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Vikas Gupta
Department of Biotechnology, DAV College, Amritsar, Punjab, India

Gurjeet Singh
JJT University, Jhunjhunun, Rajasthan, India

Correspondence
Vikas Gupta
Department of Biotechnology, DAV College, Amritsar, Punjab, India

Liver function test in diabetic patients in Punjabi population

Vikas Gupta and Gurjeet Singh

Abstract
Diabetes mellitus is a common endocrine metabolic disorder characterized by hyperglycemia. The liver plays a major role in the regulation of carbohydrate metabolism, as it uses glucose as a fuel. This key function of liver makes it vulnerable to diseases in subjects with metabolic disorders, particularly diabetes. The present study aims to study the prevalence of liver enzymes Aspartate Transaminase (AST) and Alanine Transaminase (ALT) in Diabetic subjects from Punjabi population. In order to meet the proposed objectives of this study, whole blood samples were collected from 100 diabetic and 100 non diabetic subjects. Each sample was analysed for Fasting plasma glucose (FPG), HbA1C, AST and ALT. When categorized on the basis of type of disease 20% were of type 1 diabetes mellitus and 80% were of type 2 diabetes mellitus. In our study liver enzymes i.e. AST (p=0.0007) and ALT (p=0.0005) are significantly higher in diabetes compared to non diabetes subjects. Type 1 diabetic subjects did not shows any significant difference in the level of AST (p=.468) and ALT (p=0.978) compared to non-diabetic subjects, where as type 2 diabetic subjects shows significant higher level of AST (p=<.0001) and ALT (p=<.0001) compared to non-diabetic subjects. Failure to recognize the presence of abnormal liver enzymes may be a primary cause of poor management often encountered in some of the treated diabetics. There is therefore need for the routine assay of liver profile in diabetic, particularly in type 2 patients whose conditions are difficult to manage.

Keywords: Diabetes, HbA1C, AST, ALT, FPG

Introduction
Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (Craig *et al.*, 2009) [1]. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action (ADA, 2010) [2]. The chronic hyperglycemia-of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. In developed countries, 10% or more of total health budget is spent on the management of diabetes and its complications (Zimmet *et al.*, 2003) [3]. The abnormalities in carbohydrate, fat, and protein metabolism that are found in diabetes are due to deficient action of insulin on target tissues (Craig *et al.*, 2009) [1]. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hypersomolar syndrome. Diabetic ketoacidosis is the leading cause of morbity and mortality in children with diabetes (Dunger *et al.*, 2004) [4]. Unlike in adult population, pediatric mortality is mainly due to the development of cerebral oedema (Rosenbloom, 2007) [5].
Malfunctions like lipid abnormalities, renal diseases and liver diseases which can occur in diabetes mellitus can further complicate management of patients and escalate the cause of diabetes mellitus treatment. For all these reasons there is need to look for lipid abnormalities, renal abnormalities and liver abnormalities among diabetic population. Early detection of renal functions in subjects with diabetes is of vital importance as appropriate interventions have been shown to retard the progression of end stage renal disease and chronic kidney diseases which are the major public health problems in subjects with diabetes. Estimation of liver diseases among diabetes is necessary because liver pathology among diabetes is similar to that of alcoholic liver disease, including fatty liver, steato hepatitis, fibrosis and cirrhosis. Elevated activities of two serum enzymes, serum glutamate oxaloacetate transaminase (SGOT) also called aspartate transaminase (AST) and serum glutamate pyruvate transaminase (SGPT) also

called alanine transaminase (ALT) is the most frequently measured indicators of liver disease and occur in diabetes more frequently than in general population.

Diabetes mellitus is known to be associated with a number of liver disorders (Adami *et al.,* 1996; Trombetta *et al.,* 2005) [6, 7]. These include isolated elevation of liver enzyme levels, Non alcoholic fatty liver disease (NAFLD), Chronic liver disorders like hepatitis C infection, Cirrhosis, Hepatocellular carcinoma. NAFLD is a common indolently progressive liver condition characterized by insulin resistance and hepatic fat accumulation in the absence of other identifiable causes of fat accumulation, such as alcohol abuse, viral hepatitis, autoimmune hepatitis, alpha 1 antitrypsin deficiency, medication like corticosteroids and estrogens and other conditions (Cusi, 2009) [8]. Hepatic steatosis may range from a benign indolent deposition of fat to more severe non alcoholic steato hepatitis (NASH). NASH is frequently associated with fibrosis and approximately 10% of patients develop cirrhosis (Angulo, 2002) [9]. The risk of hepatocellular carcinoma is also increased in patients with type 2 DM and NASH (Bugianesi *et al.,* 2007) [10]. The causes of hepatic steatosis may be due to the decreased insulin sensitivity found in type 2 DM which activates lipolysis. Lypolysis leads to increased plasma levels of non esterified fatty acids which results in chronic increase in fatty acid flux from the fat store to non adipose tissues such as liver (Coppack *et al.,* 1994) [11].

Elevated activities of AST and ALT may be associated with liver diseases. Elevation of levels of any of these two enzymes has been found in 7.9% of the general population (Clark *et al.,* 2003) [12], whereas the prevalence of high ALT levels may reaches 20% in diabetes (Kejariwal *et al.,* 2008) [13]. Elevation of these enzymes act as surrogate marker for the presence of NAFLD (Trombetta *et al.,* 2005) [7]. It is proposed that elevated AST & ALT levels are predictive of the presence of NAFLD if two basic criteria are followed i.e. exclusion of alternative chronic liver disease including alcoholic liver disease, hepatitis B and C infection and hemochromatosis and presence of features of metabolic syndromes. Studies from different parts of the world show association between insulin resistance and liver disorders. Knobler *et al.* (1999) [14] reported that fatty liver was strongly associated with many features of insulin resistance and abnormalities of serum liver enzymes (ALT-92%; AST-77% and GGT-52%). Marchesini *et al.* (1999) [15] reported that non alcoholic fatty liver was closely associated with insulin resistance independent of body mass index and fat distribution. Meltzer and Everhart (1997) [16] found association between DM and high ALT among Mexican-Americans. These reports formed the basis to study liver enzymes abnormalities in diabetes.

The relationship between diabetes mellitus and liver diseases has not been extensively studied in Punjab although the prevalence of diabetes mellitus is very high and increasing. It is possible that there are diabetic patients who might have liver dysfunction which may greatly affect their glycemic control. Due to the lack of adequate information about the two conditions, preventive management is difficult to plan. Keeping the above in view the objectives of the present study are to evaluate the prevalence of liver abnormalities in diabetic patients from Punjab.

Materials and Methods

The study population consisted of 100 diabetic patients including 80 type 2 diabetic and 20 type1 diabetic patients visiting the OPD and ward of department of medicine, in Civil Hospitals of Kapurthala, Jalandhar and Amritsar. An informed verbal consent was taken from each and every patient. The criteria for diagnosis of diabetes were the American Diabetic Association criteria; FPG of 110 mg/dl, random blood sugar of 200 mg/dl or taking hypoglycemic drugs and/or using insulin and did not have any episodes of ketosis in the past. The initial criteria used for separating type 1 and type 2 diabetic subjects were the physician classification based on age of onset of diabetes and dependence on Insulin Therapy alone to achieve normal plasma concentration. The non diabetes volunteers without history of DM whose FPG were less than 110 mg /dl on two occasions were taken as the control samples. These volunteers included non-diabetic subjects who came in the hospitals for routine checkups as advised by their attending physicians. The controls were not taking any drugs. The study excluded subjects suffering from rheumatoid arthritis, tuberculosis, collagen disorders, liver diseases, renal diseases, cardiac failure and gout. Blood samples were collected from all the 200 subjects. They were kept on over night fast at least for 10 hrs before blood collection. 5 ml of venous blood was taken in dry disposable syringe under aseptic conditions in sterile, dry vial for biochemical analysis. Blood sample were assayed for FPG, HbA1c, AST and ALT. FPG (normal range 70-110mg/dl), HbA1c (normal range 4.2-6.2%), AST (normal range 5-42 mg/dl) and ALT (normal range 5-40 mg/dl), were determined on semi automated clinical chemistry analyzer.

Statistical Analysis

The results obtained from the above investigation were analysed and expressed as mean $\pm$ SD. The comparison was done by student t test on number of variable of each parameter using SPSS version 10.

Results and Discussion

In order to meet the proposed objectives of this study, whole blood samples were collected from 100 diabetic and 100 non-diabetic subjects. Among the 100 diabetic subjects, 48 were male and 52 were female. Similarly among the 100 non-diabetic subjects 48 were male and 52 were females. When categorized on the basis of type of diabetes 20 were of type 1 diabetes mellitus and 80 were of type 2 diabetes mellitus. The mean age of diabetic subjects was 40.95±11.2 years with range between 18-57 years. Mean age of non-diabetic subjects was 41.09±11.1 years and range between 17-58 years. There was no statistically significant difference between both groups with respect to mean age (p value= 0.93). The mean FPG levels (157.45±14.41 mg/dl) in diabetic subjects was significantly (p=<.0001) higher than the mean (88.52±6.72 mg/dl) value in non-diabetic subjects. Similarly mean value of HbA1C (7.18±0.73 %) in diabetic subjects was significantly (p=<.0001) higher than mean (5.01±0.22 %) in non-diabetic subjects.

Liver profile in Diabetes vs non diabetes

The levels and comparison of mean AST and ALT in diabetic and non-diabetic subjects are shown in Table 1. The mean AST (33.18±8.14 U/l) in diabetic subjects was significantly (p=0.0007) higher than the mean values (30.11±3.65 U/l) in non-diabetic subjects. The mean (35.65±8.50 U/l) ALT in diabetic subjects was higher than the mean (32.38±3.61 U/l) in non-diabetic subjects and difference was statistically significant (p=0.0005).

Table 1: Levels of AST and ALT in diabetic and non-diabetic groups

Parameters	Diabetic (N=100)	Non-diabetic (N=100)	t-value	S E	p-value
	Mean ± SD	Mean ± SD			
AST (U/l)	33.18 ± 8.14	30.11 ± 3.65	3.441	0.892	0.0007**
ALT (U/l)	35.65 ± 8.50	32.38 ± 3.61	3.540	0.92	0.0005**

When categorized on the basis of type of diabetes the mean AST (29.30±7.66 U/l) in type 1 diabetic subjects was insignificantly (p=.468) lower than the mean values (30.11±3.65 U/l) in non-diabetic subjects. The mean (32.35±7.93 U/l) ALT in type 1 diabetic subjects was comparable with the mean (32.38±3.61 U/l) in non-diabetic subjects and this difference was statistically insignificant (p=0.978). While in case of type 2 diabetic subjects the mean AST (34.17±7.20 U/l) was very significantly (p=<.0001) higher than the mean values (30.11±3.65 U/l) in non-diabetic subjects. Similarly the mean (36.48 ±7.89 U/l) ALT in type 2 diabetic subjects was higher than the mean (32.38±3.61 U/l) in non-diabetic subjects and this difference was statistically very significant (p=<.0001).

Comparison of liver profile amongst Male and Female Diabetes

The levels and comparison of mean AST and ALT, FPG and HbA1c in diabetic male and female subjects are shown in Table 2. The mean AST (35.52 ±9.27 U/l) in diabetic male subjects was very significantly (p=.005) higher than the mean values (31.02±6.27 U/l) in female diabetic subjects. The mean (38.58±9.96 U/l) ALT in diabetic male subjects was higher than the mean (32.9 4±5.78 U/l) in diabetic female subjects and this difference was statistically very significant (p=.0007). The mean FPG levels (158.56±13.71 mg/dl) in diabetic male subjects was insignificantly (p=.4650) higher than the mean (156.4 ±15.08 mg/dl) value in diabetic female subjects. Similarly mean value of glycosylated hemoglobin (7.21±0.47 %) in diabetic male subjects was insignificantly (p=.6978) higher than mean (7.25±0.55 %) diabetic female subjects.

Table 2: Levels of AST, ALT, FPG and HbA1c in diabetic male and diabetic female groups

Parameters	Diabetic male (N = 48)	Diabetic female (N = 52)	t-value	S E	p-value
	Mean ± SD	Mean ± SD			
AST (U/l)	35.52 ± 9.27	31.02 ± 6.27	2.862	1.572	0.0051**
ALT (U/l)	38.58 ± 9.96	32.94 ± 5.78	3.496	1.613	0.0007**
FPG (mg/dl)	158.56 ± 13.71	156.44 ± 15.08	0.733	2.89	0.4650
HbA1c (%)	7.21 ± 0.47	7.25 ± 0.55	0.3894	0.103	0.6978

** Highly Significant

Comparison of liver profile amongst type 1 and type 2 Diabetes

The levels and comparison of mean AST, ALT, FPG and HbA1c in type 1 diabetic and type 2 diabetic subjects are shown in Table 3. The mean AST (29.30±7.66 U/l) in type 1 diabetic subjects was significantly (p=.0088) lower than the mean values (34.17±7.20 U/l) in type 2 diabetic subjects. The mean (32.35±7.94 U/l) ALT in type 1 diabetic subjects was lower than the mean (36.48±7.89 U/l) in type 2 diabetic subjects and this difference was statistically significant (p=.0391). The mean FPG levels (151.4±12.55 mg/dl) in type 1 diabetic subjects was significantly (p=.0554) lower than the mean (158.32±14.66 mg/dl) value in type 2 diabetic subjects. Similarly mean value of HbA1c (7.01±0.46 %) in type 1 diabetic subjects was significantly (p=.0450) lower than mean (7.26±0.50 %) in type 2 diabetic subjects.

Table 3: Levels of AST, ALT, FPG and HbA1c in type 1 and type 2 diabetic groups

Parameters	Type 1 diabetic (N = 20)	Type 2 diabetic (N = 80)	t-value	S E	p-value
	Mean ± SD	Mean ± SD			
AST (U/l)	29.30 ± 7.66	34.17 ± 7.20	2.671	1.823	0.0088**
ALT (U/l)	32.35 ± 7.94	36.48 ± 7.89	2.091	1.975	0.0391*
FPG (mg/dl)	151.40 ± 12.55	158.32 ± 14.66	1.939	3.569	0.0554*
HbA1c (%)	7.01 ± 0.46	7.26 ± 0.50	2.030	0.123	0.0450*

** Highly Significant, * Significant

The liver plays a major role in the regulation of carbohydrate metabolism, as it uses glucose as a fuel, it has the capability to store glucose as glycogen and also synthesize glucose from non-carbohydrate sources. This key function of liver makes it vulnerable to diseases in subjects with metabolic disorders, particularly diabetes (Levinthal & Tavill, 1999) [17].

In this study liver enzymes i.e. AST (p=0.0007) and ALT (p=0.0005) are significantly higher in diabetes compared to non diabetes subjects (Table 1). Our results are in agreement with a study from Sudan [18] comprising of 50 type 2 diabetic patients. It was reported that atleast 22% of patients had one or more abnormal liver enzyme with 12% having elevated ALT and 12% having elevated AST levels.

In our study type 1 diabetic subjects did not shows any significant difference in the level of AST (p=0.468) and ALT (p=0.978) compared to non-diabetic subjects, where as type 2 diabetic subjects shows significant higher level of AST (p=<0.0001) and ALT (p=<0.0001) compared to non-diabetic subjects. On comparing the levels amongst type 1 and type 2, Type 2 diabetic subjects had significantly higher level of AST (p=0.0088) and ALT (p=0.0391) compared with type 1 subjects (Table 3). This is in agreement with the study of Salmela *et al.* (1984) [19] who reported non-insulin-dependent diabetic patients to have abnormal LFT results more often as compared to insulin-dependent diabetic patients.

In our findings sex was the determining factor for diabetes for liver enzymes. Diabetic males had higher level of AST and ALT (Table 2) and the difference was statistically significant (p=0.0051 and p=0.0007) respectively. Our results are in agreement with a study performed on Jordian [20] population reporting elevated levels of ALT (10.4%) in type 2 diabetic population. The gender wise prevalence showed higher prevalence in men (12.8%) as compared to women (7.4%). Similarly higher levels of AST (5.4%) were reported in patient population with gender wise prevalence being 5.6% in men and 5.4% in women respectively.

Conclusion

The present study reports high level of liver enzymes among diabetic patients indicating a sign of unanticipated hepatic disorder and proposes that the failure to recognize the presence of abnormal liver profile in diabetic patients may be the main reason of poor management often encountered in some of the treated diabetics. Hence there is need for the routine assay of liver profile in diabetic, particularly in those patients whose conditions are difficult to manage.

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