ISSN: 0975-833X

Available online at http://www.journalcra.com

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

International Journal of Current Research
Vol. 13, Issue, 09, pp.18747-18751, September, 2021

DOI: https://doi.org/10.24941/ijcr.41789.09.2021

RESEARCH ARTICLE

ASSOCIATION OF THE HEPATIC AMINO TRANSFERASES LEVEL IN TYPE 2 DIABETES MELLITUS

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ARTICLE INFO

Article History:
Received 25th June, 2021
Received in revised form
20th July, 2021
Accepted 19th August, 2021
Published online 30th September, 2021

Key Words:

Diabetes Mellitus, Liver Function, FBG, Alanineaminotransferase (ALT), Aspartate Aminotransferase (AST).

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ABSTRACT

Background: Diabetes mellitus (DM) is a syndrome of disordered metabolism with abnormally high blood glucose levels (hyperglycemia). In Type-2 DM (T2DM), the loss of direct effect of insulin to suppress hepatic glucose production and glycogenolysis in the liver causes an increase in hepatic glucose production. Hence, this study was intended to study the activity of serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) in T2DM patients and compare it with that of normal healthy controls. **Methods:** A total of 100 patients of both sexes suffering from T2DM and 50 age and sex matched healthy individuals were selected for the study. From the subjects Fasting blood samples were drawn. Biochemical parameters like fasting blood glucose, liver enzymes (ALT and AST) and HbA1c were estimated in the samples. **Results:** The mean activity of serum ALT was significantly higher in diabetic patients as compared to controls while AST showed non-significant difference between patient and controls. Along with this, significantly increasing pattern of serum ALT level was found as duration of disease increased. While serum AST level was non-significant as duration of disease increased. **Conclusion:** The outcomes of the present study suggest that among the liver aminotransferases enzymes (ALT) have shown higher activity with T2DM patients than individuals who do not have DM. Hence routine monitoring of LFT along with other routine investigations in patients with type 2 diabetes is recommended.

Citation: Dr. Ashish Khandelwal, Dr. Meena, R.L., Dr. Neera Samar and Dr. Yogesh Mishra. "Association of the hepatic amino transferases level in type 2 diabetes mellitus*", 2021. International Journal of Current Research, 13, (09), 18747-18751.*

INTRODUCTION

Diabetes mellitus (DM) is a common metabolic disorders, main whole mark of the disease is high blood glucose (hyperglycemia). The prevalence of DM is increasing globally, prevalence of type 2 DM rising more rapidly than type I DM. Type 2 DM is the most common form of diabetes, accounting approximate 90% of total DM cases. Main factors associated with increased risk of having T2DM are reduced activity levels, obesity and the aging of the population. In future, DM is anticipated to be a chief cause of morbidity due to its increasing incidence. Uncontrolled or poorly controlled diabetes for a longer time leads to various acute and chronic complication such as nephropathy, neuropathy, retinopathy and arteriosclerosis. Liver enzymes are also affected by complications of diabetes mellitus. Liver is considered as an important organ which plays a central role in metabolism and carbohydrate homeostasis.

Hepatocellular glycogen accumulation leads to hepatomegaly and liver enzyme abnormalities in poorly controlled diabetic patients. Due to disturbed metabolism, increased glycogen synthesis occur in liver. This lead to accumulation of glycogen in liver hepatocytes and causing elevated aminotransferases level. But it has been found that with good glycaemic control all the disturbances associated with hepatomegaly can be reversed (Vishaldeep *et al*., 2017). Due to accumulation of glycogen there is abnormality in liver functions are observed morecommonly in diabetes mellitus than in non-diabetic population and type 1diabetes patients. Elevated levels of the serum amino transaminases; alanine transaminase (ALT) and aspartate transaminase (AST) maybe associated with liver disease. Various studies have shown status of these serum amino transferases in diabetic patients. Elevated levels of any of serum amino transferases enzymes has been found in 7.9% of the general population, whereas elevated levels of ALT has been observed with high prevalence up to 20% in diabetics.

Among the amino transferases, ALT seems to be more associated with liver fat accumulation than AST, as ALT enzyme is involved in gluconeogenesis process. Some authors have also found elevation in serum ALT level in diabetes thus suggested that minor elevation of this enzyme's level may be a good predictor of mortality from liver disease. (Wild *et al.*, 2004). The liver function changes in type 2 diabetic individuals are areas of active research. This study is aimed at studying the association of liver function in type 2 diabetic individuals attending outpatient department, RNT medical college & Hospital, Rajasthan, India.

MATERIALS AND METHODS

This is a prospective case control study. This study was conducted after approval from institutional ethical committee R.N.T .Medical College and M.B.G.H. Udaipur

Study Period: This study was conducted from the period June 2019 to November 2019.

Study Population: Total 100 diagnosed T2DM patients along with 50 age and sex matched individual included in the study. T2DM patients inclusion was done according to ADA guidelines.Written and informed consent from the patient's and as well as from healthy controls were collected during the time of sample collection.

Criteria for the Diagnosis of Diabetes Mellitus (ADA Guidelines)

- Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL) or
- Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) or • Hemoglobin Hb1c ≥ 6.5% or
- 2-h plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test

Inclusion Criteria

Patients: A total of 100 patients

- Patients with the confirmed DM by WHO criteria
- Age > 18 years
- Who gave their consent
- Both males and female's were included in the study.

Exclusion Criteria

- Diabetic patient with history of alcohol intake, hepatotoxic drugs.
- Patients who are known to be seropositive for HBsAg or HCV antibodies, and those who had a clinical or biochemical evidence of autoimmune hepatitis, primary liver cirrhosis, hemochromatosis or Wilson disease.
- Pregnant females with GDM
- Who did not give consent

Control: A total of 50 controls

Age and sex matched non diabetic, non-alcoholic and non-obese healthy individuals were enrolled in the study

Study Methods: Questionnaires were used to collect demographic information such as age, sex, residential district (urban, rural), and medical history. Blood samples was obtained from an antecubital vein in the morning after a 8-h overnight fast. Serum was separated within 30 min and will be stored at − 70°C until analysis. Fasting glucose, PP, AST, ALT levels were measured by an automatic analyzer as prescribed by manufactures protocol. The HbA1c levels were analyzed by high-performance liquid chromatography (HPLC) using the VARIANT II system (Bio-Rad, Hercules, CA, USA).

Data analysis: Data were analyzed used SPSS computer program (version, 20), independent T test and correlation test were used to obtain mean value± SD and p value at (0.05) is considered significant, and strength of the correlations.

OBSERVATION AND RESULTS

Table 1 is showing variables included in this study. Total of 100 patients diagnosed with type 2 diabetes mellitus were taken into the study. Out of 100 patients, 50 were females and 50 were males. 50 apparently healthy, non-diabetic individuals were recruited as controls for this study. Among the variables FBG and BMI showed significant difference among patients and controls. Later patients were distributed according to disease duration (Table 2). Maximum no of patients were present in (0-5) and (6-10) year duration. Minimum number of patient were present in 11-20 year disease duration

Table 1. Study variables in comparison between Diabetics and Control groups

	Diabetics (n=100)	Control (n=50)
Age (Mean ±SD)	64.29 ± 14.58	59.59 ±12.09
Sex Ratio (Male/Female)	50/50	25/25
BMI (kg/m2) (Mean ±SD)	27.76±1.026	23.24±2.6979

Table 2. Distribution of study group according to age

Age group of patients (years)	No of patients	Percentage
30-40	15	15%
41-50	41	41%
51-80	44	44%
Total	100	100

Table 3. Comparison between of liver enzyme ALT (SGPT) and AST (SGOT) in patients and control:

Parameter	Patients (n=100)	Controls (n=50)	*p* value
FBG (mg/dL) (Mean ±SD)	186.00±7.03	95.00±1.01	$p<0.001$ (significant)
SGPT (IU/dL) (Mean ±SD)	36.00±4.026	27.00±0.6979	$p<0.001$ (significant)
SGOT (IU/dL) (Mean ±SD)	30.00±1.80	27.00±0.90	$p=0.1513$ (ns)

The table 3.showing levels of amino transferases (ALT & AST) in patients 'and controls. A significant difference was observed in serum ALT levels in patients as compared to controls ($p<0.001$). While a non-significant difference was observed in serum AST levels in patients as compared to controls ($p<0.151$). Values of ALT and AST for patients and controls has been shown in Table 3. Further, upon analysis among patients according to their gender, we found non-significant (p=0.40) difference in serum ALT levels as well as for AST level (0.50) in male in comparison to females.

Table 4. Comparison between of liver enzyme ALT (SGPT) & AST (SGOT) in patients with disease duration

Duration of Disease (years)	SGPT (IU/dL) (Mean ±SD)	*p* value	SGOT (IU/dL) (Mean ±SD)	*p* value
Group I : 0-5 years (n=43)	36.00±2.17	0.02 (Group I/II)	34.00±2.52	0.35 (Group I/II)
Group II : 6-10 years (n=41)	49.00±1.94		38.00±3.58	
Group III : 11-20 years (n=41)	55.00±3.17	0.01 (Group II/III)	30.00±2.59	0.11 (Group II/III)

Later we analyzed effect of disease duration on serum ALT and AST level in patients. For this patients were categorized in three groups Group I (0-5 years), Group II (6-10 years) and Group III (11-20 years).Mean values along with Standard deviation (SD) for all the groups has been shown in Table 4 . Upon analysis, we found significant difference in serum ALT level among group I/ Group II (p=0.02) and Group II/ Group III (p=0.01). In total, we found increasing pattern of serum ALT level as duration of disease increased. In case of AST non-significant difference was observed in serum AST level among group I/ Group II (p=0.35) and Group II/ Group III (p=0.11). In total, there was no definite pattern of AST observed with disease duration.

DISCUSSION

DM is a syndrome of disordered metabolism with abnormally high blood glucose levels (hyperglycemia). Various type of complications; acute and chronic; are frequently present in diabetic patients due to impaired insulin function. Besides the acute and chronic complications, immune system of patients is also get weakened which also increases the susceptibility of a diabetic patient to different infections. Harris *et al* (2005) observed higher incidence of abnormal liver function test individuals with T2DM than individuals who do not suffer from DM. Aminotransferase such as ALT and AST activities has been suggested as a sensitive indicators of liver cell injury and considered as useful in recognizing hepatocellular diseases. Former studies have showed elevated circulating levels of liver enzymesalanine aminotransferase (ALT), gamma - glutamyl transferase (GGT) , and aspartate aminotransferase (AST) in individuals with insulin resistance and the metabolic syndrome (Wannamethee *et al*., 2005). Type 2 diabetic individuals are at higher risks of abnormal liver function than non- diabetic individuals. Subtle chronic elevations of transaminases often reflect underlying insulin resistance.

Assessment of ALT Activity: In the present study, mean level of serum ALT was 36.00±4.026 IU/L in Type-2 diabetic patients group and 27.00±0.6979 IU/L in healthy controls. The ALT levels in fasting serum sample in diabetic patients group was found to be significantly higher in comparison to the healthy control group. These findings are consistent with the results obtained from several other studies by various researchers. In patients with type 2 diabetes mellitus, elevated serum ALT enzyme activity is observed more frequently than in the general population (Meltzer AA and Everhart JE ,199754,55) Some but not all studies (Nannipieri M, *et al* .,2005; Schindhelm RK *et al*., 2005; Andre P *et al*, 2005) have demonstrated independent and significant associations of ALT with incident type 2 diabetes mellitus. We also found significant increase of ALT enzyme activity when compared to control, but non-significant difference was observed when ALT levels were compared among gender. This results agreed with Hind M. Elmahi, and AbdElkarim A. Abdrabo, (2014) who observed that the mean value of ALT and ALP of the patients with type 2 diabetes mellitus on treatment and newly diagnosed are significantly elevated compared to control subjects. In a multivariate model Ohlson *et al.* , (1988) found ALT as a predictor of type 2 diabetes mellitus incident in 451 Pima Indians within 6.9 years of duration. In their study, they also adjusted the data according to the other variables such as fasting blood glucose levels, bilirubin, body mass index, systolic blood pressure, and a family history of diabetes. In another study Vozarova *et al.,* (2002) and colleagues also found utility of higher ALT (upper compared to lower decile) as a significant and independent predictor of type 2 diabetes mellitus incident. They also adjusted the data along with other variables taken in this study such as age, sex, body fat, insulin sensitivity and acute insulin response and after adjustment found two fold increased risk in the patients. Gonem *et al.,* (2007)., also observed higher serum ALT enzyme activity in diabetic patients (n = 959) compared to healthy controls 15.7% (151). In a larger study, 18,825 Samples from United States with of African Americans and Mexican Americans were analyzed for serum ALT level by Erbey *et al*., (2000). They found increased level of serum ALT in diabetic patients (7.8%), compared to a 3.8% prevalence in those without diabetes. Among the variables taken in the study, they found significant association between weight (BMI 25-30 kg/m) and obeseity (BMI > 30 kg/m) with elevated serum ALT levels. Overweight and obese patients were more likely to have elevated ALT. According to the results of the present study.

Later, we also evaluated serum ALT level according to duration of disease and we found significant association of increased serum ALT levels with duration of disease. Our study results are in concordance with Hind M.Elmahi and Abdrbo, (2014), according to their study ALT was found to be significantly positively correlated with duration of diabetes, *p*value (0.000), while they found insignificant Correlation between duration of the disease and ALP enzyme. Similar results were observed by Odewabi *et al* ., (2013) who reported elevated levels of ALT and ALP in T2DM patients in both categories (type 2 DM on treatment and the newly diagnosed) but they suggested to usefulness of ALT as a useful biomarker for monitoring hepatic complication in T2DM without underlying hepatitis. ALT plays an important role in amino acid metabolism and in gluconeogenesis. Being a transaminases it catalyzes the reversible interconversion of, a pair of amino acid an keto acid, L-alanine and alpha-ketoglutarate to form pyruvate and L-glutamate. Alanine is the most effective precursor for gluconeogenesis. Rate of gluconeogenesis is increased in T2DM subjects which leads an increased conversion of alanine to glucose. In diabetes , expression of ALT thus might be be up-regulated as a compensatory response to support increase gluconeogenesis or, alternatively there may be may leakage of ALT out of the hepatocytes cells due to their damage by fatty infiltration (Schindhelm RK *et al*., 2006).

Assessment of AST Activity: The mean of serum AST in T2DM group was 30.00±1.80 IU/L in normal control group 27.00±0.90. The AST in fasting serum sample in diabetic patients was found to be non-significant in comparison with

the normal control group with P value 0.15. Upon correlating serum AST level with disease duration, a non-significant difference was observed. Our results agreed with Hind M .Elmahi and abdrbo, (2014), who found the means of ALT, AST, ALP, were within normal range in diabetic patients differ with Han NI *et al.* (2012) who found that ALT and AST increased among diabetic patients with higher BMI. IN a study done in japanes office workers, Nakanishi *et al*., (2003) also found no association of serum AST levels in diabetes patients after adjustment for different variables (age, family history of diabetes, alcohol intake, , BMI , physical activity, cigarette smoking, systolic blood pressure, fasting glucose, lipid profile and white blood cell count .

In contrast, in the prospective The Insulin Resistance Atherosclerosis Study, Hanley *et al*., (2004) reported that AST independently predicted type 2 diabetes after adjustment for covariates, including metabolic syndrome variables, acute insulin response, directly measured insulin sensitivity and CRP. Although AST is found in liver along with ALT and is also a marker of hepatocellular health. But it is considered a less specific marker of liver function than ALT and GGT (Lee *et al*., 2003). Therefore, it was suggested that AST may be a less specific marker of liver pathology related to development of type 2 diabetes. The outcomes from this study suggested that the among the amino transferases enzymes (ALT and AST), ALT have shown higher activity with T2DM patients than individuals who do not have DM. Along with this we also found significant association between serum ALT level with duration of disease. One of the possible reason behind the elevation of liver enzymes could be due to accumulation of fatty acid in the liver. When fatty acid accumulate in the liver, it leads damage of hepatocytes cell and leads to leakage of liver enzymes in to the circulation. Some other mechanism also have been suggested includes cell membrane disruption at high concentration, toxin formation, mitochondrial dysfunction, and impairment in the regulation of metabolism. Other possible clarifications for elevated transaminases in insulin-resistant states include peroxisomal beta-oxidation, oxidative stress from reactive lipid peroxidation, and recruited inflammatory cells. The insulin resistant state is also characterized by an increase in proinflammatory cytokines such as tumor necrosis factor, which may also contribute to hepatocellular injury.

Conclusion

From the study, we found significant alteration in serum ALT level in diabetic patients as compared to controls. Further we also observed significant correlation of ALT level with duration of disease. Dyslipidaemia, Nonalcoholic fatty liver disease (NAFLD) and liver enzyme abnormalities is frequently encountered in type 2 diabeticpatients. Hence routine monitoring of LFT along with other routine investigations in patients with type 2 diabetes is recommended.

Funding: No funding has been used to carry out the work.

Conflict of interest: none declared

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