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A STUDY OF ABNORMAL LIVER ENZYMES AND METABOLIC SYNDROME IN TYPE 2 DIABETES MELLITUS

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Abstract

Background: In type 2 diabetes mellitus (T2DM), insulin resistance is responsible for hyperinsulinemia and excess fatty acids found in insulin resistance state are known to be directly toxic to hepatocytes. There occurs increase in pro-inflammatory cytokines like tumour necrosis –α thereby contributing to hepatocellular injury and results in increased liver enzymes. Metabolic syndrome is a group of risk factors that can increase the risk of T2DM. It includes central obesity, glucose intolerance, insulin resistance, hypertension, and dyslipidemia. Early diagnosis and treatment of these disorders can help improve glycemic and lipid regulation, liver steatosis. There has been very few studies to explore association of liver enzymes and metabolic syndrome in diabetes patients. Hence this study was conducted to assess the liver enzymes and its association with diabetes mellitus and to assess the relationship of liver enzymes with metabolic syndrome in patients with diabetes mellitus. **Materials and Methods:** This is a cross sectional study conducted in Regional Institute of Medical Sciences (RIMS), Imphal from May 2022 to July 2024. All diabetic patients admitted in the Medicine ward or attending Medicine OPD or Endocrinology OPD during the study period were enrolled. A predesigned proforma, consisting of socio-demographic characteristics, body mass index (BMI), waist circumference, lipid profile, etc were recorded. Routine blood investigations including liver function test, glycosylated hemoglobin (HbA1C), fasting blood glucose (FBG), post prandial blood glucose(PPG) and lipid profile were done. SPSS (IBM) version 21 was used for statistical analysis and a p-value less than 0.05 was considered statistically significant. **Result:** A total of 139 diabetic patients were enrolled in the present study. The mean age of the patients was 61.04 ± 14.34 years with majority (31.7%), in the age group 61 to 70 years. Most of the subjects were males 63% (87).The mean BMI was 28.14 ± 4.06 kg/m2 and the mean WC was 96.45 ± 12.14 cm. Thirty-eight percent of the patients were obese, followed by overweight (33.1%) and normal BMI (28.1%).The mean value of ALT, AST, ALP and GGT were 39.46 ± 28.73 U/L, 37.62 ± 25.12U/L, 150.35 ± 79.15U/Land 34.06 ± 25.91U/L respectively. Serum AST, ALT, ALP and GGT were high in 39.6%, 31.7%, 61.2% and 17.3% of the patients respectively. The mean value of FBG was 163.96 ± 52.56 mg/dl and HbA1c was 7.16 ± 2.29%.Metabolic syndrome was present in 53% (73) of the patients. There was a significant association between gender and metabolic syndrome while no significant association was noted between metabolic syndrome and increased liver enzymes. **Conclusion:** The present study exhibited that long-standing or chronic diabetes, due to its multisystem effects, can adversely impact liver function. The study concluded that identifying elevated liver enzymes could potentially highlight T2DM patients at heightened risk of non-alcoholic fatty liver disease (NAFLD), thereby underscoring the need for monitoring and management of liver health in diabetic care.

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International Journal of Academic Medicine and Pharmacy (www.academicmed.org)
ISSN (O): 2687-5365; ISSN (P): 2753-6556

INTRODUCTION

Diabetes mellitus (DM) refers to a cluster of metabolic disorders marked by elevated blood sugar levels due to issues with insulin secretion, insulin function, or both. The persistent hyperglycemia associated with diabetes can lead to lasting harm and impaired function in various organs, including the eyes, kidneys, nerves, heart, and blood vessels.[1] In 2019, the global prevalence of diabetes was estimated at 9.3%, affecting approximately 463 million people. In India, the prevalence of DM and impaired fasting blood glucose (IFG) in 2017-2018 was9.3% and 24.5%, respectively.[2] Hyperglycemia refers to a condition where glucose production exceeds its utilization as an essential energy source. The regulation of glucose homeostasis involves multiple organs, including the brain, liver, pancreas, skeletal muscle, and adipose tissues.[3] Of these, the liver plays a crucial role in both glucose synthesis and storage. However, persistent exposure to high glucose levels (glucotoxicity) can lead to changes in liver function.[4]

Typically, the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzymes, the biomarkers of hepatic stress or injury, are localized within the healthy hepatocytes but during hepatic necrosis or proliferation they are released in the serum.[5]Along with aminotransferases, alkaline phosphatase (ALP) levels are also indicative of hepatocyte integrity. Although a healthy liver normally does not go through repeated mitosis, liver damage from endogenous or exogenous chemicals can cause the liver to proliferate and possibly increase in liver enzyme levels. Additionally, liver enzymes serve as important markers for liver health. Elevated ALT levels may indicate underlying liver disease.[6] Aspartate aminotransferase (AST) is found in the liver as well as other organs such the brain, kidney, skeletal muscle, and heart. In children, AST levels decline with age, especially in girls after 11 years of age.[7]

Serum ALP primarily originates from the liver and bones and their elevated levels can be fractionated to identify their source (liver or bones). In clinical practice, liver origin is often confirmed by concurrent elevation of other cholestasis markers.[8] Notably, mild increases in liver enzymes within the upper normal range are associated with features of metabolic syndrome and non-alcoholic fatty liver disease (NAFLD), even in recently diagnosed DM patients.[9] NAFLD is defined as chronic liver disease where excess fat builds up in the liver due to non-alcoholic causes. Among T2DM patients the prevalence of NAFLD is reported to be 70%. NAFLD has been closely associated with both insulin resistance (IR) and overweight/obesity.[10] Studies conducted in various geographical locations have reported differing prevalence rates of deranged liver enzymes, which serve as markers for asymptomatic NAFLD in individuals with DM.[11-21]This region of the country has not seen a lot of research on the relationship between metabolic syndrome and liver enzymes in people with diabetes mellitus. The goal of the present study was to examine the liver enzymes and metabolic syndrome in diabetes patients. This study information may be helpful for a better understanding of the relation between liver enzymes and metabolic syndromes, further in identifying DM as a probable diagnosis at an early stage from deranged liver enzymes.

MATERIALS AND METHODS

This is a cross sectional study conducted in Regional Institute of Medical Sciences (RIMS), Imphal from May 2022 to July 2024. All diabetic patients admitted in the Medicine ward or attending Medicine OPD or endocrinology OPD, Regional Institute of Medical Sciences, Imphal during the study period were enrolled.

Inclusion Criteria included all diabetic patients above 18 years.

Exclusion Criteria included patients with history of alcohol intake, history of liver disease [seropositive for HBsAg, HCV, autoimmune hepatitis, alcoholic hepatitis, haemochromatosis etc.], those on hepatotoxic drugs, pregnant females and those who refused to give consent.

Sample size and Sampling: The sample size for the study was based on a study by Teshome G et al [22], who reported the proportion of patient with abnormal liver function test (LFT) among diabetic patients as 33.3%, using the formula.

Sample size, $N = 1.962PQ/L2$. Taking proportion of patient with abnormal LFT among diabetic patients as 33.3% (Teshome G et al [22]), Precision (L) = 8%, Alpha = 1.96. Therefore, N = 139.

Study procedure: A pretested predesigned proforma, consisting of socio-demographic characteristics like age, sex, religion, socioeconomic status, body mass index (BMI), waist circumference (WC), lipid profile, etc were recorded. The proforma recorded the detailed clinical history of the patients, general physical examination, routine hematological, biochemical parameters including AST, ALT, GGT, ALP, total Bilirubin, direct Bilirubin, Albumin, (gylcosylated hemoglobin) HbA1C, (fasting blood glucose) FBG, (post prandial glucose) PPG and lipid profile. Diagnosis of diabetes was made using the American Diabetes Association (ADA) criteria for the diagnosis of diabetes and the diagnosis of metabolic syndrome was made using the NCEP ATP (National Cholesterol Education program's Adult treatment panel) III criteria.

Operational definition:
1) Diabetes was diagnosed based on the criteria outlined by the American Diabetes Association, which includes the following conditions [23]:

a. HbA1C $\geq$ 6.5%. This test must be conducted in a certified laboratory using an NGSP-certified method standardized to the DCCT assay.

b. Fasting plasma glucose (FPG) $\geq$ 126 mg/dL (7 mmol/L). Fasting is defined as abstaining from caloric intake for at least 8 hours.

c. 2-hour plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT), performed according to World Health Organization guidelines using a glucose load equivalent to 75 g anhydrous glucose dissolved in water.

d. In patients exhibiting classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L).

*HbA1C: glycated hemoglobin; NGSP: National Glycohemoglobin Standardization Program; DCCT: Diabetes Control and Complications Trial; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test.

In the absence of obvious hyperglycemia, the diagnosis requires two abnormal test findings from the same sample or from two different test samples.

2) According to the NCEP ATP III criteria, Metabolic syndrome is characterised by the presence of any three of the following five characteristics[24]:

a. Abdominal obesity, characterized by a waist circumference $\geq$ 102 cm (40 inches) in men and $\geq$ 88 cm (35 inches) in women.

b. Serum triglycerides $\geq$ 150 mg/dL (1.7 mmol/L) or receiving treatment for elevated triglycerides.

c. Serum high-density lipoprotein (HDL) cholesterol < 40 mg/dL (1 mmol/L) in men and < 50 mg/dL (1.3 mmol/L) in women or receiving treatment for low HDL cholesterol.

d. Blood pressure $\geq$ 130/85 mmHg or on antihypertensives.

e. Fasting plasma glucose (FPG) $\geq$ 100 mg/dL (5.6 mmol/L) or receiving treatment for elevated blood glucose.

Normal ranges:[25] The normal reference ranges used for this study were as follows:

Total bilirubin: 0.3–1 mg/dL,
ALT: 0–40 U/L,
AST: 0–40 U/L,
ALP: 30–120 U/L,
GGT: 6-50 IU/L and
Albumin: 3.5–5.5 g/dL

Statistical analysis: SPSS (IBM) version 21 was used for statistical analysis. Descriptive statistics including mean, standard deviation, and percentages were utilized to summarize the variables such as age, sex, religion, FBG, BMI, WC and lipid profile. Chi-square test and Fisher's exact test were utilised to evaluate the association between liver enzymes and metabolic syndrome. The independent t-test was employed to examine the relationship between liver enzymes (ALT, AST, ALP, etc.) and factors like gender, BMI > 30 kg/m², waist circumference > 102 cm in males (> 88 cm in females), among others. A p-value less than 0.05 was considered statistically significant.

Approval of research ethics board: Ethical approval for this study was obtained from the Research Ethics Board, Regional Institute of Medical Sciences, Imphal [No.A/206/REB-Comm(SP)/RIMS/2015/918/256/2022].

RESULTS

A total of 139 diabetic patients were enrolled in the present study. The baseline characteristics of the study subjects were given in [Table 1].The mean age of the patients was 61.04 $\pm$ 14.34 years with majority (31.7%), in the age group 61 to 70 years. The mean age of female patients (64.6 $\pm$ 12.94 years) was significantly higher than that of male patients (58.9 $\pm$ 14.79 years). Most of the subjects were males 63% (87) belonging to Hinduism, (60%, 84). Most of the patients belonged to the lower middle class (32.4%), majority participants were from the rural area (66.9%). Clinical and biochemical data of the patients in mean +SD and P value were shown in [Table 2].The mean BMI was 28.14 $\pm$ 4.06 kg/m2 and the mean WC was 96.45 $\pm$ 12.14 cm. Thirty-eight percent of the patients were obese, followed by overweight (33.1%) and normal BMI (28.1%).Clinical and biochemical data with respect to gender were given in [Table 3] and association between gender and BMI, high liver enzymes and metabolic syndrome were shown in [Table 4]. The mean BMI of females (29.3 $\pm$ 3.65 kg/m²) was significantly higher than that of male patients (27.4 $\pm$ 4.15 kg/m²). A significantly higher proportion of females were overweight and obese compared to male patients. However, males had significantly larger WC measurements (98.9 $\pm$ 13.17 cm) compared to females (92.2 $\pm$ 8.82 cm).

Table 1: Baseline characteristics of the study subjects (N = 139).

Characteristics	Study patients (N = 139), n (%)
Age (in years)	
20-30	(1.4%)
31-40	(7.9%)
41-50	(14.4%)
51-60	(18.7%)
61-70	(31.7%)
71-80	(20.1%)
>80	(5.8%)
Gender	
Male	87(63%)

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International Journal of Academic Medicine and Pharmacy (www.academicmed.org)
ISSN (O): 2687-5365; ISSN (P): 2753-6556

female	52(37%)	
Religion		
Hindu	84(60%)	
Christain	19(14%)	
Muslim	36(26%)	
Socio – economic status		
Upper class	33(23.7%)	
Upper middle class	38(27.3%)	
Lowermiddle class	45(32.4%)	
Upper lower class	15(10.8%)	
Lower class	8(5.8%)	
Address		
Urban	46(33.1%)	
Rural	93(66.9%)	
AST -Normal	84(60.4%)	
High	55(39.6%)	
ALT - Normal	95(68.3%)	
High	44(31.7%)	
ALP - Normal	54(38.8%)	
High	85(61.2%)	
GGT - Normal	115(82.7%)	
High	24(17.3%)	

Table 2: Clinical and biochemical data of the patients (N=139).

Sl.no.	Parameters	Mean ± Standard deviation		P value
		Males	**Females**	
1.	Age	58.9 ± 14.79	64.6 ± 12.94	0.023
2.	BMI	27.4 ± 4.15	29.3 ± 3.65	0.008
3.	Waist circumference	98.9 ± 13.17	92.2 ± 8.82	0.002
4.	HbA1c	7.2 ± 2.43	7.0 ± 2.07	0.711
5.	Triglycerides level	163.5 ± 83.12	147.3 ± 69.79	0.239
6.	HDL cholesterol	58.3 ± 19.73	56.7 ± 13.92	0.609
7.	ALT	38.5 ± 27.87	41.0 ± 30.32	0.624
8.	AST	38.6 ± 26.57	35.8 ± 22.63	0.528
9.	ALP	152.1 ± 80.23	147.5 ± 78.00	0.745
10.	GGT	34.8 ± 27.71	32.7 ± 22.77	0.631
11.	FBG	162.2 ± 54.89	166.9 ± 48.76	0.610

Table 3: Clinical and biochemical data with respect to gender (N=139).

Sl.no.	Parameters	Mean ± Standard deviation		P value
		Males	**Females**	
1.	Age	58.9 ± 14.79	64.6 ± 12.94	0.023
2.	BMI	27.4 ± 4.15	29.3 ± 3.65	0.008
3.	Waist circumference	98.9 ± 13.17	92.2 ± 8.82	0.002
4.	HbA1c	7.2 ± 2.43	7.0 ± 2.07	0.711
5.	Triglycerides level	163.5 ± 83.12	147.3 ± 69.79	0.239
6.	HDL cholesterol	58.3 ± 19.73	56.7 ± 13.92	0.609
7.	ALT	38.5 ± 27.87	41.0 ± 30.32	0.624
8.	AST	38.6 ± 26.57	35.8 ± 22.63	0.528
9.	ALP	152.1 ± 80.23	147.5 ± 78.00	0.745
10.	GGT	34.8 ± 27.71	32.7 ± 22.77	0.631
11.	FBG	162.2 ± 54.89	166.9 ± 48.76	0.610

Table 4: Association between gender and BMI, high liver enzymes and metabolic syndrome (N=139).

Sl.no.	BMI	Gender, n(%)			P value
		Male	**Female**	**Total**	
1	Normal (< 25 kg/m2)	31 (35.6)	8 (15.4)	39 (28.1)	0.035
2	Overweight (25-29.9 kg/m2)	25 (28.8)	21 (40.4)	46 (33.1)	
3	Obese (≥ 30 kg/m2)	31 (35.6)	23 (44.2)	54 (38.8)	
	Liver enzymes				
1	High AST(>40)	34 (63.1)	21 (36.9)	55 (39.6)	0.510
2	High ALT(>40)	27 (61.4)	17 (38.6)	44 (31.7)	0.492
3	High ALP(>120)	54 (63.5)	31 (36.5)	85 (61.2)	0.456
4	High GGT(>50)	16 (66.7)	8 (33.3)	24 (17.3)	0.417
	Metabolic syndrome				
1	Yes	39 (44.8)	34 (65.4)	73 (52.5)	0.019
2	No	48 (55.2)	18 (34.6)	66 (47.5)	

Table 5: Association between metabolic syndrome and liver enzymes (N=139).

Sl.no.	Liver enzymes	Metabolic syndrome, n (%)			P value
		Yes	No	Total	
1	High AST(>40)	31 (56.4)	24 (43.6)	55 (39.6)	0.288
2	High ALT(>40)	23 (52.3)	21 (47.7)	44 (31.7)	0.556
3	High ALP(>120)	46 (54.1)	39 (45.9)	85 (61.2)	0.382
4	High GGT(>50)	11 (45.8)	13 (54.2)	24 (17.3)	0.310

The mean value of ALT, AST, ALP and GGT were 39.46 ± 28.73 U/L, 37.62 ± 25.12U/L, 150.35 ± 79.15U/L, 34.06 ± 25.91U/L respectively. Serum AST was high in 39.6% of the patients. Similarly ALT, ALP and GGT were high in 31.7%, 61.2% and 17.3% of the patients. The mean value of FBG was 163.96 ± 52.56 mg/dl and HbA1c was 7.16 ± 2.29%. There were no significant differences between the mean values of HbA1c, triglycerides, HDL cholesterol, ALT, AST, ALP, GGT, and FBS between males and females. There was no significant association between gender and liver enzymes (AST, ALT, ALP and GGT).

Metabolic syndrome was present in 53% (73) of the patients. More number of females (65.4%) was seen to have metabolic syndrome in comparison to only 44.8% of males. There was a significant association between gender and metabolic syndrome. There were no significant association between metabolic syndrome and increased liver enzymes, as shown in [Table 5].

DISCUSSION

Out of 139 diabetic patients, 63% (87) were males and remaining 37% (52) were females which was comparable to the study by Bora K et al,[12] (58.75% males, 41.25% females) and Rashid MHO et al,[19] (56% males). While Alzahrani SH et al and Ni H et alshowed female predominance of 67.8% and 67.9% in their study population respectively.[22-26] The mean age of our study population was 61.04 ± 14.34 years, which was similar to the studies by Sakharkar P et al,[4] (mean age of 61.1 ± 0.40 years and majority above 65 years) and Alzahrani SH et al,[26] (mean age of 60 ± 13.43 years). Maximum of the patients (31.7%) in this study were in age group 61 to 70 years which was comparable to the study by Chilay A et al,[27](majority (37.69%) above 60 years. The mean age of female patients (64.6 ± 12.94 years) were significantly higher than the male patients (58.9 ± 14.79 years).

The mean BMI in this study was 28.14 kg/m2 which was similar to the BMI reported by various studies by Abro MUR et al,[20](27.34±5.99 kg/m2) and Ohlson LO et al(27.4 ± 2.9 kg/m2).[27,28]While Sakharkar P et al,[4] reported a higher mean BMI of 31.6±0.19 kg/m2 in his study. But Ni H et al,[14] reported a lesser mean BMI of 25.84 kg/m2 among their study population. The mean BMI of females (29.3 ± 3.65 kg/m2) were significantly higher than the male patients (27.4 ± 4.15 kg/m2).The mean WC was 96.45 ± 12.14 cm and males (98.9 ± 13.17 cm) were significantly more than the females (92.2 ±

8.82 cm). Thirty eight percent of the patients were obese followed by overweight (33.1%) and normal BMI (28.1%). Maximum of the females were overweight and obese significantly in comparison to male patients in this study.

Likewise in this study the mean value of ALT, AST, ALP, GGT,FBG and HbA1c were 39.46 ± 28.73 U/L, 37.62 ± 25.12 U/L, 150.35 ± 79.15 U/L, 34.06 ± 25.91 U/L and 163.96 ± 52.56 mg/dl and 7.16 ± 2.29%.respectively. In proportion, AST, ALT, ALP and GGT were high in 39.6%, 31.7%, 61.2% and 17.3% of the patients respectively in this study. Sakharkar P et al,[4] reported 10.9% of their study patients with high ALT value (>40 U/L) which is lesser than this study. Similarly, they reported high AST and ALP only in 7.9% and 5.4% of the study population respectively. Another study by Kwo PY et al,[12] in another northeast state reported abnormal AST, ALT and ALP in 32.5%, 37.5% and 41.2% of their study population which is similar to this study findings.[13] Ni H et al,[14] reported in their study with 18.5%, 14.8%, 6.2% and 0% abnormal ALT, AST, ALP and GGT value among their diabetic study population. Ghimire S etal,[21] in his study reported increased level of AST in 46%, ALT in 57%, ALP in 7% of diabetic patients. Thus, it was seen from many studies that the liver enzymes (AST, ALT, ALP and GGT) were increase in good proportion among diabetic patients which is in line to this study finding.

In gluconeogenesis, Alanine is the most effective precursor among the amino acids. Gluconeogenesis is increased in subjects with T2DM due to increased substrate delivery (e.g., alanine) thereby leading to an increased conversion of alanine to glucose. ALT might thus be up-regulated as a compensatory response to the impaired hepatic insulin signaling due to diabetes or, alternatively, may leak more easily out of the hepatocytes as a consequent of fatty infiltration and subsequent damage.[13]AST function normally to transfer Aspartate to a keto acid, producing pyruvate and oxaloacetate, respectively. It is located in the cytoplasm of the hepatocyte; an alternative form of AST is also located in the hepatocyte mitochondria. ALP in the liver is found to be associated with cell membrane which adjoins the biliary canaliculus, and so high plasma concentration of the liver isoenzyme indicates cholestasis rather than simply damage to the liver cells. Therefore raise in these liver enzymes indicates liver damage. But, it is important to clarify if DM-induced abnormal liver function or abnormal liver functions were predisposing factors for DM. However, circumstantial evidence implies abnormal

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International Journal of Academic Medicine and Pharmacy (www.academicmed.org)
ISSN (O): 2687-5365; ISSN (P): 2753-6556

liver functions may have followed DM and DM may be responsible for abnormal liver functions.[19]

In this study, metabolic syndrome was present in 53% (73) of the patients, with a higher prevalence observed in females (65.4%) compared to males (44.8%). There was no significant association found between metabolic syndrome and elevated liver enzymes. In contrast to our findings, Forlani G et al,[15] demonstrated in their study that metabolic syndrome was associated with abnormalities in liver enzymes.

CONCLUSION

The present study concluded that the mean values of liver enzymes (ALT, AST, ALP, and GGT) exceeded the normal upper limits in diabetic patients which may be due to reduction in hepatic function. The study emphasizes the importance of testing ALT and AST to screen for underlying fatty liver, especially in males that a significant proportion of diabetes patients may exhibit abnormal liver function, potentially serving as a detecting marker for NAFLD/non-alcoholic steatohepatitis (NASH) and insulin resistance in diabetes patients with metabolic syndrome.

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International Journal of Academic Medicine and Pharmacy (www.academicmed.org)
ISSN (O): 2687-5365; ISSN (P): 2753-6556