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PREVALENCE OF ELEVATED SERUM TRANSAMINASE LEVELS IN SOUTH INDIAN TYPE 2 DIABETES INDIVIDUALS AND THEIR IMPORTANCE IN CLINICAL PRACTICE

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ABSTRACT

Objective: To find out the prevalence of elevations of serum transaminase levels in south Indian type 2 diabetes individuals and associated risk factors. **Research design and methods:** 403 type 2 diabetes subjects were randomly selected, 203 from Karnataka institute of endocrinology and research an urban diabetic centre and 200 from Bagalkot rural diabetic centre. BMI and waist circumference were measured. A fasting and post prandial blood sample was drawn for estimation of plasma glucose by hexokinase method. HBA1C was measured by the high-performance liquid chromatography method using the Bio-rad Variant 2 turbo analyzer. Diagnosis of diabetes was made by using ADA criteria of fasting plasma glucose ≥126 mg/dl and HBA1c ≥6.5%. Liver function tests and lipid profile were analyzed in cobot C 311 biochemistry analyzer by standard methods. **Results:** Age distribution-18 to 90 years. Male diabetes subjects were 64.8%. Duration of diabetes range from new to >10 years. BMI range from <18.5 to >30 kg/square meters. Waist circumference range from <80 cms to >100 cms. AST was more than 31 units/L in 26.1% (105) and ALT was more than 30 units/L in 22.8% (92) of the type 2 diabetes individuals studied. Elevated ALT was found to have a statistically significant association with increasing waist circumference, increased fasting and post prandial glucose, increased triglycerides, total and direct bilirubin levels. Elevated AST was found to have a statistically significant association with increased LDL, TG, total and direct bilirubin levels. **Conclusions:** AST was more than 31 units/L in 26.1% (105) and ALT was more than 22.8% (92) of the type 2 diabetes individuals studied. Elevated ALT was found to have a statistically significant association with increasing waist circumference, fasting and post prandial glucose, triglycerides, total and direct bilirubin levels. Marginal elevation of ALT levels can be used as a marker to suspect NAFLD in type 2 diabetes.

KEYWORDS: AST, ALT, Triglyceride, liver function.

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders of carbohydrates, lipids and proteins characterized by hyperglycemia.[1] Globally, more than 415 million people, aged 20-79 years, were affected by DM and the figure is expected to rise up to 642 million in 2040. An epidemic growth of DM has occurred in developing countries in which 75% of patients with DM live in the low and middle-income countries. In addition, DM affects the working age in the low and middle-income countries.[2]

The exact pathophysiological mechanism of DM to induce abnormalities in liver biomarkers is still unclear. The first possible explanation that DM induces liver function abnormality is the deposition of fat in the liver which is the characteristics of nonalcoholic fatty liver disease (NAFLD). The other possible assumption is the vulnerability of individuals with metabolic syndrome like DM to inflammation of the liver which alters the function of liver and induces a change in liver biomarkers.[3]

Liver function tests (LFTs) are used in clinical practice to screen liver disease, to monitor the progression of a known liver disease and to monitor the effects of potentially hepatotoxic drugs. The most commonly used LFTs include the serum aminotransferases, alkaline phosphatase (ALP), bilirubin, total protein (TP), albumin, and prothrombin time. Measurement of serum aminotransferases, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) serve as a marker of hepatocytes injury. ALP, gamma-glutamyltranspeptidase (GGT) and bilirubin act as markers of biliary function and cholestasis whereas total

protein, albumin and prothrombin time reflect liver synthetic function.[4]

Individuals with type 2 diabetes have a higher incidence of liver function test abnormalities than individuals who do not have diabetes. Mild chronic elevations of transaminases often reflect underlying insulin resistance. Elevation of transaminases within three times the upper limits of normal is not a contraindication for starting oral antidiabetic or lipid-modifying therapy. In contrast, antidiabetic agents have generally been shown to decrease alanine aminotransferase levels as tighter blood glucose levels are achieved.[5]

AST (SGOT) is normally found in a variety of tissues including liver, heart muscle, kidney, and the brain. It is released into the serum when any one of these tissues is damaged. For example, AST level in serum is elevated in heart attacks or with muscle injury. It is therefore, not a highly specific indicator of liver injury as its elevation can occur as a result of other injured tissues. ALT (SGPT) is, by contrast, normally found largely in the liver. This is not to say that it is exclusively located in the liver, but that is where it is most concentrated. It is released into the bloodstream as the result of liver injury. Thus, it serves as a fairly specific indicator of liver status.[5]

The most common cause of elevated LFTs in type 2 diabetic patients is nonalcoholic fatty liver disease (NAFLD). NAFLD is a clinicopathological condition representing a spectrum of histological findings from hepatic steatosis or fat accumulation in hepatocytes without inflammation, to hepatic steatosis with a necroinflammatory component that may or may not have fibrosis, or NASH.

NAFLD is defined by the absence of or minimal alcohol consumption, liver biopsy showing macrovesicular steatosis with or without necro-inflammatory activity, and exclusion of other forms of liver disease. Although the pathogenesis is still unclear, it is characterized by accumulation of triglycerides within the hepatocytes. Insulin resistance is thought to play an important role in the triglyceride accumulation. Excess intracellular fatty acids, oxidant stress, ATP depletion, and mitochondrial dysfunction all contribute to hepatocyte injury and inflammation followed by fibrosis.[6]

The most common laboratory abnormality in patients with NAFLD is mild to moderate elevation of serum aminotransferases. The aminotransferases AST and ALT are normally < 30-40 units/l. Kim H.C.et al estimated that the best cut-off values for identifying men who are risk of death from liver disease were 31 IU/l for aspartate aminotransferase and 30 IU/l for alanine aminotransferase. The areas under the receiver operating characteristic curve were 0.83 and 0.78, respectively. They could not establish the cutoff value in women, but it was expected to be lower than in men.[7] So they have taken cut off value of 31 IU/L for AST and 30 IU/L for ALT. Chronic mild elevation of transaminases are frequently found in type 2 diabetic patients.

The literature indicates a comparatively high prevalence of abnormal serum liver enzymes, specifically ALT and AST, in diabetic patients.

In this study we studied prevalence of mild elevations of AST and ALT in type 2 diabetes and their clinical importance in individuals attending two diabetes centers in Karnataka. We have taken cut off value of 31 IU/L for AST and 30 IU/L for ALT in this study.

Research design and methods- 403 type 2 diabetes subjects were randomly selected, 203 from Karnataka institute of endocrinology and research an urban diabetic centre and 200 from Bagalkot rural diabetic centre. Measurements of weight, height, and waist circumference were obtained using standardized techniques. The BMI was calculated using the following formula: weight (kg)/height (m^2). Blood pressure was recorded in the sitting position in the right arm. Two readings were taken 5 min apart, and the mean of the two values was taken as the final blood pressure reading. The study was approved and informed consent was obtained from all the participants.

A fasting and post prandial blood sample was taken for estimation of plasma glucose by hexokinase method. HBA1C was measured by the high-performance liquid chromatography method using the Bio-rad Variant 2 turbo analyser. Liver function tests and lipid profile were analyzed in cobot C 311 biochemistry analyzer by standard methods.

Diagnosis of diabetes was made by using ADA criteria of fasting plasma glucose ≥126 mg/dl and HBA1c ≥6.5%.

Inclusion criteria

Type 2 diabetes patients aged more than 18 years attending, Karnataka institute of endocrinology and research, Bangalore and Shri Tulasigirish diabetes hospital and research foundation, Bagalkot were randomly selected.

Exclusion criteria

Patients with history of consumption of alcohol, chronic liver disease, chronic kidney disease and on hepatotoxic drugs were excluded from the study.

Statistical Methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, **Assumptions: 1.**Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, Cases of the samples should be independent

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven`s test for homogeneity of variance has been performed to assess the homogeneity of variance. A t-test is a statistical test that is used to compare the means of two groups. It is often used in hypothesis testing to determine whether a process or treatment actually has an effect on the population of interest, or whether two groups are different from one another with the null hypothesis (H_0) is that the true difference between these group means is zero and the alternate hypothesis (H_a) is that the true difference is different from zero.

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Fisher exact test used when cell samples are very small.

Significant figures

+ Suggestive significance (P value: 0.05<P<0.10)
* Moderately significant (P value:0.01<P ≤ 0.05)
** Strongly significant (P value : P≤0.01)

Statistical software: The Statistical software namely SPSS 22.0, and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

RESULTS

Age distribution-18 to 90 years, male diabetes subjects were 64.8%, duration of diabetes range from new to >10 years, BMI range from <18.5 to >30 kg/square meters, waist circumference range from <80 cms to >100 cms of the total 403 patients studied.

Mean age 53.67±0.62, mean BMI 25.87±0.23, mean waist circumference 90.72±0.50, mean HBA1c-9.29±0.40, mean total cholesterol-176.63±3.22, mean LDL-112.21±1.54, mean HDL-41.20±0.42, mean triglycerides-150.36±4.33and mean bilirubin 0.64±0.02 mg/dl in the total number of 403 type 2 diabetes patients studied in this study done in 2 diabetic centres (one urban and one rural) in the state of Karnataka.

Table 1: Age distribution of patients studied.

Age in years	No. of patients	%
<20	1	0.2
20-30	13	3.2
31-40	50	12.4
41-50	90	22.3
51-60	128	31.8
61-70	92	22.8
71-80	23	5.7
>80	6	1.5
Total	403	100.0

Table 2: Gender distribution of patients studied.

Gender	No. of patients	%
Female	142	35.2
Male	261	64.8
Total	403	100.0

Table 3: Duration of diabetes in Months frequency distribution of patients studied.

DD Months	No. of patients	%
0	7	1.7
0-2	12	3.0
2.1-6	74	18.4
6.1-12	94	23.3
12.1-24	30	7.4
24.1-36	15	3.7
36.1-60	17	4.2
60.1-120	48	11.9
>120	106	26.3
Total	403	100.0

Table 4: BMI (kg/m^2) frequency distribution of patients studied.

BMI (kg/m^2)	No. of patients	%
<18.5	20	5.0
18.5-25	162	40.2
25-30	152	37.7
>30	69	17.1
Total	403	100.0

Mean ± SD: 25.87±4.66

Table 5: WCR-frequency distribution of patients studied.

WCR	No. of patients	%
<80	34	8.4
80-100	319	79.2
>100	49	12.2
NA	1	0.2
Total	403	100.0

Table 6: AST/ALT frequency distribution of patients studied.

	No. of patients (n=403)	%
AST units/L		
• <31	298	73.9
• >31	105	26.1
ALT units/L		
• <30	311	77.2
• >30	92	22.8

Table 7: Comparison of baseline clinical variables according to AST levels of patients studied.

variables	AST units/L		Total	P value
	<31	>31		
Age	53.98±0.72	52.78±1.26	53.67±0.62	0.398
DD months	89.46±5.61	29.89±5.37	73.94±4.57	<0.001**
BMI	25.74±0.25	26.23±0.56	25.87±0.23	0.354
WCR	90.74±0.59	90.66±0.95	90.72±0.50	0.942
SBP (mm Hg)	134.23±1.03	131.04±2.23	133.40±0.96	0.144
DBP (mm Hg)	80.83±0.74	80.84±0.90	80.83±0.59	0.995
FPG	161.10±3.89	165.45±6.80	162.23±3.38	0.572
PPPG	241.35±5.80	255.34±10.37	245.00±5.07	0.226
HBA1C %	9.37±0.46	9.09±0.80	9.29±0.40	0.763
TC	173.93±4.18	184.28±3.40	176.63±3.22	0.159
LDL	109.32±1.76	120.42±3.01	112.21±1.54	0.001**
HDL	40.50±0.50	43.16±0.70	41.20±0.42	0.005**
TG	155.97±5.65	134.43±4.09	150.36±4.33	0.029*
Total Bilirubin	0.61±0.02	0.72±0.03	0.64±0.02	0.006**
DIRECT	0.28±0.01	0.37±0.03	0.30±0.01	<0.001**
INDIRECT	0.37±0.03	0.37±0.02	0.37±0.03	0.967

Table 8: Comparison of baseline clinical variables according to ALT levels of patients studied.

variables	ALT units/L		Total	P value
	<30	>30		
Age	54.26±0.72	51.68±1.22	53.67±0.62	0.083+
DD months	74.35±5.30	72.53±8.98	73.94±4.57	0.867
BMI	25.64±0.26	26.64±0.48	25.87±0.23	0.071+
WCR	90.08±0.59	92.88±0.91	90.72±0.50	0.019*
SBP (mm Hg)	132.93±1.10	135.00±1.98	133.40±0.96	0.366
DBP (mm Hg)	80.60±0.70	81.60±1.04	80.83±0.59	0.482
FPG	157.75±3.73	177.38±7.54	162.23±3.38	0.014*
PPPG	235.32±5.49	277.68±11.60	245.00±5.07	<0.001**
HBA1C %	9.03±0.40	10.18±1.08	9.29±0.40	0.229
TC	176.27±4.02	177.81±3.81	176.63±3.22	0.841
LDL	112.07±1.72	112.67±3.43	112.21±1.54	0.871
HDL	41.48±0.47	40.23±0.91	41.20±0.42	0.208
TG	140.82±3.36	182.59±14.77	150.36±4.33	<0.001**
Total Bilirubin	0.61±0.02	0.75±0.04	0.64±0.02	<0.001**
DIRECT	0.28±0.01	0.38±0.04	0.30±0.01	<0.001**
INDIRECT	0.36±0.03	0.40±0.02	0.37±0.03	0.579

Table 9: Gender distribution of patients studied.

Gender`	AST units/L		Total
	<31	>31	
Female	109(36.6%)	33(31.4%)	142(35.2%)
Male	189(63.4%)	72(68.6%)	261(64.8%)
Total	298(100%)	105(100%)	403(100%)

Table 10: Gender distribution of patients studied.

Gender`	ALT units/L		Total
	<30	>30	
Female	124(39.9%)	18(19.6%)	142(35.2%)
Male	187(60.1%)	74(80.4%)	261(64.8%)
Total	311(100%)	92(100%)	403(100%)

AST was more than 31 units/L in 26.1% (105) and ALT was more than 30 units/L in 22.8% (92) of the type 2 diabetes individuals studied. Elevated ALT was found to have a statistically significant association with increasing waist circumference, increased fasting and post prandial glucose, increased triglycerides, total and direct bilirubin levels. Elevated AST was found to have a statistically significant association with increased LDL, TG, total and direct bilirubin levels.

DISCUSSION

J.West et.al in their study of 1353 patients included, 836 (61.9%) had type 2 diabetes. Elevated ALT was found in 9.5% (95%CI 7.1-12.3%) of patients with type 1 diabetes, and 12.1% (95%CI 9.9-14.5%) of those with type 2 diabetes. The risk of elevated ALT in patients with type 2 diabetes increased with increasing body mass index (p (trend) = 0.04), and was lower in those taking insulin.[8]

Shreyas saligram et al in their study found that ALT was elevated in 155 patients (25.6%) who tended to be older, heavier and more likely to be male with higher

triglycerides (median difference 0.2 mmol/l, $P = 0.001$) and lower HDL cholesterol (mean difference 0.09 mmol/l (0.02, 0.15), $P = 0.001$). There were no statistically significant differences in HBA1C or total cholesterol.[9]

Sami H.Alzaharani et al in their study of 211 type 2 diabetes patients found serum AST levels were elevated in 6.16% (10.3% in males, 4.2% in females). Elevated ALT levels were found in 7.58% (11.8% in males, 5.6% in females). No statistically noteworthy association was observed between elevated levels of AST and ALT with gender, age, body mass index (BMI), glycated hemoglobin (HbA1c), TG, total cholesterol (TC), LDL-C, and high-density lipoprotein cholesterol (HDL-C) levels, smoking, or hypertension.[10]

Gowri et al studied One hundred and thirty-seven patients with type 2 diabetes mellitus (47 males and 90 females) and found elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT) in 6.5% ($n = 9$) and 8.7% ($n = 12$) of their patients respectively. Male gender (OR = 2.97, CI: 0.88–9.95), and high triglycerides levels (OR = 2.03, CI: 0.58–7.09) were associated with increased risk of elevated ALT levels. The prevalence of elevated AST level increased with increased age (OR = 2.09 for patients aged 25–45 and OR = 2.77 for those who were over 65 years old) and increased triglycerides levels (OR = 8.51, CI: 1.03–70.07).[11]

It is proposed that the elevated levels of ALT in diabetic patients and metabolic syndrome are chiefly due to fat accumulation in the liver (12) Furthermore, elevated levels of ALT without any liver disease is usually taken as a surrogate marker of NAFLD (13) A proposed pathophysiological mechanism is that elevated transaminases may indicate inflammation that weakens insulin signaling in the liver systemically.[14,15]

The prevalence of abnormal LFTs was higher in the type 2 diabetes group than the prevalence observed in control group. The most frequent abnormal LFT was ALT (23.3%, 95%Cl=17%-30.2%) which was followed by AST (21.4%, 95%Cl=14.5%-28.3%). This is in line with the studies conducted in Finland (16), Scotland (17) and England (18) reported a 17%, 23.1% and 25.6% prevalence of abnormal ALT in T2DM patients, respectively.

Our study shows that AST was found to be >31 units/L in 26.1% (105) and ALT was >30 units/L in 22.8% (92) of the type 2 diabetes individuals studied. Elevated ALT was found to have a statistically significant association with increasing waist circumference, increased fasting and post prandial glucose, increased triglycerides, total and direct bilirubin levels. Elevated AST was found to have a statistically significant association with increased LDL, TG, total and direct bilirubin levels. The prevalence of elevated aminotransferase in our study was in accordance with previously reported high prevalence rates of aminotransferase elevation in patients with type 2 diabetes mellitus in other populations.

It is not practicable to do ultrasound scanning abdomen in all type 2 diabetes patients. So by analyzing ALT and AST levels, even if there is mild elevation of these enzymes such patients can be subjected for ultrasound scanning abdomen or fibrascan to rule out NAFLD. ALT is more specific to liver so elevated ALT levels should be given more importance than AST levels. Our study suggests that approximately about 20 to 25% of T2DM patients are at higher risk of developing NAFLD. In these individuals attention could be focused on modification of metabolic risk factors, such as weight loss, treatment of hypertension, control of dyslipidemia, tighter glycemic control, thereby potentially preventing significant mortality and morbidity.

CONCLUSIONS

AST was more than 31 units/L in 26.1% (105) and ALT was more than 22.8% (92) of the type 2 diabetes individuals studied. Elevated ALT was found to have a statistically significant association with increasing waist circumference, fasting and post prandial glucose, triglycerides, total and direct bilirubin levels. Marginal elevation of ALT levels without liver disease can be used as a marker to suspect NAFLD in type 2 diabetes.

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Abbreviations

DM-Diabetes mellitus
ADA-American diabetes association.
AST- aspartate aminotransferase
ALT- Alanine aminotransferase.
LFT-Liver function tests.
NAFLD-Non alcoholic fatty liver disease.
BMI-Body mass index.
LDL-Low density lipoprotein.
HDL-High density lipoprotein.
TG-Triglycerides
HBA1c-Glycosylated haemoglobin.

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