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KEY WORDS:

PREVALENCE OF ABNORMAL LIVER FUNCTION TEST IN TYPE II DIABETES MELLITUS IN IN URBAN SOUTH-INDIAN POPULATION

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ABSTRACT

BACKGROUND Abnormal liver function test results are more common in diabetes mellitus than in the non diabetic population as well as in patients with type 2 diabetes than in those with type 1 diabetes. The aim of this study was to determine prevalence of abnormal liver function test in patients with type 2 diabetes and to determine associated risk factors.

MATERIALS AND METHODS The present study was a cross sectional study done on patients with diabetes of any duration, attending the diabetology OPD of Institute of social obstetrics and Kasturba Gandhi general hospital between January 2016 to June 2017. Total no of 160 patient were selected by convenient sampling method after satisfying the inclusion criteria. The selected patients underwent clinical and biochemical evaluations. The results were calculated using SPSS software and expressed in percentage.

RESULTS: Of these 160 patients, Serum ALT and AST was found to be elevated in 43 patients(27%), Serum alkaline phosphatase was found to be elevated in 10 patients (6%), Serum bilirubin was found to be elevated in 4 patients (3%). There was no significant alteration in serum protein or albumin globulin ratio.

CONCLUSION A high proportion of patients with diabetes mellitus have abnormal liver function tests that may be a marker for NASH and insulin resistance. Routine liver function screening is not being advocated in type 2 diabetics but emerging evidence suggests that abnormal LFT may be a marker for metabolic syndrome.

INTRODUCTION:

Diabetes mellitus is a complex metabolic condition defined by level of hyperglycemia giving rise to micro vascular and macro vascular complications. Various complications related to micro or macro vascular diseases like retinopathy, nephropathy, neuropathy, ischemic heart diseases and peripheral vascular disease have been reported. Liver diseases is often overlooked as a complication of DM. Diabetes mellitus is known to be associated with a number of liver disorders including isolated elevation of liver enzyme levels, nonalcoholic fatty liver disease (NAFLD), and other chronic liver disorders like hepatitis C infection (HCV), cirrhosis and hepatocellular carcinoma[1,2,3]. Elevated activities of the two serum transaminases; alanine transaminase (ALT) and aspartate transaminase (AST) associated with liver disease is strongly related to obesity, diabetes and dyslipidemia. Of the two enzymes, ALT appears to have a role in gluconeogenesis,[4] and seems to be more related to liver fat accumulation than AST.[5]

THEORIES BEHIND LFT ELEVATION IN DIABETES:

The liver helps to maintain normal blood glucose concentration in the fasting and postprandial states. Loss of insulin effect on the liver leads to glycogenolysis and an increase in hepatic glucose production. Abnormalities of triglyceride storage and lipolysis in liver are an early manifestation of conditions characterized by insulin resistance.[6] Chronic hyperinsulinemia is found to predispose the liver to relative resistance to insulin. This is characterized by a failure of insulin to signal an increase in insulin receptor substrate-2 mediated insulin signaling pathway, the up-regulation of SREBP-1c and subsequent simulation of de novo lipogenesis in the liver leads to increased intracellular availability of triglycerides, promoting fatty liver.[6] Thus, hyperinsulinemia might directly lead to hepatic insulin resistance with associated fatty changes. The insulin-resistant state is also characterized by an increase in proinflammatory cytokines such as tumor necrosis factor- (TNF-), which may also contribute to hepatocellular injury.[7] The above theories all attribute elevated transaminases to direct hepatocyte injury.

NAFLD is a clinicopathological condition representing a spectrum of histological findings from simple hepatic steatosis or steatosis with mild inflammation(type 1 & 2), to hepatic steatosis with a necroinflammatory component that may or may not have fibrosis, or NASH(type 3 & 4).

Currently NAFLD is considered to be hepatic manifestation of metabolic syndrome.[8] Diabetic patients with NAFLD are at increased risk of advanced liver diseases, cirrhosis and HCC. NAFLD is an important cause of cryptogenic cirrhosis.[9,10] Elevated AST or ALT levels are predictive of the presence of NAFLD if two basic criteria are met: 1) exclusion of alternative chronic liver diseases, e.g. alcoholic liver disease, hepatitis B or C infection, and hemochromatosis; and 2) presence of features of the metabolic syndrome.

AIM OF THE STUDY

1. The aim of this study was to determine prevalence of abnormal liver function test in patients with type 2 diabetes
2. To determine associated risk factors like age, BMI, central obesity, glycemic control and dyslipidemia and its impact on abnormal liver function test. .

MATERIALS AND METHODS

The study was conducted in Institute of social obstetrics and Kasturba Gandhi general hospital between January 2016 to June 2017. It was a cross sectional study in which patients were interviewed and their data were recorded in a standardized proforma. Data collected included age, gender, duration of diabetes, drug history and co-morbid conditions like hypertension and coronary heart diseases etc.

The following are the patients inclusion and exclusion criterias.

INCLUSION CRITERIA:

Presence of type 2 diabetes mellitus of any duration.

EXCLUSION CRITERIA:

1. Consumption of alcohol.
2. Seropositivity of HbsAg and antiHCV antibody.
3. Seropositivity of HIV ELISA.
4. Patient on drugs that are proven to cause steatohepatitis

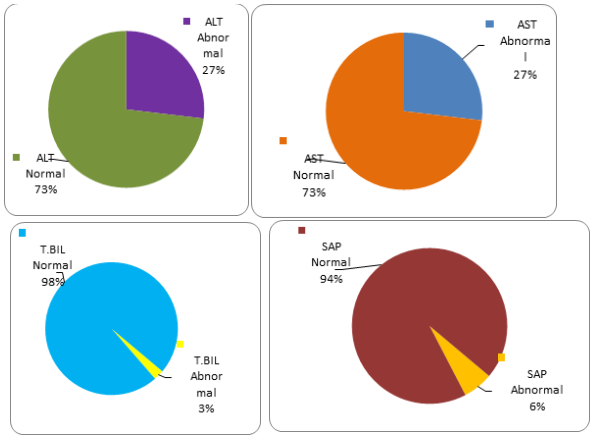
(steroids, amiodarone, oral contraceptive pills, and other estrogen containing preparations).
5. Patients with renal failure.

A total of 160 type 2 diabetic patients who met the inclusion criteria were studied during this period. Both inpatients and outpatients attending diabetology outpatient department were included in the study.

Body weight , Height, Waist circumference and hip circumference was measured. All the above patients were examined and screened for HbsAg, antiHCV antibody, HIV ELISA. Morning samples of venous blood were collected from patients after fasting blood glucose, urea, creatinine , HbA1C, liver function test and lipid profile. Ultrasound abdomen was done for all patients.

STATISTICAL ANALYSIS:
Data analysis was performed using the Statistical Package for Social Sciences (SPSS).

RESULTS
A total of 160 type 2 DM patients (male =65 pts and female =95 pts) who met the inclusion criteria were studied during the study period. Of these 160 patients Serum ALT and AST was found to be elevated in 43 patients (27%), Serum alkaline phosphatase was found to be elevated in 10 patients (6%), Serum bilirubin was found to be elevated in 4 patients (3%). There was no significant alteration in serum protein or albumin globulin ratio.



AGE WISE DISTRIBUTION OF ABNORMAL ALT & AST:

	ALT & AST	
Age Group	**Abnormal**	**Normal**
30-40 yrs	0 (0%)	7 (100%)
41-50 yrs	15 (31%)	33 (69%)
51-60 yrs	23 (33%)	46 (67%)
61-70 yrs	5 (15%)	28 (85%)
71-80 yrs	0 (0%)	3 (100%)

	ALT & AST	
Gender	**Abnormal**	**Normal**
Female	25 (26%)	70 (74%)
Male	18 (28%)	47 (72%)

The mean age of patients with abnormal ALT and AST was 53.23 yrs.

SEX DISTRIBUTION OF ABNORMAL ALT & AST:

BMI	**ALT & AST**		
	Abnormal	**Normal**	**P value= 0.000**
Underweight	0 (0%)	2 (100%)	
Normal	1 (2%)	59 (98%)	
Over weight	22 (36%)	39 (64%)	
Obese	20 (54%)	17 (46%)	

BODY MASS INDEX DISTRIBUTION:

study, The abnormal ALT and AST was seen in 36% of overweight patients and 54% of obese patients (p value =0.000).The mean BMI in patients with abnormal ALT and AST was 29.64.

In total of 18 males who had elevated transaminases, 14 (77 %) of them had waist hip ratio >1. In total of 25 females who had elevated transaminases, 25(100%) of them had waist hip ratio >0.8.Thus the patients with abnormal ALT & AST was significantly associated with central obesity (p value 0.000).

The elevated ALT & AST was common in the patients with abnormal ALT and AST was found to have poor glycemic control as evidenced by HBA1C. 88% of patient with abnormal ALT and AST have HBA1C >7%. Mean HBA1C in patients with abnormal ALT and AST was 9.98% (p value =0.002)

The elevated ALT & AST was common in 38% patients with serum cholesterol >200mg/dl and serum triglyceride >180 mg/dl.

Generally in NAFLD the ratio of AST to ALT is less than 1, but this ratio increases as fibrosis advances. In our study AST/ALT ratio <1 was seen in 31 patients(72%) and AST/ALT ratio >1 seen in 12 patients(28%).

In our study we have noticed that 72(46%) patients with type 2 DM has USG evidence of fatty liver. Of this 72 patients 44% patients have normal ALT and AST and 56% had abnormal ALT and AST.

DISCUSSION:
Because the liver plays a critical role in the maintenance of carbohydrate homeostasis, glucoregulation, and insulin degradation, it is not surprising that its functions may be affected as a result of diabetes mellitus [11]. The prevalence of elevated transaminases levels in type 2 diabetes mellitus is not well known in the Indian population. In our present prevalence of elevated ALT & AST was found in 27% of patients, elevated ALP was seen in 6% of patients and raised serum bilirubin in 3% of patients. According to a previous study conducted by Salmela et al [12], in type 2 DM prevalence of abnormal transaminases was found to be 22.9% and raised serum bilirubin is 10.2% . In our study, elevated transaminases was seen 31% of patients in the age group of 41-50 yrs, 33% in the age group of 51-60 yrs and 15 % in the age group of 61-70 yrs. Supported by earlier studies, [13,14] this finding suggested that severe steatosis denoted by a higher release of the ALT enzyme in response to hepatocytes derangement, tends to occur earlier in the disease process. In our study the mean duration of diabetes in patients with abnormal transaminases is 6.34 yrs which was consistent with finding of Salmela et al[12] and Layla Judi et a l[15]. In our study elevated transaminases seen in 28% males and 26% females. However in our study we are not able to demonstrate significant sex difference in prevalence of abnormal transaminases, Erbey et al.[16] reported prevalence rates of 10.7% and 5.3% in type 2 diabetic men and women respectively and West et al.[17] reported a rate of 12.1%; 14.4% in men and 9.3% in women with type 2 diabetes mellitus. In our study we have noticed that elevated transaminases was seen in 36% of overweight category patient and 54% of obese category patients (p value =0.000). These findings are consistent with previous large scale studies by Salmela et al [12] and Erbey et al [16] who reported that prevalence of abnormal transaminases was common in patients with BMI >25 kg/m^2 .

Also in our study the patients with elevated transaminases was significantly associated with central obesity (p value 0.000) which was consistent with study conducted by Layla Judi et al.[15] In our study patients we noticed that patients with elevated transaminases had a poor glycemic control as evidenced by HbA1C. Mean HBA1C in patients with elevated transaminases was 9.98 (p value =0.002), which was consistent with finding of Salmela et al[12] who demonstrated a mean HBA1C OF 11.2% in patients with elevated transaminases indicating poor glycemic control. We have also observed like other people that raised transaminases is closely related to other features of metabolic syndrome in addition to type 2 diabetes , like obesity and serum

triglycerides more than180 mg/dl. 38% of our patients had a fasting serum triglycerides level of more than 180 mg/dl which was found to be statistically significant (p value=0.001).[18] Our results are consistent with findings of Shahid ahmed et al[19] who reported 42.6% patients with elevated transaminases had serum triglycerides >180 mg/dl. All patients with elevated transaminases showed fatty liver on ultrasound and Though we did not do liver biopsies in these patients, ultrasonographic appearance of fatty liver has a good predictive value for NAFLD. NAFLD is the commonest cause of elevated aminotransferases in type 2 diabetic patients, and our study confirms that too. Since all our patients included in our study were on Oral hypoglycaemic agents (metformin and sulphonylureas) ,we are not able to substantiate the difference in the prevalence of abnormal transaminases in insulin and OHA groups.

Our study has limitations. First, the prevalences of raised transaminases may still be underestimates as fluctuation in the ALT levels is recognized in patients with chronic liver disease, and a single measurement can underestimate disease burden[20]. Since all our patients were on oral hypoglycaemic agents, we are not able to substantiate the difference in the prevalence of abnormal transaminases in insulin and OHA groups. In our study we didn't do a liver biopsy as most of the patients being asymptotatic denied consent for invasive procedure.

CONCLUSION

A high proportion of patients with diabetes mellitus in our catchment population have abnormal liver function tests that may be a marker for NASH and insulin resistance. Currently, routine liver function screening is not being advocated in type 2 diabetics but emerging evidence suggests that abnormal LFT may be a marker for metabolic syndrome and insulin resistance in type 2 diabetes. Such patients would thus warrant more intensive metabolic control particularly of their hyperglycaemia and dyslipidaemia and also their obesity and hypertension to not only reduce cardiovascular risk attributed to by their insulin resistance but also to prevent progression to significant hepatic dysfunction like cirrhosis and hepato-cellular carcinoma.

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