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RESEARCH ARTICLE
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LIVER ENZYMES IN TYPE-2 DIABETES MELLITUS PATIENTS

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Abstract:
Background: Diabetes is a strong-growing metabolic ailment across the globe. The occurrence of diabetes everywhere the world affects more than 8% of the global population. "Type 2 diabetes (T2D) is

a major public health concern distressing lots of people globally." "Nearly 70% of patients with type 2 diabetes mellitus (T2DM) have a fatty liver."
Aims and objectives: We aimed to detect the rise of liver enzymes and its association with Type-2 diabetes mellitus associated with liver dysfunction. The aim of the study was to measure the level of liver enzymes.
Material and methods: A case-control type of study was enrolled total of 60 age sex matched subjects, where subject were further categories into 30 type-II diabetic mellitus attending Endocrinology outpatient of Sri Venkateswara Institute of Medical Sciences, Tirupati and 30 healthy individuals of in and around of institution. A confirm diagnosis of type-II DM was based on standard ADA criteria. Statistical analysis was done by using SPPS version 16.
Results: A total of 60 subjects were assessed for liver profile and diabetic profiles. A data was presented in mean and SD form. The mean age of participants was 46.77 ± 7.74. Blood sugar levels (fasting & PP2) and liver enzymes were significantly increased, while mean levels of protein fractions were significantly decreases in cases as compared to controls ($p<0.005$)
Conclusion: Biomarkers will play a crucial role in early suspicion, diagnosis, monitoring, and recognition of complications, management, and disposition of patients. Each of these components in turn can have crucial implications on the healthcare system and the administrative machinery, directly impacting patient care.
Key words: Glucose, ALT, AST, GGT, Total protein, Albumin, Total bilirubin, Conjugated bilirubin.

Introduction:
Diabetes mellitus is a worldwide health problem, distressing more than 170 million individuals and all age groups worldwide. In more developed societies, occurrence of diabetes mellitus has reached about 6 % **(1)**. Diabetes is defined as a state of chronic hyperglycemia and is classified into type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). Type 1 diabetes is due to the total failure of pancreas to secrete insulin, due to the autoimmune destruction of insulin-secreting cells in the islets of Langerhans and is also known as Insulin Dependent Diabetes mellitus (IDDM) **(2)**. Type 2 DM or Non-Insulin Dependent Diabetes mellitus (NIDDM) is a heterogeneous, multifactorial, polygenic disease characterized by a defect in insulin secretion and is associated with insulin resistance and qualitative and quantitative insulin deficiency caused by alterations in several gene products. Type 2 DM or adult-onset diabetes has become an epidemic and is the most common type accounting for 80-90% of diabetic population. NIDDM is less severe than IDDM. The causative factors of NIDDM include genetic and environmental factors **(3)**. In this condition, β-cell function in pancreas declines gradually over a period of time before the onset of clinical hyperglycemia. Several mechanisms have been proposed, including increased non-esterified fatty acids, inflammatory cytokines, adipokines, and mitochondrial dysfunction for insulin resistance, and glucotoxicity, lipotoxicity and amyloid formation for β-cell dysfunction **(1).** In addition to the above-mentioned complications, type 2 DM was found to be associated with a large number of liver disorders such as fatty liver disease, elevated liver enzymes, cirrhosis, acute liver failure and even hepatocellular carcinoma **(4).**

Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), γ-glutamyl transferase (GGT) and Lactate dehydrogenase (LDH) are the predictors and the most widely used enzymes to assess hepatocellular function as well as injury. Liver enzymes were also found to be strong indicators of future diabetes and insulin resistance. Increased activities of liver enzymes including AST, ALT and GGT are the strong indicators of hepatocellular injury **(5).**

Liver acts as storage organ for glucose in the form of glycogen and also is the site for synthesizing glucose from non-carbohydrate sources. Hence, liver is vulnerable to diseases in subjects with metabolic disorders, particularly diabetes mellitus. Insulin resistance is assigned a central place in metabolic disturbances associated with obesity and type 2 diabetes mellitus **(6).** In insulin resistance state, adipose tissue is known to express and secrete a variety of metabolites, hormones and cytokines that have been implicated in development of atherosclerosis **(7).** Insulin resistance also leads to increased activities of enzymes such as Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), γ- glutamyl transferase (GGT) and Lactate dehydrogenase (LDH). Accumulation of intracellular glycogen due to increased glycogenesis in hyperglycaemic states in the hepatocytes was known to cause mild to moderately elevated aminotransferases **(8).**

Material and methods:

Thirty (30) patients attending Endocrinology outpatient Department of Sri Venkateswara Institute of Medical Sciences, Tirupati and diagnosed with type 2 diabetes mellitus based on ADA criteria **(9)** were included in the present study. 30 age and sex matched healthy individuals were included as controls. Informed consent was obtained from all the study participants and the study was approved by Institutional ethics committee.5 mL of venous blood was collected into plain tubes from all the subjects after an overnight fast for 8-12 hrs. The samples were allowed to stand for 30 minutes and then centrifuged for 10 minutes. Serum was separated and stored in vials at -80°C until further analysis. liver is vulnerable to diseases in subjects with metabolic disorders, particularly diabetes mellitus. Insulin resistance is assigned a central place in metabolic disturbances associated with obesity and type 2 diabetes mellitus **(6**). In insulin resistance state, adipose tissue is known to express and secrete a variety of metabolites, hormones and cytokines that have been implicated in development of atherosclerosis **(7).** Insulin resistance also leads to increased activities of enzymes such as Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), γ- glutamyl transferase (GGT) and Lactate dehydrogenase (LDH). Accumulation of intracellular glycogen due to increased glycogenesis in hyperglycemic states in the hepatocytes was known to cause mild to moderately elevated aminotransferases **(8).**

LIVER ENZYMES

Hepatocytes contain many enzymes that allow them to perform various metabolic functions. In conditions of hepatocellular injury, the liver enzymes are released into plasma and their activity can be measured and is used as indicator of liver damage. Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), γ-glutamyl transferase (GGT) and Lactate dehydrogenase (LDH) are the predictors and the most widely used enzymes to assess hepatocellular function as well as injury. Liver enzymes were also found to be strong indicators of future diabetes and insulin resistance. Increased activities of liver enzymes including AST, ALT and GGT are the strong indicators of hepatocellular injury **(5).**

Criteria for cases:

Inclusion criteria

1. Subjects between 30 and 60 years of age
2. Patients diagnosed with diabetes mellitus based on ADA criteria

Exclusion criteria: Acute or chronic liver disease, Cancer**,** Anemia**,** Clinical and sub clinical hypothyroidism**,** Patients on drugs such as tamoxifen, corticosteroids, amidarone**,** Acute or chronic infections**,** Pregnant women**,** History of alcoholism and smoking**,** Patients not willing to participate in the study were excluded from the study.

Criteria for controls:
Inclusion criteria:
1. Subjects between 30 and 60 years
2. Subjects with fasting plasma venous glucose in the range 70-110 mg/dL

Exclusion criteria: Acute or chronic liver disease, Diabetes, Cancer, Hypothyroidism, History of smoking and alcoholism, Subjects with acute or chronic infections, Subjects not willing to participate in the study were excluded from the study.

Statistical analysis: Data were expressed as mean ± SD. Difference in the biochemical parameters studied between diabetic patients and controls was assessed using Mann-Whitney 'U' test as appropriate. Statistical analysis was performed using Microsoft excel spread sheets and SPSS for windows version 11.5. A 'p-'value <0.05 was considered to be statistically significant.

Results & Observation:

Table 1: Methods and Instrumentation

Parameter	Method	Instrument
Glucose	Glucose Oxidase peroxidase method	Beckman Unicel DXC 600
Alanine aminotransferase	Enzymatic rate method	
Aspartate aminotransferase		
Gamma glutamyl transferase		
Total proteins	Biuret method	
Albumin	Bromocresol green method	
Total bilirubin	Diazo method	
Conjugated bilirubin		

Table: 2 Demographic Data of the Study Groups

Parameter	Controls (N=30)	Cases (N=30)	p-Value
Age	45.77 ± 7.89	46.77 ± 7.74	0.622
BMI	24.72±3.70	24.62±4.7	0.932
Male/Female	15 / 15	16 / 14	--
FBS (mg/dL)	82.27 ± 12.31	181.63 ± 59.05	0.000*
PPBS (mg/dL)	110.33 ± 7.85	296.67 ± 89.88	0.000*

*Data expressed as Mean ± SD, *Statistically significant, FBS-fasting blood sugar; PPBS-post prandial blood sugar*

Table no: **2** Shows the demographic characteristics and blood sugar values of patients and controls. Both fasting and 2 hour post prandial sugar values were significantly higher in Diabetic patients than in controls (p=0.000).

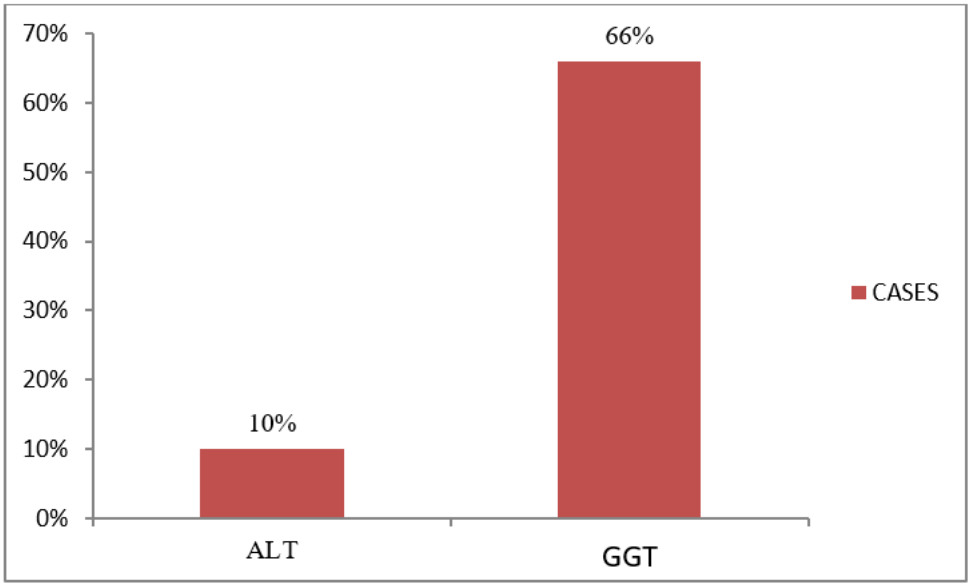
Table: 3 Liver Function Parameters Studied:

Parameter	Controls (N=30)	Cases (N=30)	p-Value
ALT (IU/L)	15.80 ± 6.47	21.20 ± 9.39	0.012*
AST (IU/L)	24.13 ± 5.56	23.63 ± 5.65	0.731
GGT (IU/L)	23.63 ± 8.70	46.27 ± 29.01	0.000*
Total Proteins (G/dL)	7.93 ± 0.62	7.42 ± 0.82	0.009*
Albumin (G/dL)	4.31 ± 0.24	4.40 ± 0.66	0.485
Total Bilirubin (mg/dL)	0.74 ± 0.25	0.64 ± 0.33	0.162
Conjugated Bilirubin (mg/dL)	0.13 ± 0.05	0.12 ± 0.04	0.250

*Data expressed as Mean ± SD, *Statistically significant, ALT-alanine aminotransferase; AST-aspartate aminotransferase; GGT- Gamma Glutamyl transferase*

Table no: 3 Shows the liver function parameters studied in patients with diabetes and controls. Among the liver enzymes, ALT and GGT were significantly higher in patients with diabetes when compared to controls (p=0.012 and 0.000, respectively); whereas AST showed no significant difference between patients and controls. Among the other parameters studied, serum total proteins levels were significantly lower in patients with diabetes when compared to controls (p=0.009). Serum albumin, total and conjugated bilirubin levels showed no significant difference between patients with diabetes and controls.

Figure: 1 Prevalence of Elevated Liver Enzymes in Diabetic Patient



ALT: >40 IU/ L, GGT: M>45 IU/L; F>32 IU/L

Figure: 1 shows the prevalence of elevated liver enzymes in diabetic patients. Higher levels of ALT and GGT above cut-off were observed in 10% and 66% of patients with diabetes respectively.

The following findings were observed:

1. Among the liver enzymes studied, ALT and GGT levels were found to be significantly elevated in patients with type 2 diabetes mellitus when compared to controls (p=0.012 and 0.000, respectively).
2. Among the other parameters studied, total protein levels were found to be significantly

Discussion:

Diabetes mellitus, one of the major non-communicable diseases is presently emerging as an important threat to human health. A rapid increase in the number of people diagnosed with diabetes is being observed, especially during the past two decades. In India, the number of individuals with diabetes is increasing rapidly and is expected to reach 57.2 million numbers by the year 2025 (**10)**. Two major forms of diabetes are distinguished, type 1 or Insulin dependent diabetes mellitus and type 2 or non-insulin dependent diabetes mellitus. Type 2 Diabetes, characterized by insulin resistance accounts for the largest number of cases diagnosed with Diabetes. Genetic and environmental factors are the main causes of type 2 Diabetes.

The diagnosis of diabetes is mainly based on plasma glucose levels. A fasting plasma glucose > 126 mg/dL and a two-hour post-glucose > 200 mg/dL during an oral glucose tolerance test form the criteria for the diagnosis of diabetes. Recently, an international expert committee has added HbA1C > 6.5% as another option for the diagnosis of diabetes **(4).** During its course, diabetes mellitus is associated with various acute and chronic complications and is a major cause of morbidity and mortality. It was reported that Diabetes is the third leading cause of death in many developed countries. The complications of diabetes mainly affect the eye, kidney and nervous system **(5).**

Liver is a major organ that plays an important role in a number of functions of the body including carbohydrate, lipid and protein metabolism, synthesis and secretion of bile, synthesis of plasma proteins including clotting factors, synthesis of lipoproteins, detoxification, decomposition of red blood cells **(10,11).** Thus, liver plays a central and crucial role in the maintenance of carbohydrate homeostasis. It helps to maintain glucose concentration in normal levels during fasting as well as post prandial states **(12).** The key role played by liver in metabolic processes also makes it vulnerable to diseases in individuals with metabolic disorders, especially, diabetes mellitus **(8).** Studies have shown that type 2 diabetes is associated with large number of liver disorders that range from elevation of liver enzymes, fatty liver disease, cirrhosis, hepatocellular carcinoma and acute liver failure **(13).** It was reported that in diabetes, the risk of chronic liver disease is doubled, independent of alcoholic liver disease or viral hepatitis **(14).** In this context, liver function tests that are commonly used to screen patients with liver disease have been evaluated in patients with diabetes in several studies.

In the present study, serum levels of ALT were found to be significantly increased in patients with type 2 Diabetes when compared to controls (p=0.012). Although significantly increased, the levels were found to be within normal range. Serum AST levels showed no significant difference between diabetic patients and controls (p=0.731). Idris AS et al., **(8**) studied liver function tests in type 2 diabetic patients in Sudan and observed significantly increased ALT and AST levels in patients compared to controls. Though significantly elevated, the levels were found to be within normal range in their study. Takhelmayum et al., (**11**) and Elmahi HM et al., **(5)** also reported significantly increased ALT and AST levels in diabetic patients when compared to controls.

The important role played by liver in glucose homeostasis also makes it vulnerable to injury in disorders involving glucose metabolism. Diabetic patients with poorly controlled glucose levels were found to develop hepatocellular glycogen accumulation that leads to hepatomegaly and abnormalities in the liver enzymes. During conditions of hyperglycemia, increased hepatocellular glycogen accumulation occurs as a result of increased glycogen synthesis further resulting in typical biochemical findings of elevated transaminases **(4).** Chronic mild elevation of transaminases was frequently reported in type 2 diabetic patients **(5).** Serum aminotransferases such as ALT and AST act as indicators of hepatocellular injury due to their leakage into the circulation. Type 2 DM is regarded as an Insulin resistant state. Abnormalities of triglyceride storage and lipolysis in tissues sensitive to insulin such as liver are considered as early manifestations of conditions characterized by insulin resistance (5). Further, the excess free fatty acids found in insulin resistant state are known to be directly toxic to the hepatocytes and might ultimately result in the leakage and elevated levels of transaminases. Other reasons for increase in transaminases in insulin resistant states include presence of oxidative stress from reactive lipid peroxidation, peroxisomal beta-oxidation and recruitment of inflammatory cells. Moreover, hepatocellular injury may also be a result of increase in pro-inflammatory cytokines such as tumor necrosis alpha (TNF-α) that are observed in insulin resistant states (5).

Although both ALT and AST serve as markers of hepatocellular injury, elevated ALT is found to be the most common abnormality in diabetes (4). Moreover, ALT is exclusively cytosolic in distribution and hence is a more specific marker of liver damage with exception in alcoholic hepatitis, cirrhosis and neoplasia of liver (11). In this context, West J et al., (13) reported that the prevalence of elevated ALT is three – four times higher in patients with type 1 or type 2 diabetes, than in the general population. Increased levels of ALT above cut-off were observed in 10% of diabetic patients in the present study.

Gamma-glutamyl transferase (GGT) is an enzyme involved in the catabolism of an important thiol antioxidant, glutathione. In the present study, serum levels of GGT were found to be significantly increased in patients with diabetes when compared to controls (p=0.000). Similarly, Iqbal AS et al., **(10)** also reported significantly increased GGT in patients with diabetes. GGT is a non-specific marker and is found to increase in patients with type 2 diabetes **(5)**. Paruk IM et al., **(15)** in their attempt to determine the prevalence of abnormal liver enzymes in type 2 diabetic patients observed GGT to be

the most frequently encountered liver function test abnormalities along with ALP. Elevated liver enzymes could be a result of excess fat deposition in the liver which is observed in insulin resistance

syndrome. Cellular GGT level was found to be closely related to in vivo indicators of oxidative stress and increased GGT could be a result of its response to oxidative stress that might be present in insulin resistant states leading to increased transport of glutathione into the cells **(11)**. This could be the reason for the increased GGT levels observed in the diabetic patients in the present study. However, the oxidant-antioxidant status was not evaluated in the present study. Increased GGT levels above cut-off were observed in 66% of patients with diabetes in the present study.

Among the other liver function parameters that were evaluated in the present study, serum total protein levels were found to be significantly decreased in patients with diabetes, when compared to controls (p=0.009). However, serum albumin levels showed no significant difference between diabetic patients and controls (p=0.485). Idris AS et al., **(8)** observed significantly decreased total protein as well as albumin levels in diabetic patients compared to controls. On contrary, Elmahi HM et al., (**5**) reported significantly increased total protein and albumin levels in type 2 diabetic patients. Serum bilirubin measurement is an indicator of biliary function and cholestasis and is a common component of liver function tests. Serum levels of total bilirubin in the present study showed no significant difference between diabetic patients and controls (p=0.162). However, earlier studies **(5,11)** have reported increased total bilirubin levels in diabetic patients. However, in one of the studies, total bilirubin levels were found to be within normal range. Serum conjugated bilirubin showed no significant difference between diabetic patients and controls in the present study (p=0.250). This is similar to an earlier study (5).

The findings of the present study show that patients with type 2 diabetes which is an insulin resistant state have elevated liver enzymes, ALT and GGT. These findings further support earlier reports that patients with diabetes have a higher incidence of abnormal liver function tests than individuals who do not have diabetes. Abnormalities in aminotransferase levels were reported to be the most common liver function test abnormality. A study by Salmela et al., **(14**) reported that patients with type 2 diabetes more frequently had elevated ALT and GGT levels than those with type 1 diabetes. The excess deposition of free fatty acids in hepatocytes, presence of oxidative stress and increase in pro-inflammatory cytokines such as TNF-α that are observed in insulin resistant states form the possible explanations for the elevated liver enzymes. Although a wide spectrum of liver diseases was observed in patients with diabetes, the most common cause of elevated LFTs in type 2 diabetic patients was reported to be non-alcoholic fatty liver disease (NAFLD) and mild to moderate elevation of aminotransferases is the most common laboratory abnormality in patients with NAFLD. However, elevated transaminase activity does not predict the histological severity of the liver disease (**12**). Nonetheless, the abnormal liver function tests may indicate altered hepatocyte function and integrity and indicates further evaluation of these patients.

Conclusion:

Lower in patients with type 2 diabetes mellitus when compared to controls (p=0.009).

The findings of the present study show the presence elevated liver enzymes in patients with type 2 diabetes mellitus. Increased hepatocellular glycogen accumulation that occurs in conditions of hyperglycaemia may lead elevation in aminotransferase levels. Moreover, the excess free fatty acids found in insulin resistant states were found to be directly toxic to the hepatocytes and might result in the leakage and elevation of aminotransferases, thus ultimately leading to abnormalities of liver function parameters in patients with type 2 diabetes mellitus.

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