ORIGINALARTICLE

Assessment of Liver Marker Enzymes in Type 2 Diabetes Mellitus Patients

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Abstract:

Background and objectives: Hepatocyte injury and changes reflected in the levels of liver marker enzymes have been elucidated in various studies on type 2 diabetes mellitus. These changes have been linked to the high blood sugar levels, free radicals and oxidative stress produced in the same. Liver marker enzymes including ALT, AST, GGT, ALP, have been associated with poor glycemic index. Many studies have linked one or two of the liver marker enzymes with type 2 diabetes mellitus, but in our study we attempted to find the link between the four hepatic enzymes with type 2 diabetes mellitus. *Methods:* Sixty cases of type 2 diabetes mellitus among the age group of 35 to 60 years and 35 healthy age and sex matched controls were chosen. Various tests including fasting blood glucose, serum triglycerides, total cholesterol, ALT, AST, GGT and ALP were performed. *Results:* In the present study, type 2 diabetes mellitus cases and fasting blood sugar showed a statistically significant association with serum ALT (p=0.003), AST(p=0.017), GGT (p=0.00019) and no correlation with ALP (p=0.96). Also, there was a weak positive correlation for AST (p=0.02) and ALT (p=0.06) with Triglycerides, but the hepatic enzymes did not correlate with BMI or total cholesterol levels. *Interpretation and conclusion:* This case-control study is unique in assessing the levels of serum ALT, AST, GGT, ALP with FBS, BMI, T.CHOL, TGL levels among type 2 diabetes mellitus cases living in Triplicane, Chennai. We assessed whether liver marker enzymes can be used as biomarkers for insulin resistance and thereby for diagnosing high risk patients for developing type 2 diabetes mellitus, for their management and to monitor the complications.

Keywords: alanine aminotransferase, alkaline phosp - hatase, aspartate aminotransferase , fasting blood glu - glucose, gamma glutamyl transferase, insulin resistance, liver marker enzymes, total cholesterol, triglycerides, type 2 diabetes mellitus.

Introduction:

Type 2 diabetes mellitus is a heterogeneous group of disorders affects almost all the organs including liver, which plays a major role in nutrient metabolism in our body [1]. De Marco et al, observed that one of the major causes of death due to diabetes was liver cirrhosis [2]. Almost all types of liver diseases are seen to be associated with type 2 diabetes mellitus, including liver cirrhosis, abnormal liver enzymes, non-alcoholic fatty liver disease (NAFLD), liver cancer and acute liver failure. Low insulin sensitivity in type 2 diabetes leads to glycation, peroxisomal beta oxidation and lipid peroxidation which causes oxidative stress to develop in the tissues [3]. This oxidative stress coupled with cytokine production, in the hepatic tissue, leads to liver damage, thereby changing the levels of the liver enzymes [4]. Nonalcoholic steatohepatitis cases are very abundant in Asia, foretelling diabetes. Fatty acid influx into the liver leads to reduced insulin sensitivity, β cell failure and type 2 diabetes mellitus [5]. Elevated levels of Alanine amino transferase (ALT) in the blood may indicates not only liver injury, but also defective insulin signaling, independent of familial diabetic history, plasma glucose, lipid, bilirubin, AST or obesity [6]. When there is an excess of lipid in the body (as in obese individuals), and when the adipose tissue is saturated, the extra fat tends to accumulate in other areas, including the liver. Non oxidative pathways for fatty acid metabolism are induced, which leads to formation of reactive lipid entities, that cause liver cell damage. Thus, liver enzymes, including AST, leak out of the cells into serum, whereas in the liver, insulin resistance develops, which leads to diabetes mellitus [7]. Gamma glutamyl transferase (GGT) is a microsomal enzyme present on the outer surface of almost all cells and it helps in uptake of glutathione from the cell surface indicating inflammation and oxidative stress. It acts as a marker for biliary function. It acts as a marker for nonalcoholic steatohepatitis (NASH) and reduced insulin sensitivity as it increases with body mass index and blood sugar [8]. Alkaline Phosphatase (ALP) is an ectoenzyme found in bone and liver. It act as a marker of

cholestasis. Insulin resistance activates glycogenolytic and gluconeogenetic pathways which cause ALP to leak out of hepatocytes especially due to fat infiltration [9]. There are only a few studies relating type 2 diabetes mellitus and liver injury. Our study is first of its kind to assess alanine amino transferase, aspartate amino transferase, gamma glutamyl transferase, alkaline phosphatase with fasting blood sugar, body mass index, total cholesterol and triglycerides in recently diagnosed type 2 diabetes mellitus patients. We hope that this study will bridge the gap, fill in the existing loopholes and prove as emerging evidence about the association of liver enzymes with type 2 diabetes mellitus. The objectives of the current study were, A) To evaluate and compare the BMI, total cholesterol, serum triglycerides and fasting blood glucose levels in type 2 diabetes mellitus patients and controls. B) To assay the serum levels of liver marker enzymes and examine their relation to total cholesterol, serum triglyceride levels, BMI and fasting blood glucose levels in type 2 diabetes mellitus patients.

Material and Methods:

This case-control study included diagnosed diabetes mellitus patients (using WHO guidelines) of past five years duration without any complications with an age group of 35-60 years of both sexes presenting to Department of internal medicine, Government Medical College, Chennai between February-March 2021 with 35 healthy age and sex matched controls. Known Type 2 Diabetes mellitus patients with history of Alcoholic Liver disease, Smoking, Consumption of hepatotoxic drugs, Hepatitis B and C virus infection, Pregnancy, Type 1 diabetes mellitus, Serious infections, Chronic hypertension, thyroid disease, cardiovascular disease, renal failure, lung disease, hemolysis, Current immunosuppressive therapy were excluded. The study protocol was approved by the local Ethics Committee in Chennai, India. After obtaining informed consent from each subject, 5ml of overnight fasting venous blood sample was collected. Serum was separated and used for following analysis: Fasting blood sugar by GOD/POD method, serum Total Cholesterol by CHOD-PAP, serum Triglyceride by GPO-PAP, serum ALT by using alanine amino transferase reagent without pyridoxal phosphate, serum AST by using aspartate amino transferase reagent without pyridoxal phosphate, serum GGT by using kinetic colorimetric IFCC method, serum ALP by using ALP-AMP method. All biochemical investigations were done using random access clinical chemistry Auto analyzer of Trans Asia Bio-Medicals Ltd. Anthropometric indices like height, weight, hip and waist circumference was taken to calculate the body mass index and waist to hip ratio respectively. Statistical analysis performed using SPSS package v21.0. The results were expressed as mean ± standard deviation (SD). Independent sample student's'‘t’ test was used to compare mean values.P<0.05 was considered statistically significant. Pearson correlation was applied to correlate between the parameters.

Results:

A total of 85 people were enrolled for this study. The mean age of the study participants was 48.8 ± 7.2. The parameters like BMI (p<0.001), W:H ratio (p<0.001), FBS (p<0.001), Triglycerides (p<0.001), ALT (p= 0.02), AST (p= 0.02), GGT (p = 0.023) between the cases and controls were statistically significant. However, total cholesterol between the two groups was not statistically significant (p =0.6) as shown in the table I.

TABLE-I: Parameters (Mean±SD) among Type 2 diabetic cases and controls

Sr. No.	PARAMETERS	DIABETES MELLITUS CASES	CONTROLS
1	**BMI** (kg/m^2)	26.20 ± 4.0	20.70 ± 1.3
2	**W/H ratio**	1.12 ± 0.059	0.91 ± 0.2
3	**FBS** (mg/dl)	268.7 ± 108.6	99.5 ± 19.7
4	**T.CHOL** (mg/dl)	173.9 ± 51.6	169.1 ± 39.5
5	**TGL** (mg/dl)	209.8 ± 88.9	124.8 ± 22.9
6	**ALT** (IU/L)	21.51 ± 8.1	18.3 ± 7.17
7	**AST** (IU/L)	22.6 ± 8.4	19.3 ± 7.6
8	**GGT** (IU/L)	46.7 ± 26.73	36.2 ± 22.8
9	**ALP** (IU/L)	99.3 ± 45.5	78.88 ± 14.38

Body mass index (BMI), Waist:hip ratio (W/H ratio), Fasting blood sugar (FBS), Total cholesterol (T.CHOL), Triglycerides (TGL), Alanine amino transferase (ALT), Aspartate amino transferase (AST), Gamma-glutamyl transferase (GGT), Alkaline phosphatase (ALP) There is no correlation between ALT (p=0.25), AST (p=0.30), GGT (p=0.16), ALP (p=0.58) with BMI among cases. We found a weak correlation between ALT (p=0.06), AST (p=0.02) and Triglycerides among cases. However, GGT (p=0.23), ALP (p=0.15) did not show any correlation. And no correlation was seen between ALT (p=0.17), AST (p=0.64), GGT (p=0.25), ALP (p=0.17) with Total Cholesterol among cases.

FIGURE I: This bar chart compares Body Mass Index, Fasting Blood Glucose, Total cholesterol and Triglycerides between type 2 diabetes mellitus cases and controls.

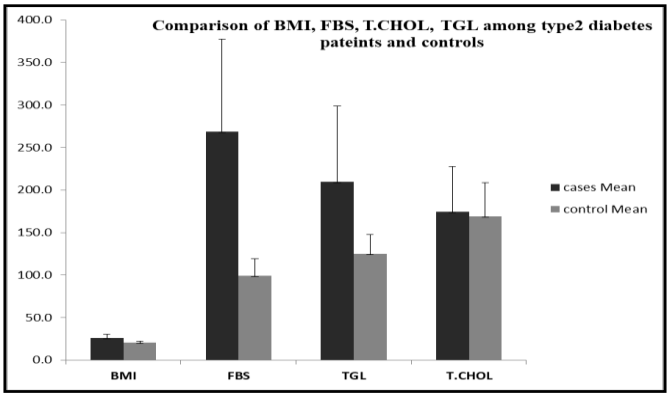


FIGURE II: Correlation between alanine amin - otransferase (mg/dl) and fasting blood glucose (mg/dl) among type 2 diabetes mellitus cases shows positive correlation and is statistically significant (p=0.003).

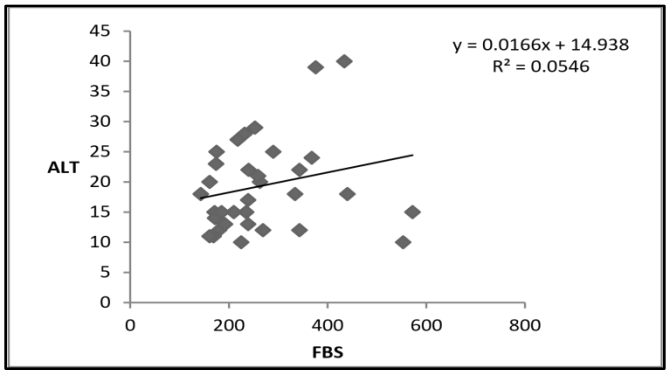


FIGURE III: Correlation between aspartate amino transferase (mg/dl) and fasting blood glucose (mg/dl) among type 2 diabetes mellitus cases shows weak positive correlation and is statistically significant (p=0.017).

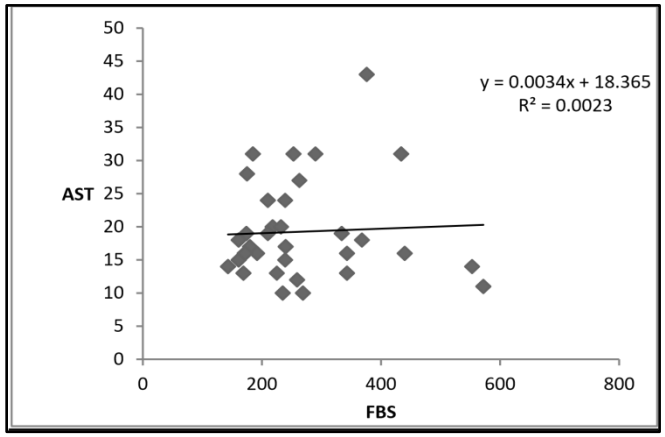


FIGURE IV: Correlation between gamma-glutamy l transferase (mg/dl) and fasting blood glucose (mg/dl) among type 2 diabetes mellitus cases shows a positive correlation and is statistically significant (p=0.00019).

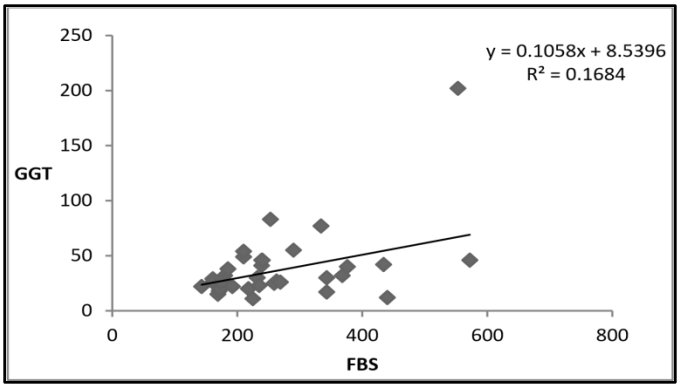
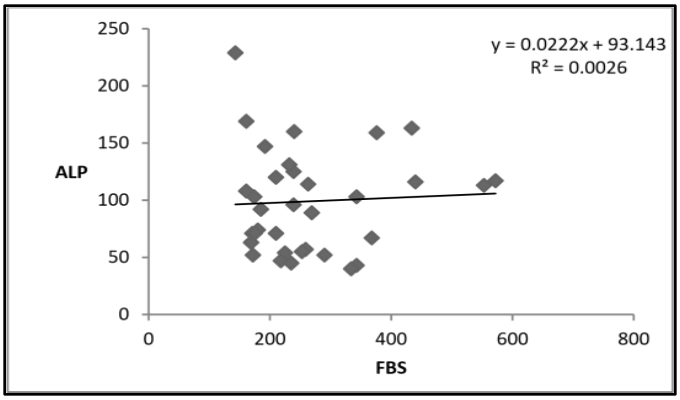


FIGURE V: Correlation between alkaline phosphatase (mg/dl) and fasting blood glucose (mg/dl) among type 2 diabetes mellitus cases shows no correlation and is not statistically significant. (p=0.96)



Discussion:

In the year 2019, 9.3% of the world's population suffered from diabetes mellitus and by 2045, it has been approximated to increment by 11%, that is, 700 million people would be enduring the disease. One of the primary organs which get affected in type 2 diabetes mellitus is the liver. Liver injury leads to leakage of liver marker enzymes from the hepatocytes into serum. We found significant correlation between fasting blood glucose, serum triglycerides, waist: hip ratio, BMI among diabetic cases and control groups. We also found statistically significant values among liver marker enzymes among type 2 diabetes mellitus cases and controls. This finding is in accordance with various studies like the one by VikasRaikwar et al, GulabKanwar et al, Raiza Philip et al, Choudhary et al etc. [10, 11, 12, 13]. In the present study, there is a positive correlation

between ALT and GGT, independently with fasting blood glucose in type 2 diabetes mellitus cases, and a weak positive correlation for AST, no correlation of ALPamong cases. Whereas there is no association of liver enzymes with other parameters like BMI, total cholesterol and serum triglyceride levels among cases. K Fatema et al found positive correlation of ALT, AST, GGT with fasting blood glucose [14]. Nakanishi et al conducted a study among Japanese men and concluded a significant link between GGT and FBS, although no significance was found between ALT, AST and ALP [15].Sunitha et al observed a statistically significant correlation between FBS and AST, ALT and ALP in type 2 diabetes mellitus cases [16]. The most possible explanation for elevation of liver enzymes in our study is because of excess fat deposition leading to NAFLD. This hepatic expression is a part of metabolic syndrome which includes obesity, diabetes mellitus, hypertension, insulin resistance. As a consequence of hepatic steatosis, liver cells get injured and all the liver marker enzymes leak out, into the plasma. These changes have been related to oxidative stress and chronic inflammation produced due to insulin resistance. Presently, liver function tests are not being ordinarily assessed in type 2 diabetes mellitus patients. These are easy and cost effective routine tests which do not even need prior fasting by patients. So, it will be a clinical delight to find out that these simple tests can be used as a biomarker for insulin resistance. Hence, it can be used for diagnosing patients who are at a high risk for developing type 2 diabetes mellitus, for management and for monitoring the complications of such patients. We propose for future studies in a larger population and additional investigations indicating hepatocyte injury and its stages in type 2 diabetes mellitus.

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