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Original Research Article

Liver Enzymes as Predictors of Risk of Diabetes among First Degree Relatives of Type 2 Diabetes Patients

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ABSTRACT

Background and objectives: Increased concentration of liver enzymes has been implicated in the pathogenesis of type 2 diabetes. The aim of our study was to determine the association between liver enzymes and risk of type 2 diabetes among first degree relatives (FDR) of type 2 diabetes patients.
Methodology: 150 non-diabetic FDR of type 2 diabetic patients were enrolled. Detailed history of participants was taken, followed by anthropometric measurements and estimation of biochemical parameters was done. According to American Diabetic Association criteria, the participants were classified into euglycemic, prediabetic and diabetic groups based on their fasting blood glucose value. The associations between liver enzymes and risk of diabetes were analyzed using correlation and receiver operating characteristic curve analysis (ROC).
Results: In the present study 150 FDR's of type 2 diabetic patients were grouped into euglycemic (54), pre diabetic (47) and diabetic (49). Statistically significant positive correlation between liver enzymes Gamma glutamyl transferase (GGT) Vs Aspartate Transaminase (AST) (r=0.394), GGT Vs Alanine transaminase (ALT) (r=0.466) & AST Vs ALT (r=0.630) was observed. ROC analysis of liver enzymes with fasting blood glucose showed the cut-off predictive values for type 2 diabetes were >29U/L, >21U/L and >16U/L for GGT, AST and ALT respectively. Area under the curve (AUC) value for GGT was more as compared to AST and ALT.
Conclusion: The present study showed that increased levels of liver enzymes within its normal range can predict risk of development of diabetes. Among the liver enzymes GGT emerged as a biomarker to assess the risk of diabetes among FDR of type 2 diabetic patients.

Key words: Type 2 diabetes, First Degree Relatives, Gamma Glutamyl Transferase, Aspartate Transaminase, Alanine transaminase.

INTRODUCTION

Diabetes mellitus is recognized as one of the leading cause of global death and disability across the world wide. According to world health organization (WHO) the total number of people with diabetes mellitus in 2000 was 171 million and it is expected to rise 366 million by 2030. [1] Obesity, dyslipidemia, hypertension and being first degree relatives of type 2 diabetic patients are considered as risk factor for the development of type 2 diabetes. [2]

Liver is an important organ involved in the metabolism of carbohydrates, lipids and proteins. It also plays a role in the maintenance of fasting as well as post prandial blood glucose levels. Liver functions are routinely assessed by

estimating liver enzymes such as GGT, AST and ALT.

Liver has been entailed in the pathogenesis of type 2 diabetes. Hepatic dysfunction results in Insulin resistance leading to development of type 2 diabetes. Serum AST and ALT are surrogate markers of hepatocellular health. Serum Gamma glutamyl transferase (GGT) has been used as a marker of hepatobiliary disease and alcohol consumption. [3]

Serum ALT is predominantly found in the liver cells and AST is present in liver as well as in other tissues like heart, skeletal muscles, kidneys, brain, pancreas, lungs, white blood cells and red blood cells hence ALT is considered to be the most specific marker of liver injury. Few studies have shown that excess deposition of fat in the liver termed as nonalcoholic fatty liver disease has strong association with obesity, insulin resistance and type 2 diabetes. [4-6]

GGT is an ectoplasmic enzyme which plays an important role in glutathione homeostasis. Considering the antioxidant activity of glutathione, increased level of GGT may be linked to greater oxidative stress. Increased oxidative stress has β cell dysfunction and decreased insulin action. Therefore, serum GGT activity could reflect several different processes relevant to diabetes pathogenesis. [7]

There are few prospective studies showing elevated levels of serum hepatic enzymes, within their normal reference range may be associated with increase in the risk of type 2 diabetes. [8,9, 10]

Hence the present study was designed to determine the association between liver enzymes and risk of diabetes among first degree relatives of type 2 diabetes patients.

METHODOLOGY

This was a cross sectional study conducted on first degree relatives of type 2 diabetic patients. The study was initiated after obtaining clearance from Institutional Scientific Committee and Institutional Ethics Committee of MIMS, Mandya. A total of 150 participants aged between 25-65 years were included. Participants with co-morbid conditions like alcoholism, hepatitis, liver disorders, myocardial infarction, thyroid disorders, renal disease, inflammatory disease or taking any other medications were excluded from the study.

The study was conducted at the Clinical Biochemistry section of Central diagnostic laboratory, MIMS, Mandya. Written informed consent was taken from the study participants. Detailed profoma was taken from the study participant; it includes Socio demographic history, family history, past history and treatment history.

Anthropometric measurements like height (cm) which was measured by stadiometer and weight by using analog weight scale. Body mass index (BMI) was calculated using the formula (weight in kg / height in m^2) and classified according to WHO (Table 1).

Table 1 Classification of BMI according to WHO [11]

BMI	Classification
< 18.5	Underweight
18.5–24.9	Normal weight
25.0–29.9	Overweight
≥ 30.0	Obesity

Waist circumference (WC) was measured at the level midway between the lower rib margin and the iliac crest. Blood pressure was measured by using mercury sphygmomanometer.

On the previous day of lab tests, patients were asked to fast at least 8-10 hrs and not to take any medications that affect carbohydrate metabolism. 3ml of fasting venous blood was drawn under aseptic precautions and collected into non-vacuum plain tubes with clot activator. The tubes were allowed to stand for about 25-30 minutes followed by centrifugation at 3500rpm for 15- 20 min. The serum was separated and processed in the Clinical Biochemistry section of Central Diagnostic Laboratory MIMS, Mandya using the fully automated clinical chemistry analyzer Abbott (ci4100) for parameters like glucose, total cholesterol (TC), triglycerides (TG), Low density lipoprotein (LDL), High

density lipoprotein (HDL), GGT AST and ALT.

Fasting blood glucose was measured by hexokinase method. TC was analyzed by cholesterol oxidase peroxidase CHOD-POD method. Triglyceride levels were estimated by glycerol peroxidase (GPO-PAP) method. Direct enzymatic assay was used for the estimation of HDL & LDL-C was calculated by using Friedewald's equation.

[LDL-C] = [Total-C] – [HDL-C] – [Triglyceride] / 5.

Friedewald's equation used in routine practice for LDL-c is not suitable for triglyceride value > 400 mg/dL; in such cases direct homogenous assay is performed.

GGT was measured by enzymatic method. The reference range of GGT by this method is 12-64 U/L. AST and ALT was measured by NADH (without P-5'-P) method and the reference range for AST is 5-34U/L and for ALT is 0-55U/L.

According to American Diabetes Association (ADA) [12] based on the FBS value the study subjects were classified into euglycemic (FBG<110mg/dl), prediabetic (110mg/dl - ≤125mg/dl) and diabetic groups (FBG ≥126mg/dl).

Statistical Methods:

The collected data were entered into Microsoft excel sheet and analyzed using SPSS 22.0, ver.3.2.2. Descriptive statistics like mean, percentage and standard deviation and inferential statistics like Analysis of variance (ANOVA), Chi-square/ Fisher Exact were used. P value <0.05 were considered statistically significant. Correlation was sought by Pearson's correlation. A receiver operating characteristic curve (ROC) analysis and Area under the curve of ROC was used to predict the outcome.

RESULTS

Among150 participants who were FDR'S of type 2 diabetic patients, 77(51%) were females and 73 (49%) were males. According to ADA criteria, based on their fasting blood glucose values, subjects were categorized into euglycemic, pre diabetic and diabetic (Table -2).

Table 2 - Distribution of study participants based on their fasting glucose values

Study Participants	Gender	
	Female	Male
Euglycemic	29(37.7%)	25(34.2%)
Prediabetic	23(29.9%)	24(32.9%)
Diabetic	25(32.5%)	24(32.9%)
Total	77(100%)	73(100%)

p> 0.05

As seen in Table 3, it was found that there was a statistically significant difference in WC, TC, TGL among study participants. Whereas BMI, LDL & HDL did not show significant difference among the study participants.

Table 3: Comparison of clinical variables according to FBS of patients studied

Variables		Fasting Plasma Glucose			P
		Euglycemic	Prediabetic	Diabetic	
BMI	< 25 kg/m^2	18	25	23	0.079
	≥25 kg/m^2	36	22	26	
WC	< 90 cm	34	17	17	0.004*
	≥ 90 cm	20	30	32	
TC	<200 mg/dl	36	33	23	0.039*
	≥200 mg/dl	14	18	26	
TGL	<150 mg/dl	33	17	15	0.005*
	≥150 mg/dl	21	32	34	
LDL	<100 mg/dl	19	12	12	0.393
	≥100 mg/dl	35	33	39	
HDL	≤ 35 mg/dl	27	20	20	0.213
	>35 mg/dl	27	27	29	

* Statistically significant p<0.05

Table-4 shows the distribution of mean values of GGT, AST & ALT among the various study group, it was found that, even though the levels of liver enzymes were within

the normal range, prediabetic and diabetic participants had higher values of GGT, ALT and AST as compared to euglycemic participants and it was statistically significant with p<0.05.

Table 4 - Distribution of mean values of biochemical parameters among study groups.

Biochemical parameters	Fasting Plasma Glucose			p value
	Euglycemic	Prediabetic	Diabetic	
GGT(IU/L)	21.78±9.35	34.57±17.95	35.78±20.82	<0.001*
AST(IU/L)	21.14±5.68	23.97±10.13	28.06±14.29	0.005*
ALT(IU/L)	21.57±9.70	26.21±14.01	28.57±17.51	0.037*

* Statistically significant p<0.05

Table-5 shows the correlation analysis between liver enzymes among study participants. It was found that statistically significant positive correlation between GGT Vs AST (r=0.394, P<0.001) GGT Vs ALT (r=0.466, P<0.001) and ALT Vs AST (r=0.630, P<0.001). This shows that GGT, AST and ALT were interrelated.

Table 5: Pearson correlation:

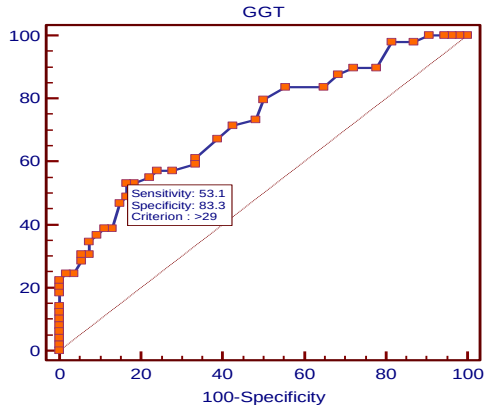
Pair	r value	p value
GGT(IU/L)vs AST(IU/L)	0.394	<0.001*
GGT(IU/L)vs ALT(IU/L)	0.466	<0.001*
ALT(IU/L)vs AST(IU/L)	0.630	<0.001*

* Statistically significant p<0.05.

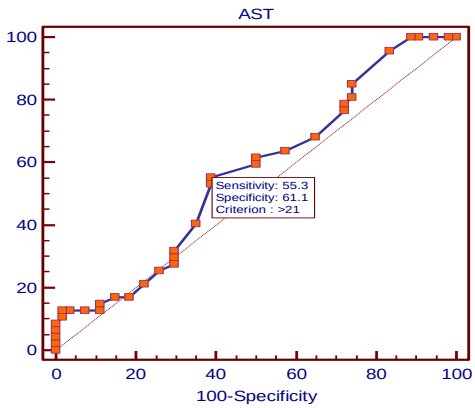
As seen in table 6,it was found that, the area under the curve (AUC) for GGT was 0.722 and the cut off value to predict diabetes was >29U/L (Graph 1), AUC for AST was 0.658 (Graph 2) with predictive value as >21U/L and for ALT, AUC was 0.617 (Graph 3) with predictive value of >16U/L. Area under the curve for GGT was more as compared to ALT and AST. Among the three liver enzymes, GGT emerged as an important biomarker to predict diabetes.

Table 6: ROC curve analysis

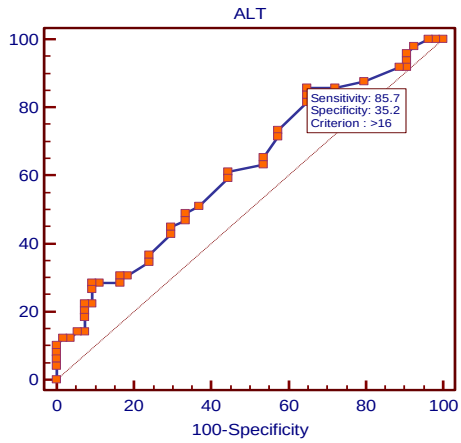
Variables	ROC results to predict diabetic				Cut-off	AUROC	SE	p value
	Sensitivity	Specificity	LR+	LR-				
GGT (IU/L)	53.06	83.3	3.18	0.56	>29	0.722	0.049	<0.001**
AST(IU/L)	67.35	61.11	1.73	0.53	>21	0.658	0.054	0.003**
ALT (IU/L)	85.71	35.19	1.32	0.41	>16	0.617	0.055	0.035*



Graph 1: ROC curve to compare GGT with fasting blood glucose level



Graph 2: ROC curve to compare AST with fasting blood glucose level



Graph 3: ROC curve to compare ALT with fasting blood glucose level

DISCUSSION

Diabetes mellitus is a syndrome of disordered metabolism with abnormally high blood glucose levels. Type 2 DM has a strong genetic component. First degree relatives of type 2 diabetic patients are

considered as high risk group for developing diabetes according to ADA criteria. [2]

The liver is a large, complex organ designed for its important role in carbohydrate, protein and lipid metabolism. Markers of liver injury, such as GGT, AST and ALT have been shown to be good surrogate markers of non-alcoholic fatty liver disease. This chronic liver condition is characterized by excess deposition of fat in the liver and is associated with hepatic insulin resistance and development of type 2 diabetes. [10]

Few prospective studies have found that high levels of GGT are an independent risk factor of diabetes. Aminotransferases such as AST and ALT are considered as sensitive indicators of liver cell injury and are helpful in diagnosing hepatic diseases but chronic mild elevations of liver enzymes are frequently found in type 2 diabetes patients. [3,13,14]

Our study results as shown in Table 3were in accordance with the study done by Ko SH et al where they observed that higher percentage of patients with type 2 diabetes had increased BMI, WC, BP and altered lipid profile as compared to non-diabetes subjects. [15]

In our study we found that although the liver enzymes were within the normal range, prediabetic and diabetic FDR's had higher concentrations of GGT, AST and ALT as compared to euglycemic study participants. This is in concurrence with the study done by Wang YL et al, he demonstrated that type 2 diabetes patients had higher levels of liver enzymes as compared to controls. [16] (Table 4)

Elevated GGT levels may be linked to three possible mechanisms for increasing the risk of type 2 diabetes. Nonalcoholic fatty liver disease may lead to elevation of serum GGT through hepatic insulin resistance and hyperinsulinemia.GGT serves as oxidative marker which plays an important role in the antioxidant system. Another possible mechanism is by subclinical inflammation which also contributes to the development of type 2 diabetes. [7]

As seen in Table 5correlation analysis of liver enzymes showed that there was statistically significant positive correlation between the liver enzymes among the study participants indicating that the liver enzymes were moderately interrelated. Similar observations were made by Wannamethee SG et al in their prospective study where they showed that correlation coefficient between the liver enzymes was significantly higher in those who developed diabetes. [9]

According to the results (Table 6) of ROC curve analysis, cutoff predictive values for type 2 diabetes were29U/L for GGT, 21U/L for AST and 16U/L for ALT. The sensitivities and specificities of the cut off points were 53.06% and 83.3% for GGT, 67.35% and 61.11% for AST and 85.7% and 35.19% for ALT. Wang YL et al in their study on Chinese population showed that increased levels of GGT and ALT are associated with increased risk of type 2 diabetes and the best cut off values for GGT and ALT in their study were 23U/L and 21U/L respectively. [16]

As seen in Graph 1, 2 & 3 GGT, AST and ALT are associated with risk of developing diabetes in the study population but the increase in the risks associated with ALT & AST was substantially lower than that related to serum GGT.

Limitations:

There are few limitations in the present study; oral glucose tolerance test was not performed to categorize the study subjects into euglycemic, prediabetic and diabetic. In the present study single measurement of liver enzymes and fasting blood glucose were used, which can vary within the individuals at various time.

CONCLUSION

Our study suggests that liver enzymes are closely associated with the risk of diabetes among FDR's of type 2 diabetic patients but on comparison serum GGT

emerged as the most powerful predictor for developing diabetes. The cut off values were 29U/L, 21U/L and 16 U/L for GGT, AST and ALT respectively. The measurement of liver enzymes is simple, inexpensive and well standardized procedures. Therefore liver enzymes can be used as convenient markers to identify people at higher risk for developing diabetes.

Conflict of interest: None
Source of support: Nil

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