoglycemic drugs are used at present for treatment of type 2 diabetes mellitus. Along with other toxicities, these drugs such as sulphonylureas, biguanide, Meglitinides, pioglitazone and even α-glucosidase inhibitors cause hepatotoxicity[2]. Most of the reports of hepatotoxicity are available with glitazones.

The statins are well tolerated by most persons and only rarely transamnitis occurs [3, 4]. The fact whether transaminase elevation with statin therapy constitutes true hepatotoxicity has not been determined.

In our clinical practice, most of the patients of type 2 diabetes mellitus get more than one oral hypoglycemic drugs (OHA) and lipid modifying drugs (statins) simultaneously. Some of these patients often report asymptomatic elevation of liver enzymes or other abnormalities. So here we have tried to assess the prevalence the liver function test (LFT) abnormality in type 2 diabetes mellitus patients with special reference to intake of OHA and statins.

Aims & objectives

1. To determine the prevalence of LFT abnormalities in T2DM patient not receiving OHA & statins.
2. To determine the prevalence of LFT abnormalities in T2DM patient taking OHA & statins.
3. To compare the prevalence of LFT abnormalities between the two groups.

Patients and Methods

This was an observational, hospital based, cross sectional, case control study. The study population was chosen following ADA criteria for diabetes, from Indoors and Out Patient Department, Department of Medicine, Medical College Hospital, Kolkata, and the Diabetic Clinic, Medical College Hospital, Kolkata. The study period was from 1st April, 2010 to 31st December 2011. We separated diabetic patients who have taken OHA and statins at least for last 6 months from those without such history. The latter group of patients included the newly diagnosed T2DM cases and those who had left therapy or only on lifestyle modification. Patients who were taking at least a glitazone and a statin (atorvastatin) with or without other hypoglycemic drugs were included in the study. The cause of taking glitazone as a mandatory drug of this group is because most of the reports of hepatotoxicity are with a glitazone.

Exclusion Criteria included Patients of known type 1 diabetes, alcoholism, HIV infection, patients having chronic liver disease or using hepatotoxic drugs, cor-pumonale or congestive cardiac failure and patients having proteinuria at least one plus (+) in qualitative dip stick method. We at first had 209 patients enrolled in the study, of which 108 were excluded due to various reasons.

After proper history and clinical examination, Fasting and post prandial blood sugar values (FBS, PPBS); Glycated Hemoglobin (HbA1C) & LFT values (serum bilirubin with its two fractions, Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline Phosphatase (ALP), total serum protein and albumin and prothrombin time) were measured in the two groups. Serum Gamma Glutamyl Transferase (GGT) was done to exclude alcoholism. The measurement was done in automated instruments (ERBA XL 300) supplemented with manual testing. Data was at first arranged in Microsoft Excel 2007 (Redmond, WA) worksheet. Data are expressed as mean ± SD for continuously distributed variables, and in absolute numbers and percentages for the discrete variables. Tests of significance were done with Unpaired Student's t-test. Software used for statistical analysis included freely available online software like GraphPad and MedCalc. A *p* value of <0.05 was considered significant. Normal levels considered: bilirubin: 1.04 mg/dl; AST: 45 U/L ALT: 45 U/L, ALP: 280 U/L serum protein: 6-8 g%. [Ref.: Liver Function Tests: National Liver Foundation; Mumbai. [Cited 2012 Feb 15]. Available online from http://www.nlfindia.com/liverZone/liver_function_test.asp and also the *respective* kit inserts of the tests]

Results and Analysis

Total 101 patients of Type 2 Diabetes mellitus (T2DM) were selected for the study. Among those diabetic patients 50 were on oral hypoglycemic drugs (OHA), including pioglitazone and statins for at least last 6 months. These group of population are denoted here as 'patients with drugs' group. Another 51 patients who were diabetic but not using OHA and Statins at least for last 6 months is considered here as 'patients without drugs' group. Of 101 subjects 53 were males (52.47%) and 48 females (47.53%). Mean age of 'patients with drugs' group was 52.82 ± 11.92 years and that of the other group was 51.37 ± 10.37 years (p=0.52, Student's t test). Among the subjects 44% was rural and 56% urban.

Fasting and post prandial blood sugars were measured in the two groups. **Fig. 1** shows the distributions of fasting blood sugar level in the two groups. **Table 1** shows that

Fig. 1
Bar diagram showing FBS in the patients

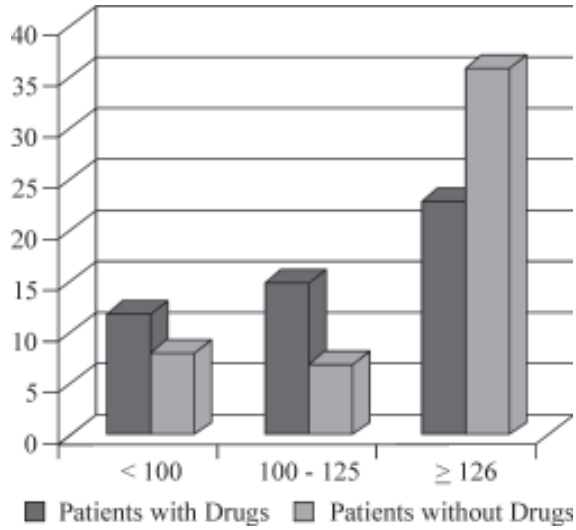
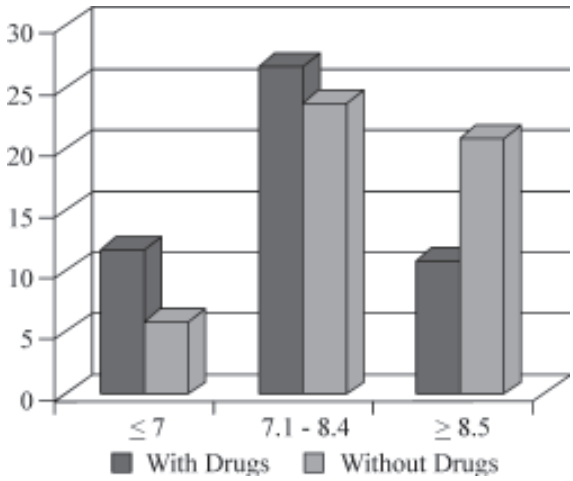


Table 1
Table showing distribution of PPBS in the two groups

PP Sugar (mg)	With Drugs	Without Drugs
<140	11(22%)	5(9.8%)
140 – 199	33(66%)	20(39.21%)
≥ 200	6(12%)	26(50.98%)

Fig. 2
Bar diagram showing HbA1C in the patients (%)



there was significant difference in distributions of PP blood sugar level between the two groups. Especially in the "patients without drugs group", 51% of patients had PPBS >200 mg/dL. There was no significant difference between the distributions of HbA1C level between the two groups (p value =0.09) (**Fig. 2**).

In 'patients with drugs' 78% had normal bilirubin level, 9% had raised bilirubin and 4% had bilirubin > 2.5 mg/dL. Among the 'patients without drugs' group, 72.54% patients had normal bilirubin level, 21.57% patients had raised bilirubin & 5.88% had bilirubin > 2.5 mg/dl. Mean distribution of bilirubin in the two groups was similar (p=0.1 by chi square test; **Table 3**). Altogether, 5 (4.95%) of the study patients had bilirubin>2.5 mg/dL although they had no known liver disease. Among the 'patients with drugs' group, 78% patients had normal ALT level, 12% have ALT within 41 – 80 U/L (1-2 times of upper level of normal), 6% had with in 81 – 100 U/L (2-2.5 times of upper limit of normal) and 4% had >100 U/L (**Table 2**). Among the 'patients without drugs' group 72.55% patients had normal ALT, 11.78% patients had ALT within 41 – 80 U/L (1-2 times of upper level of normal), 9.8% had within 81 – 100 U/L (2-2.5 times of upper limit of normal) and 5.88% have >100 U/L (**Table 2**). AST levels showed a similar trend (**Tables 2, 3**). 5 (4.95%) of the patients had ALT >100 U/L (vide **Table 3**). The mean alkaline phosphatase level in 2 groups was similar (213.96± 46.2 vs. 222.75 ±42.52 U/L; p= 0.32 table 3). The serum protein levels in the two groups

Table 2
Table showing level of transaminases in the two groups

	With Drug		Withour Drug	
	AST	ALT	AST	ALT
≤ 4O	35(70%)	39(78%)	31(60.78%)	37(72.55%)
41 - 80	10(20%)	6(12%)	15(29.41%)	6(11.74%)
81 - 100	4(8%)	3(6%)	2(3.92%)	5(9.8%)
≥ 101	1(2%)	2(4%)	3(5.88%)	3(5.88%)

were also similar (7.14 ± 0.65 vs. 6.96± 0.54 g/dL; p=0.12). Prothrombin time, as expressed by international normalized ratio (INR) was abnormal in 9 (8.9%) of the patients; however, there was no difference in the two groups (**Table 3**; p>0.05). No patient had INR>2 in our study.

Discussion

Liver dysfunction is a known association with diabetes. The different liver abnormalities in diabetes cover the entire spectrum from asymptomatic transamnitis to cirrhosis[2]. Liver disease is an important cause of death in type 2 diabetes. In the population-based Verona Diabetes Study [5], cirrhosis was the fourth leading cause of death and accounted for 4.4% of diabetes-related deaths. One study published in 2006, done by West *et al*, showed that elevated ALT was found in 9.5% (95%CI 7.1–12.3%) T2DM patients [6]. In their study, the prevalence of elevated ALT is 3–4 times higher in patients with either type 1 or type 2 diabetes than in the general population[6].

Another important study conducted by Sherif Gonem *et al* in 2007 tried to assess the prevalence of abnormal liver function tests in patients with diabetes mellitus[7]. Salmela *et al*.[8] studied the prevalence of abnormal LFTs and their relationship to clinical findings in 175 unselected diabetic outpatients in Finland. 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. 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.

It is also hypothesized that elevation in alanine aminotransferase (ALT), a gluconeogenic enzyme whose gene transcription is suppressed by insulin, could indicate impairment in insulin signaling rather than purely hepatocyte injury[9]. Ohlson *et al*.[10] 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, aspartate aminotransferase (AST), bilirubin concentrations, and family history of diabetes.

Table 3
Table showing distribution of liver test parameters among the two groups

Parameter		Patients with Drug (n=50)		Patients without Drug (n=51)		p value
Bilirubin		≤ 1.2	39(78%)	≤ 1.2	37(72.54%)	0.1
		1.2 – 2.5	9(18%)	1.2 – 2.5	11(21.57%)	
		> 2.5	2(4%)	> 2.5	3(5.88%)	
ALT		45.98 ± 26.09		51.1 ± 27.69		0.35
AST		37.02 ± 16.08		38.94 ± 22.76		0.62
ALP		213.96 ± 46.2		222.75 ± 42.52		0.32
Protein		7.14 ± 0.65		6.96 ± 0.54		0.12
Prothrombin time (INR)	≤ 1.2	45		46		Not significant
	> 1.2	5		4		

Many therapeutic drugs for diabetes target both fasting and postprandial hyperglycemia and other metabolic parameters involved in the diabetes-associated complications. These drugs are directed towards increasing insulin secretion, decreasing insulin resistance, and increasing insulin penetration into the cells. First generation Sulphonylureas were known for hepatotoxicity. For Glimepiride, a second-generation sulfonylurea, there have been no reports of hepatotoxicity in English literature; however, hepatotoxicity has been reported in French literature[11, 12]. The newer drugs in the thiazolidinediones class have a much larger margin of safety for liver toxicity. Very rare reports of liver toxicity, usually milder and reversible, have been seen with these drugs. Very few case reports have implicated it as a cause of hepatocellular injury and granulomatous hepatitis[13, 14, 15]. Elevated hepatic transaminases generally occur in 0.5% to 2.0% of cases of statin use and are dose-dependent[3, 4]. Progression to liver failure specifically due to statins is exceedingly rare if it ever occurs[16].

In our study, there has no significant difference among the distribution of bilirubin levels between the two groups of population. But the average bilirubin level in 'patients without drugs' group is more than the 'patients with drugs' group (1.30 compared to 1.12; $p>0.05$). According to previously mentioned studies this difference is mainly due to higher average fasting and post prandial sugar level in group 2.

Like bilirubin level of two groups if we compare the ALT, AST and alkaline phosphatase levels of the two patients, the distributions of ALT, AST, and alkaline phosphatase show similar insignificant difference. But in all cases the average levels are greater in 'Patient Without Drugs' group. Altogether, 70 (69.3%) of our patients had at least one liver test abnormality, including mild transaminase elevation. But none of them had any symptoms of liver dysfunction.

All these observations suggest that oral hypoglycemic drugs and statins (here atorvastatin) have no significant effect on liver (manifested by enzymes abnormalities). However, untreated diabetes itself is a risk factor for derangement of liver function and glycemic control helps to normalize them to a large extent. The main limitations of our study include the small study population and lack of invasive procedures like liver biopsy to better assess the liver structural changes. Also we did not follow up the patients to know further progression.

Conclusion

The prevalence of elevated liver enzymes is more in Diabetic patient than the normal population but the oral hypoglycemic drugs and statins were not found to have added hepatotoxicity in diabetic population. A large multicenter prospective randomized trial would be needed to exactly find the effect of these drugs on liver.

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