Evaluation of Hepatic Enzymes and its association with Glycemic Control among Non - Obese Type 2 Diabetes Mellitus Patients.

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Abstract

Background: Liver plays a key role in regulating the carbohydrate, lipid and protein metabolisms and in maintaining the blood glucose levels in the body. Oxidative stress plays an additional role in causing liver damage in diabetic patients, increasing damage to the hepatic cells further worsens the glycemic control causing hyperglycemia and complications of diabetes.

Aim: To Estimate the liver enzymes in patients with Type 2 Diabetes Mellitus and its correlation with glycemic control among non-obese Type 2 Diabetes mellitus patients.

Material and method: A Cross sectional analytical study conducted in a tertiary care hospital and Research center from January 2019 to July 2020 and 96 patients were included in the study. Patients were divided into 2 groups of 48 each, Group 1 consists of Type 2 Diabetes mellitus patients on oral hypoglycemic drugs and Type 2 Diabetes mellitus patients on insulin therapy in Group 2. Liver enzymes AST, ALT, GGT, ALP and HbA1C was estimated in both the groups. The data obtained was subjected to appropriate statistical analysis.

Results: The participants in both the groups had BMI of <30kg/m. The mean levels with Standard error (SE) of hepatic enzymes and HbA1C in Group I and Group II was AST (26.38±2.3and 27.75±1.7), ALT (25.54±3.1and 26.38±1.97), GGT (33.60±4.5 and 27.48±2.4), ALP (101.23±4.7and 107.08±4.0) and HbA1C(9.96±0.29 and 9.26±0.24)respectively.

Conclusion: Liver enzymes could be within normal limits in non-obese Type 2 Diabetes Mellitus patients on regular physical activity and treatment, USG abdomen along with Liver enzymes estimation to be considered during follow-up of non-obese Type 2 Diabetes Mellitus patients with normal serum triglyceride (TG) levels.

Key words: Liver enzymes, Type 2 Diabetes mellitus, HbA1C

Introduction

Diabetes mellitus is a metabolic disorder involving predominantly carbohydrate, protein and lipid metabolism. Liver plays a key role in regulating the above metabolisms and in maintaining the blood glucose levels in the body[1]. Previous studies have shown the elevation of liver enzymes to predict the development of type 2 diabetes mellitus (T2DM) in these patients in future[2,3]. Insulin resistance is an important cause for developing Diabetes mellitus, studies have shown a significant association between insulin resistance and development of liver disease in diabetic patients. Further hyper glycaemia seen in diabetic patients causes glycation of proteins, a forerunner for developing complications in diabetic patients, glycation facilitates the expression of various cytokines and induce oxidative stress which results in organ damage seen as minor and major complications of diabetes mellitus[4,5]. Oxidative stress plays an additional role in causing liver damage in diabetic patients, increasing damage to the hepatic cells further worsens the glycemic control causing hyperglycemia and complications of diabetes, it is thus important to identify the liver damage by monitoring the hepatic enzyme levels in patients with type 2 diabetes mellitus.

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There are studies that have evaluated the hepatic enzyme levels in Type 2 diabetes mellitus patients on diabetic treatment but very few studies that have correlated the abnormal liver enzymes with glycemic control. Hence the aim of our study was to measure the hepatic enzyme levels Alanine aminotransferases (ALT), Aspartate aminotransferases (AST), Alkaline phosphatase (ALP), Gamma-Glutamyl Transferase (GGT), among non-obese Type 2 diabetes mellitus patients and compare their levels with the normal biological reference ranges of the lab and correlate the levels of these enzymes with glycosylated hemoglobin (HbA1c) an indicator of glycemic control. Correlation of hepatic enzyme levels with glycemic control can also help in considering alteration in the drug treatment and make suitable modifications in management of Type 2 Diabetes mellitus patients. If a correlation between glycemic control and hepatic enzymes levels which determine the liver function is established, estimation of hepatic enzymes may be considered an imperative investigation in the management of Type 2 Diabetes Mellitus patients.

Material and Method: This cross-sectional analytical study conducted in a tertiary care hospital and Research center attached to a Medical College from January 2019 to July 2020.

Sample size: Sample size was estimated based on a study by Tewodros Shibabaw et al considering mean difference AST IU/L, to detect an effect size of 60% increase in AST among Type 2 Diabetes Mellitus patients with 90% power, 1% α-error, n-Master 2.0 was used to calculate the sample size. Total sample size estimated was 96, 48 subjects per group, The study was approved by the Institutional ethical committee, informed consent was obtained from the patients recruited for the study.

Inclusion criteria: Patients aged 40-60 years diagnosed with T2DM and with a Body Mass Index (BMI) <30 Kg/m ^{2} and on treatment for T2DM.

Exclusion Criteria: Known cases of hepatic disease, Thyroid disorders, Malignancy, Pregnancy, history of gall bladder Surgery, Immune disorders, Chronic alcohol consumption.

Detailed clinical history and physical examination of the enrolled patients was documented, including measurements of BMI. Then 0f 5mL Blood sample was collected from these patients and the following parameters were analyzed; Fasting blood glucose, liver enzymes Alanine Amino Transferase (ALT), Aspartate Amino transferase (AST), Alkaline phosphatase (ALP), Gamma-Glutamyl Transferase (GGT) and glycosylated hemoglobin (HbA1c).

The study subjects were divided into two groups according to the treatment they are taking.

Group 1: Type 2 Diabetes Mellitus Patients on oral hypoglycemic drugs (n=48).

Group 2: 48 Type 2 Diabetes Mellitus Patients on insulin Therapy n=48).

HbA1c measured by High Performance Liquid Chromatography in the Bio Rad D10 analyzer from Bio Rad. Plasma fasting glucose, ALT (Alanine Transaminases), AST (Aspartate Transaminases), Alkaline phosphatase(ALP), Gamma glutamyl transferase(GGT) were analyzed by Vitros Dry chemistry analyzer from Ortho Clinical Diagnostics. Internal quality control was run and verified for these parameters before sample analysis.

Statistical Analysis: Collected data was analyzed using SPSS 22 version. Quantitative measure expressed by Mean, Standard error of mean, Comparison of the data to test the significance was done using Student t test. Pearson's correlation, p values < 0.05 is considered as statistically significant.

Results

A total of 96 patients were included in the study, 48 subjects were included in the Group I and the subjects in the age group of 55-65years of age were 24, 22 patients were between 45 to 54 years and 2 patients were above 65 years. 48 subjects were included in the Group II and the subjects in the age group of 55-65years of age were 23, 22 patients were between 45 to 54 years and 3 patients were above 65 years. Of the 96 patients with T2DM 59 were male patients and 37 were female patients. (Table 1) shows the Socio - demographic data of the study participants, all the participants belonged to the rural background with middle to lower socioeconomic status.

Table 1: Demographic data of the study subjects

Characteristics		Subjects (N=96)
Age In Years (Mean)		54.65
Height In Meters (Mean)		1.69
BMI<30 kg/m^2 (Mean)		26.7
FBS (Mean)	Group 1	212.12
	Group 2	183.41
Occupation	Merchants	56(58.3%)
	Farmers	24(25.0%)
	Others	16(16.6%)
Education	Literates	61(63.5%)
	Illiterates	35(36.4%)

Table 2: Biochemical parameters between Group I and Group II T2DM patients.

Parameters	Group	n	Mean	Std. Error Mean	P Value
AST	1	48	26.38	2.3	0.629
	2	48	27.75	1.7	
ALT	1	48	25.54	3.1	0.822
	2	48	26.38	1.97	
GGT	1	48	33.60	4.5	0.231
	2	48	27.48	2.4	
ALP	1	48	101.23	4.7	0.346
	2	48	107.08	4.0	
AST/ALT	1	48	1.17	0.06	0.385
	2	48	1.27	0.10	
HbA1C	1	48	9.96	0.29	0.064
	2	48	9.26	0.24	
TC	1	48	151.98	6.59	0.010*
	2	48	172.83	4.34	
TG	1	48	155.52	11.73	0.343
	2	48	141.69	8.51	
HDL	1	48	35.88	2.35	0.059
	2	48	42.46	2.52	
LDL	1	48	84.06	4.80	0.02
	2	48	100.13	4.44	

*p value < 0.05 was considered statistically significant.

Table 2 shows the mean levels, standard error of mean and comparison of mean levels of biochemical parameters between Group I and Group II T2DM patients. The mean levels of hepatic enzymes in Group I and Group II T2DM patients were within the normal biological reference range, and also there were no statistically significant alteration in liver enzymes in Group I T2DM patients on Oral Hypoglycemic drugs Compared with Group II T2DM patients on Insulin treatment. However, the FBS and HbA1c levels in both the group patients were elevated. There was no significant difference between the groups with regards to Triglycerides, HDL and LDL levels. However, we found statistically significant higher total cholesterol in Group II subjects compared to Group I.

The participants in both the groups had a BMI of<30kg/m^2. The concentrations of AST, ALT, ALP and GGT were within the normal range when compared these values with Glycated hemoglobin (HbA1C) levels in both the groups. There was no significant correlation between the HbA1c levels with the Liver enzymes in the study subjects.

Discussion:

This cross-sectional study focused on evaluating the levels of Hepatic enzymes and their association with glycemic control among non-obese Type 2 Diabetes Mellitus patients on regular treatment. The study found that none of the Liver enzymes i.e. ALT, AST, GGT and ALP were significantly altered beyond the biological reference interval in these patients, unlike the findings made in a few studies which showed high ALT and AST levels with normal GGT levels among Type 2 Diabetes mellitus patients as compared to control group, and was attributed to impaired hepatic insulin communication transduction, causing fat accumulation in the hepatic cells consequently resulting in hepatic cell injury releasing enzymes from the injured hepatocyte[1]. One study done on Nepalese population with T2DM showed significantly higher ALT levels compared to normal levels of AST, GGT and Alkaline phosphatase enzymes, suggesting that ALT can be independently associated with non-alcoholic fatty liver disease in T2DM patients. However, in the present study the levels of Alanine transaminases were not increased. Previous studies on lipid levels and its ratios in Type 2 Diabetes Mellitus patients with acute myocardial infarction have observed that there was a higher dyslipidemia in females as compared to male subjects[6], and interestingly we also found the serum Triglyceride (TG) levels were within the normal limits, with an increase in the Total cholesterol (TC)levels. A study by Kayo Kaneko et.al have stated that the elevation of Liver enzymes due to the intra hepatic fat leads to systemic infiltration and insulin resistance, also the insulin resistance may lead to intrahepatic fat deposition and increase of liver enzymes that could cause the development of T2DM eventually[7]. A study by Ballestri S et.al observed a significant association of increased ALT and GGT towards increased Type 2 Diabetes Mellitus risk irrespective of alcohol intake and obesity in these patients, but this association was justified only in patients with higher TG levels[8]. In this study we found that patients had normal levels of TG, ALT and GGT. The association of AST levels with T2DM is not very clear, as studies show controversial findings with respect to the role of elevated AST and risk of Type II DM and its cardiovascular complications[9,10]. A study by Vazarova B et.al and Monami M et.al found no association of AST with Type 2 Diabetes Mellitus[11,12]. However, one study done in Japanese population found a strong association of AST among male population compared to female population with Type 2 diabetes mellitus[13]. In the present study the levels of AST were not elevated among the Type 2 diabetes mellitus patients.

A study by Ghimere et.al showed the levels of transaminases to be increased in females than male diabetic patients[10]. Previous studies claim that the elevated levels of transaminases in diabetic

population is especially true with Non-Alcoholic Fatty Liver Disease (NAFLD) than non NAFLD, and the presence of higher Triglyceride levels, low HDLc levels and elevated transaminases levels are associated strongly with Non Alcoholic Steatohepatitis (NASH) which can lead to cirrhosis and hepatocellular carcinoma[14]. Interestingly we did not observe any of these findings in our study. This may be because of the fact that these patients are on regular diabetic treatment and follow-up, with regular physical activity and a controlled Lipid level, this might have reduced the incidence of gross hepatic cell injury and leak of hepatic enzymes in circulation. However, the incidence of NAFLD in these patients cannot be completely ruled out, because the mechanism for the development of fatty liver in diabetic patients is due to increased Lipolysis due to insulin resistance, resulting in the deposition of non-esterified fatty acids, elevated fat accumulation in hepatocytes directly injures the hepatocytes resulting in elevated transaminases[15,16]. The Type 2 Diabetes Mellitus patients in both the group 1 and group 2 subjects in our study showed an increased Mean fasting blood glucose and Mean HbA1c levels as compared to the biological reference range of the laboratory, which is of course an expected finding in patients with T2DM. Further there was no significant correlation between FBS and HbA1c levels with the liver enzymes in the study subjects.

Conclusion:

Liver enzymes could be within the normal limits in non-obese Type 2 diabetes mellitus patients on regular physical activity, regular treatment and follow-up. The possibility of NAFLD cannot be completely ruled out by evaluating only the hepatic enzymes. Regular ultrasound examination of abdomen along with Liver enzymes estimation to be considered during the follow-up of Type 2 diabetes mellitus patients especially those who are non-obese with normal TG levels.

Limitation: We did not include the USG abdomen findings in these patients, or the gold standard Liver biopsy to completely rule out Liver pathology in these patients and its role in glycemic control in diabetic patients on regular treatment.

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Conflict of Interest: None to Declare

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