PREVALENCE OF ELEVATED HEPATIC ENZYMES AMONG NORTH INDIAN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Juhi Agarawal

Assistant Professor, Dept. of Biochemistry, Santosh Medical College Hospital, Ghaziabad, India
Email: jaggarwal38@gmail.com

ABSTRACT

This study was planned to evaluate the liver function in patients with type 2 diabetes mellitus by measuring bilirubin (total and direct), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), total protein, albumin and glycosylated hemoglobin (HBA1c) .The study was carried out in Santosh Medical College & Hospital, Ghaziabad. 100 patients with type 2 diabetes mellitus (49 males and 51 females) were included in the study. Their ages ranged between 32 and 55 years. Hundred matched normal individuals were taken as control group. In the present study, we concluded that the mean values of ALT, AST and GGT were significantly higher in patients as compared to the controls (P<0.05). Total protein and albumin concentrations in patients were lower as compared to the control group (P<0.05). The mean of serum glucose and glycosylated hemoglobin concentrations in patients revealed significant difference (P<0.001) as compared to the control group.

Keywords: *Type 2 Diabetes Mellitus, liver function test, glycosylated hemoglobin.*

INTRODUCTION

Diabetes is one of the major non – communicable diseases, whose prevalence is increasing exponentially. Globally, Type 2 Diabetes Mellitus is the most common form accounting for about 90% of all the cases[1]. There exists an association between diabetes and liver injury as diabetes mellitus is known to be associated with a number of liver disorders, including isolated elevation of liver enzyme levels, nonalcoholic fatty liver disease (NAFLD), and other chronic liver disorders like hepatitis C infection (HCV) and cirrhosis[2]. The liver has a central role in glucose homeostasis in the fasting and post prandial concentrations and in liver diseases, this hepatic carbohydrate metabolism is generally altered[3, 4].

As shown in animal models, chronic hyperinsulinemia state predisposes liver to relative insulin resistance. Also, a cascade of reactions leading to increased lipogenesis and associated fatty changes[5]. The excess in free fatty acid concentration found in this insulin resistant state is known to be directly toxic to hepatocytes which include suggestive mechanisms of cell membrane disruption at high concentration, mitochondrial dysfunction, oxidative stress from reactive lipid peroxidation and an increase in pro inflammatory cytokine such as Tumor Necrosis Factor, which also contribute to hepatocellular injury [6, 7].

There is evidence that the disturbance in hepatic glucose metabolism may be involved in the pathogenesis of Type 2 Diabetes Mellitus[8]. It is stated that the disturbances in liver function tests are well recognized in some diabetic patients[9].Increased activities of liver enzymes such as Alanine transaminase (ALT), Aspartate transaminase (AST) and Gamma glutamyl transferase (GGT) which are indicators of hepatocellular injury, are associated with insulin resistance and Type 2 Diabetes Mellitus[10, 11].

It was found in a study of 35 patients that HBA1c results should be used in patients with advanced liver disease when evaluating long term glucose control in such patients[12]. Further, increased levels of ALT, AST and GGT are known to be markers of nonalcoholic fatty liver disease (NAFLD)[13]. There is increased prevalence of NAFLD in the Diabetes Mellitus and it is regarded as a predisposing factor for insulin resistance and hyperinsulinemia[14]. The present study is aimed to evaluate the prevalence of elevated hepatic enzymes among North Indian patients with Type 2 Diabetes Mellitus as compared to the non- diabetic control group.

MATERIALS AND METHODS

This is a hospital based study conducted in the Department of Biochemistry and Central Laboratory, Santosh Hospital, Ghaziabad. Patients were taken from medicine OPD. Ethical consideration of the study was approved by the Institution's Ethical Committee. The objectives and detailed procedure involved in the study were explained to all the eligible subjects. Written informed consent forms were obtained from all the participants of the study.

Specimen collection: 100 new type 2 diabetic patients were recruited for the study, by random selection. They were distributed into 2 groups as x males and y females.

For the control group, 100 samples, which constitute x males and y females, non- diabetics, aged between 32 to 55 years were voluntarily included in the study.

Patients selected for the study were selected according to the ADA- 2010 criteria.

Excluded criteria of subjects:

1. History of alcohol consumption.
2. Patients taking hepatotoxic drugs like amidarone, antituberculous drugs.
3. Pregnant women.
4. History of liver disease including clinical or biochemical evidence of acute hepatitis, autoimmune hepatitis, primary liver cirrhosis, hemochromatosis or Wilson disease.
5. Subjects with positive hepatitis B and C virus infection (seropositive for HBsAg and HCV antibodies).

Blood sample collection: 5ml of venous blood was drawn from each subject in fasting state using disposable syringe and immediately transferred to plain tubes for further sample processing. Also, 2ml venous blood was drawn from each subject for the Post prandial blood glucose measurement. The samples were analyzed for ALT, AST, GGT, Alkaline Phosphatase [to measure the quantitative determination of the catalytic enzyme activity, supplied by Merck Diagnostics], Bilirubin (total & direct), Total protein, albumin, fasting blood glucose, post prandial blood glucose [using the Enzymatic Colometric method supplied by Merck Diagnostics] and glycosylated hemoglobin [using Immunoturbidimetric inhibition method by Aggape Diagnostics] .

STATISTICS

The data obtained was analyzed using GRAPH PAD PRISM (Version 5.0). Unpaired t-test was used to compare controls & patients. P value less than 0.05 was taken as significant. Results are expressed as mean±S.D.

RESULTS

The mean values of age in control were 45.6±5.2 & patients 47±3.8. The patients were age & sex matched. In the current study, Table-1 shows comparison of controls with patients of altered liver function with cases of Type 2 diabetes mellitus in which we compared ALT, AST, GGT, albumin ,total protein, bilirubin(total and direct) & Table-2 depicts Blood sugar (fasting and post- prandial) and HBA1c in the same. As shown in Table 1, mean values of ALT, AST and GGT liver enzymes were significantly higher in type 2 diabetic patients than in the control group ($P \leq 0.05$). In contrast, values of total protein and albumin concentrations were significantly lower in diabetic cases as compared to the control group ($P \leq 0.05$). The mean value of serum glucose & HBA1c is clearly higher in diabetic patients than in controls ($P<0.001$).

Table 1: Shows comparison of controls with patients of altered liver functions

Parameters	Controls	Patients	P value
Albumin	3.868 ± 0.07485	3.383 ± 0.09744	0.0002
Total Protein	6.842 ± 0.1005	6.078 ± 0.1149	0.0001
Globulin	2.997 ± 0.07829	2.757 ± 0.09793	0.0613
Bilirubin(T)	0.8065 ± 0.02421	2.034 ± 0.5710	0.0366
Bilirubin(D)	1.223 ± 0.8713	0.9192 ± 0.2799	0.7416
GGTP	32.04 ± 1.958	62.38 ± 15.51	0.0579
SGOT	24.00 ± 1.470	148.3 ± 38.68	0.0023
SGPT	25.46 ± 0.9531	196.2 ± 64.31	0.0106
Alkaline Phosphatase	131.0 ± 8.905	293.2 ± 42.54	0.0005

Table 2: Shows comparison of controls with patients for Blood sugar parameters

Parameters	Controls	Patients	P value
Fasting Blood sugar (F)	90.82 ± 2.716	133.8 ± 7.569	0.0001
Post prandial Blood Sugar(PP)	123.0 ± 2.537	209.4 ± 11.92	0.0001
HBA1c	5.00±0.14	9.8±0.35	0.0001

DISCUSSION

Several serum enzymes have been studied in diabetic patients, but the data reported are often unrelated and controversial[15,16]. In this study, we have studied many sensitive LFTs & there variation in diabetic patients. Previous studies have demonstrated that a high prevalence of unexplained altered liver enzymes (ALE) has been found in Western populations. In an earlier study, which included 175 unselected Finnish patients with type 1 and type 2 diabetes, Salmela et al reported that the prevalence of higher ALE was 57% and glycosylated haemoglobin was averaged at 11.2±2.4%. One recent study has confirmed the high prevalence of ALE in patients with type 2 diabetes mellitus, with rates ranging from 15-30%[17,18]. In this study, the most frequently encountered abnormalities were those of SGOT, SGPT and ALP, rather than GGT. The few available reports have highlighted ALP as the most frequent abnormality in subjects with type 2 diabetes mellitus[19, 20]. However, this is not a universal finding and transaminase abnormalities have been shown to be the most common abnormality in some studies, higher transaminases would be more suggestive that NAFLD is the probable cause in such patients [14]. Meltzer and Everhart noted a greater prevalence of abnormal alanine aminotransferase levels among Mexican Americans with diabetes and disagree with the study of Erbey et al[21,22]. In their study, 4.1% had elevated ALT. Those with type 2 diabetes, had prevalence of elevated ALT which was 7.8% as compared to 3.8% prevalence in those without diabetes. A data of 10,065 patients was investigated for the correlation between HBA1c and plasma glucose in patients with different levels of increased liver enzyme concentrations and it was found that the correlation between HBA1c and plasma glucose was high in all groups with r=0.77(in males) and r= 0.78 (in females) ($p< 0.001$)[23] .

Many factors linked to diabetes per se or to associated disorders or treatment regimens may affect LFT results in diabetic patients[24, 25]. Complications and enzymatic adaptations due to long-term diabetes result in increases in serum enzymes that are not directly linked to liver damage[15]. Such mechanisms could explain the poor correlations between the histologic findings and the values of serum ALP and Bilirubin in the IDDM patients with normal livers[26,27]. LFTs are not sufficiently reliable to correctly and consistently identify the presence of those histologic alterations that could represent intermediary steps in the progression of fatty liver to hepatic cirrhosis[28]. Many studies showed that younger diabetic patients were more likely to have high ALT values than the older patients. However, the older patients showed elevated AST activity and ALT elevation was found to be more common in men than to women[29]. It was also stated that there is a significant association of elevated ALT levels with the duration of diabetes. Other risk factors for elevated ALT were younger age and larger waist circumference. Patients on insulin appeared to have lower ALT readings. These findings necessitate interference by lifestyle modification and early therapeutic measures to control risk factors, especially obesity, in younger diabetics which might help to prevent chronic liver disease.

Supported by earlier studies this finding suggested that severe steatosis denoted by a higher release of the ALT enzyme in response to hepatocytes derangement, tends to occur earlier in the disease process[30]. As a marker of hepatocyte integrity the ALT activity decreases as steatosis progresses whereas inversely a rise in the AST level has been noticed in the older patients. The latter observation can be attributed to the fact that the clearance of this enzyme is mainly accomplished by the liver sinusoidal cells. While there is no effect from the necroinflammatory activity on AST level, advancing fibrosis which injures the sinusoidal cells leads to the relative increase in serum AST[31]. In a study by West J et al it was reported that the prevalence of elevated ALT is 3-4 times higher in patients with either type 1 or type 2 diabetes mellitus than in the general population [32].

CONCLUSION

The results of this study are in accordance with previously reported high prevalence rates of ALE in patients with type 2 diabetes mellitus in other populations. Raised ALT and AST are more common among the diabetes patients as compared to controls AST elevation was also significant among men. Abnormal liver function tests among diabetes patients can be indicator of associated non alcoholic fatty liver disease. There has been a direct correlation between HBA1c and elevated liver enzymes, in accordance with previous studies. Checking for liver enzymes, ALT and AST should be carried out to screen the possibility of underlying fatty liver, which might need further evaluation and early intervention to prevent from progression into cirrhosis and chronic liver disease, especially in male patients with Diabetes & high BMI.

Although there are currently no consensus guidelines or recommendations regarding LFT screening in patients with type 2 diabetes mellitus, these findings lend support to the practice of routine liver function monitoring in subjects with type 2 diabetes mellitus.

Furthermore, the high prevalence of severe derangements also highlights the importance of performing LFTs in these otherwise asymptomatic patients, as they may harbor potentially treatable co-morbid illnesses. Many of these patients would

require further laboratory, radiological and histological investigation.

Therefore, if LFT screening is to be adopted, it would be incumbent on the physician to ensure that abnormal findings are appropriately investigated, or that the patient be timorously referred to a tertiary institution with the necessary facilities.

REFERENCES

1. Amos A F, McCarty D J, Zimmet P. The rising global burden of diabetes and its implications: estimates and projections to the year 2010. Diabetes med1997; 14(5): 81-85.
2. Caldwell S H, Oelsner D H, Lezzoni J C, Hespenheide E E, Battle E H and Driscoll C J. Cryptogenic cirrhosis: clinica characterization and risk factors for underlying disease: ; Hepatology, 1999, 29 (3), 664-69.
3. Felig P, Sherwin R, Carbohydrate homeostasis, liver and diabetes. In progress in liver disease, Vol 5. Popper H and Schaffner F, Eds. New York, Grunne and Stratton, 1976, 149-72.
4. Johnston D G, Alberti K G M M, Binder C, Faber o K, Wright R and Orskov H. Hormonal and metabolic changes in hepatic cirrhosis. Horm. Metab. Res. 1982, 14: 34-39.
5. Shimomura I, Matsuda M, Hammer R E, Bashmakov Y, Brown M M, Goldstein J L. Decreased IRS-2 and increased SREBP -1c lead to mixed insulin resistance and sensitivity in lives of lipodystrophic and ab/ab mice. Mol. Cell 2000, 6, 77-86.
6. Leffert H L, Koch K S, Moran T and Rubalcava B. Hormonal control of rat liver regeneration. Gastroenterology 1979, 76, 1470-82.
7. Jeanrenaud B. Insulin and obesity, Diabetologia 1979, 17; 133-38.
8. DeFronzo R A, Ferrannini E and Koivisto V. New concepts in the pathogenesis and treatment of NIDDM. Am. J. Med. 1983; 74: 52-81.
9. Levinthal G N and Travill A S. Liver disease and diabetes mellitus. Clinical Diabetes, 1999. 17 (2).
10. Marchesini G, Brizi M and Bianchi G. Non alcoholic fatty liver disease: A feature of metabolic syndrome. Diabetes: 2001, 50: 1844-1850.
11. Wannamethee S G, Shaper A G, Lennol L, Whincup P H. Hepatic enzymes, the metabolic syndrome and the risk of type 2 diabetes mellitus in older men: 2005,Diabetes Care, 28: 2913-918.
12. Theresa L, Karin H, Rottraut L, Rainer WL, Robert K, Randie RL, Wolfgang JS. Determination of glycated hemoglobin in patients with advanced liver disease. World Journal of Gastroentrology, 2004, 10 (15), 2284-68.
13. Perry I J, Wannamethee S G and Shaper A G. Prospectiev study of serum gamma glutamyltransferase and risk of NIDDM. Diabetes Car, 21; 732-37.
14. Hanley AJ, William K, Wagen Knecht L E, D' Agostino R B Jr, Kempf J, Zinman B, Haffner S M. Elevations in markers of liver injury and risk of type 2 diabetes: the insulin resistance atherosclerosis study. Diabetes, 53, 2623-32.
15. Leevy, C. M., Ryan, C. M., and Fineberg, J. C.: Diabetes mellitus and liver dysfunction. Am. J. Med. 1950; 8:290-99.
16. Goldberg, D. M., Martin, J. V, and Knight, A. H.: Elevation of serum alkaline phosphatase activity and related enzymes in diabetes mellitus. Clin. Biochem. 1977; 10:8-11.
17. Forlani G, Di Bonito P, Mannucci E, Capaldo B, et al. Prevalence of elevated liver enzymes in type 2 diabetes mellitus and its association with the metabolic syndrome. J Endocrinol Invest. 2008; 31(2):146-152.
18. Salmela PI, Sotaniemi EA, Niemi M, Maentausta O. Liver function tests in diabetic patients. Diabetes Care, 1984; 7:248-254.
19. Gonem S, Wall A, Parijat De. Prevalence of abnormal liver function tests in patients with diabetes mellitus. Endocrine Abstracts. 2007; 13:157.
20. Everhart JE (1995). Diabetes in America. 2nd ed. National Institute of Health. National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: GPO: 457-483.
21. Meltzer AA, Everhart JE (1997). Association between diabetes and elevated serum alanine aminotransferase activity among Mexican Americans. Am. J. Epidemiol., 146: 565–571.
22. Erbey JR, Silberman C, Lydick E (2000). Prevalence of abnormal serum alanine aminotransferase levels in obese patients and patients with type 2 diabetes. Am. J. Med., 109: 588–590.
23. Christtian SR, Rasmussen LM, Nyto H, Steenstrup T, Nyto M. The relationship between glycosated hemoglobin and fasting plasma glucose in patients with increased plasma liver enzyme measurements, Diabet Med 2012, 29(6): 742-47.
24. Belfiore, F., LoVecchio, L., and Napoli, E.: Serum enzymes in diabetes mellitus. Clin. Chem. 1973; 19: 447-52.
25. Berkowitz, D.: Metabolic changes associated with obesity before and after weight reduction. JAMA 1964; 187: 399-403.
26. Zimmerman, H. J., and Maddrey, W. C: Toxic and drug induced hepatitis. In Diseases of the Liver. Schiff, L., and Schiff, E. R., Eds. Philadelphia, J. B. Lippincott Co., 1982:621-92.
27. Trombetta M, Spiazzi G, Zoppini G, Muggeo M. Review article: Type 2 diabetes and chronic liver disease in the Verona diabetes study. Aliment Pharmacol Ther. 2005; 22:S24–7.
28. Coppack SW, Jensen MD, Miles JM. In vivo regulation of lipolysis in humans. J Lipod Res. 1994; 35:177–93.
29. Layla J, Ala T, Yousef K, Kamel A, Amer MK.
30. Prevalence of elevated hepatic transaminases among Jordianian patients with type 2 diabetes mellitus. Ann Saudi Med. 2010 Jan-Feb; 30(1): 25–32.
34. Ioannou GN, Boyko EJ, Lee SP. The prevalence and predictors of elevated serum aminotransferases activity in the United States in 1999-2002. Am J Gastroenterol. 2006; 101:76–82.
35. Kamimoto Y, Horiuchi S, Tanase S, Morino Y. Plasma clearance of intravenously injected aspartate amminotransferase isoenzym: Evidence for preferential uptake by sinusoidal liver cells. Hepatology. 1985; 5: 367-75.
36. West J, Brousil J, Gazis A, Jackson L, Mansell P, Bennett A, Aithal GP. Elevated serum alanine transaminase in patients with type 1 or type 2 diabetes mellitus. QJM. 2006 Dec; 99(12):871-6.