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Research Article

ELEVATED LIVER ENZYMES AS PREDICTOR FOR TYPE 2 DM IN HIGH RISK INDIVIDUALS

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ABSTRACT

Background: The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. According to the World Health Organization, at least 171 million people world wide have diabetes. This figure is likely to double by 2030. The WHO predicts that developing countries will bear the brunt of this epidemic in the 21st century.

Aim &Objective: To test the hypothesis that elevated liver enzymes conventionally associated with liver dysfunction predict the occurrence of type2 diabetes in high risk individuals.

Methods: About 100 nondiabetic subjects aged between 30-59 years who had risk factors for diabetes defined by the ADA and had elevated liver enzymes were included and followed up for FBS and PPBS at one year.

Results: GGT was found to have positive association with FBS ($r = 0.58$ and $P < 0.001$) and PPBS ($r = 0.43$ and $P < 0.001$) and ALT was also found to have positive association with FBS ($r = 0.53$ and $P < 0.001$) and PPBS ($r = 0.48$ and $P < 0.001$). These enzymes were also found to have positive correlation with BMI (GGT: $r = 0.22$ and $P < 0.05$ and ALT: $r = 0.20$ and $P < 0.05$) Systolic Blood Pressure (GGT: $r = 0.34$ and $P < 0.01$ and ALT: $r = 0.32$ and $P < 0.01$). There was a negative correlation with HDL (GGT: $r = -0.23$ and $P < 0.05$ and ALT: $r = -0.20$ $P < 0.05$) and positive with Triglyceride levels (GGT:$r= 0.52$ and $P < 0.001$ and ALT: $r = 0.48$ and $P < 0.001$). At the end of one year 3 subjects who were nondiabetic had raised fasting glucose levels and became glucose intolerant.

Conclusion: Our study findings indicate that elevated levels of liver enzymes mainly GGT and ALT are markers of risk of type2 diabetes in high risk individuals and suggests a potential role of the liver in the pathogenesis of type2 diabetes mellitus.

INTRODUCTION

Diabetes Mellitus is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both[1].Diabetes is accompanied by progressive tissue damage secondary to micro and macrovascular complications. It is the leading cause of End-Stage Renal disease, a major cause of non-traumatic amputations, responsible for 30% of the preventable blindness and a leading cause of cardiovascular mortality. The prevalence of diabetes is rapidly rising all over the globe at an alarming rate[2].

According to the World Health Organization, at least 347 million people worldwide have diabetes. The WHO predicts that developing countries will bear the brunt of this epidemic in the 21st century.

WHO reports show that 32 million people had diabetes in India in the year 2000 and this number is likely to be 71.4 million in 2030[2].The identification of elevated liver enzymes may provide very powerful tool to identify individuals at high risk of diabetes who may be amenable to intervention, there by reducing the risk of developing diabetes and its complications.

Aims & Objectives

To test the hypothesis that elevated liver enzymes, conventionally associated with liver function may predict the occurrence of Type 2 Diabetes Mellitus in high risk individuals.[3]

MATERIAL & METHODS

This study included 100 non-diabetic subjects aged between 30 to 59 years, who attended the outpatient department at Santhiram medical college, Nandyal.

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Subjects with High Risk (defined by American Diabetes Association) were identified by detailed history and clinical examination.

Exclusion criteria

- Those subjects who had previous history of jaundice, elevated liver enzymes more than 3 times the normal limit (infective hepatitis) were excluded.
- Subjects who were alcoholic were excluded as alcohol was thought to act as a confounding factor for elevated liver enzymes.

History was taken mainly to know any family history of diabetes in a parent or sibling, history of gestational diabetes, hypertension and ischemic heart disease.

Clinical examination was mainly done to identify hypertensive subjects (BP >140/90mmHg) and to record height (in mts) and weight (in kgs) Body mass index was calculated by the Broca's formula.

Inclusion Criteria of High Risk Individuals

Family history of diabetes, BMI >25kg/m2, Physical inactivity, History of GDM or delivery of baby >4kg, Hypertension (BP >140/90mmHg), HDL cholesterol < 35mg/dl and for TG >250mg/dl, PCOD or acanthosis nigricans and History of vascular disease Elevated liver enzymes in the range of upper normal limit i.e., between 30-40 U/L for ALT, AST and GGT and 90-112U/L for ALP and increased not more than 1.5 times the normal limit were considered.

After detailed history and examination, the following baseline investigations were performed. Blood routine, LFT's i.e., SGOT, SGPT, GGT and ALP: by ERBA commercial kit, FBS, PPBS: by commercially available kit., Lipid profile: Cholesterol, HDL, CDL and TG's by commercially available kits, Renal profile: Blood urea and serum creatinine. and USG abdomen. All patients who had liver enzymes in the upper normal limit or elevated less than 1.5 times the normal limit were included and followed after 1 year.

RESULTS

Out of 100 subjects in our study 67 were males and 33 were females.
Table – 1: Sex Distribution
Male Female Total
Number 67 33 100
Percent (%) 67 33 100

All the subjects were between the defined age limit between 30 – 59 yrs.

The minimum age being 30 yrs and maximum being 58 yrs. The mean age was 42.9 ± 8.3 yrs

Table 2 Age and Sex Distribution in the Study

Age	Male	Female	Total
30-39	22	18	40
40-49	26	12	38
50-59	19	03	22

Most of the subjects were in the age group of 30-39 years,40%. This was followed by the age group 40 – 49 yrs (38%) and then in the age group of 50 – 59 yrs (22%).

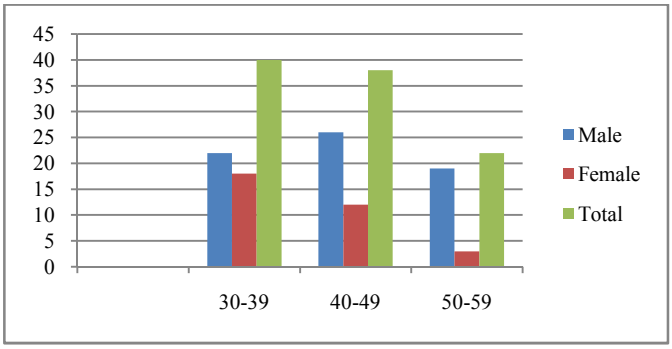


Table 3 Percentage Risk Factors in Study Group

Risk Factor	No. of Cases	Percentage
Family History of Diabetes	39	39.00
Obesity	50	50.00
Physical Inactivity	00	0.0
History of Gestational Diabetes	02	02.00
Hypertension	48	48.00
HDL≤ 35, TG ≥ 250	02	02.00
History of Vascular Disease	10	10.00
PCOD	08	08.00

In our study, 39% of the subjects had family history of parent or sibling with diabetes.

Fifty percent of the subjects were obese defined as BMI ≥ 25 Kg/m2.

Forty eight percent of the subjects had either the history of hypertension or were found to be hypertensive on examination.

Ten percent of the subjects had history of ischemic heart disease.

Eight subjects had polycystic ovarian disease diagnosed by ultrasound of abdomen and pelvis.Two subjects had history of gestational diabetes and one had HDL ≤ 35 mg/dl and one had triglycerides > 250 mg/dl.

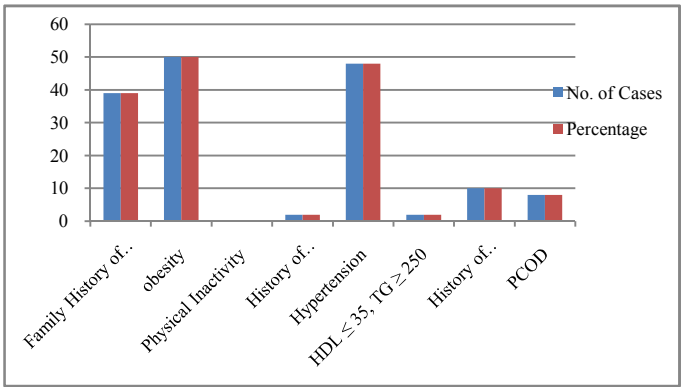
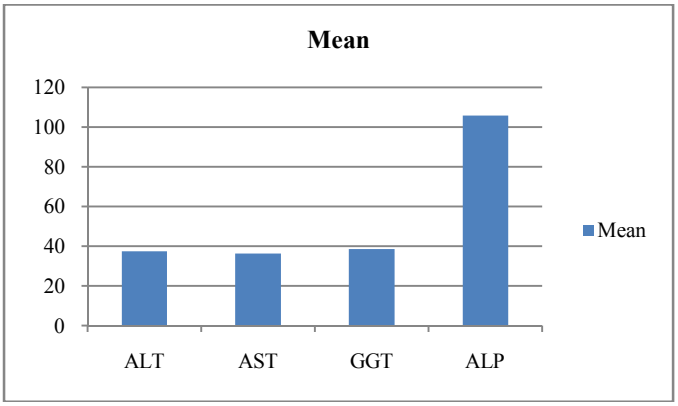


Table 4 Mean Enzyme Levels

Enzyme U/L	Mean	SD
ALT	37.45	± 7.3
AST	36.23	± 4.5
GGT	38.55	± 6.7
ALP	105.75	± 12.10



The mean level for ALT was 37.45 with a standard deviation (SD) of ± 7.3. The lowest level being 30U/L and highest being 60 U/L.

Mean level for AST was 36.23 and a SD of ± 4.5. Lowest value was 30 U/L and the highest was 49 U/L.

Mean level for GGT being 38.55 and a SD of ± 6.7. Lowest value is 30 U/L and highest being 58 U/L.

The mean level for ALP was 105.75 with a SD of ± 12.10, lowest being 90 U/L and highest being 147 U/L.

Table 5 Subjects with More than one Risk Factor

More than 1 risk factor	No. of cases	Percent
Family history and HTN	11	11
Obesity and HTN	22	22
Obesity and history of vascular disease	04	04
HTN and history of vascular disease	07	07
PCOD and obesity	04	04

Eleven subjects (11%) had family history of diabetes and also were hypertensive.

Twenty two subjects (22%) were obese and also were hypertensive.

Four subjects (4%) who were obese had the history of vascular disease.

Seven subjects (7%) who were hypertensive also had history of vascular disease.

Four subjects (4%) who had PCOD were obese and 9 subjects (9%) had 3 risk factors (not shown in the table).

Table 6 Mean Enzyme Levels in Three Important Risk Group

Risk Factor	ALT	AST	GGT	ALP
Family history	35.89	35.37	37.51	108.51
Obesity	39.02	36.95	40.14	107.31
HTN	39.28	36.05	39.52	105.66

The mean level of GGT was higher in obesity group and the mean level of ALT was higher in hypertensive group.

Table 7 Mean Fasting and Post Prandial Glucose Levels at Baseline

Blood Glucose (mg/dL)	Mean	SD
FBS	91.89	± 7.7
PPBS	114.90	± 12.32

The mean FBS at baseline was 91.89 mg/dl with a SD of ± 7.7 and the mean

PPBS at baseline was 114.90 mg/dl with a SD of ± 12.32.

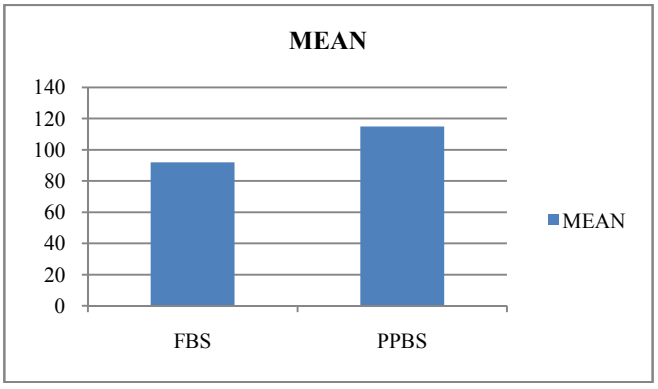


Table 8 Mean Serum Lipid Profiles

Lipid Profile (mg/dL)	Mean	SD
Cholesterol	193.6	± 35.99
HDL	39.92	± 2.5
LDL	131.5	± 30.9
Triglycerides	133.1	± 38.46

The mean cholesterol level was 193.6 mg/dl with a SD of ± 35.99.

The mean HDL was 39.92 mg/dl with a SD of ± 2.5.
Mean level for LDL was 131.5 mg/dl and a SD of ± 30.9.
Mean TG level was 133.3 mg/dl with SD ± 38.46.

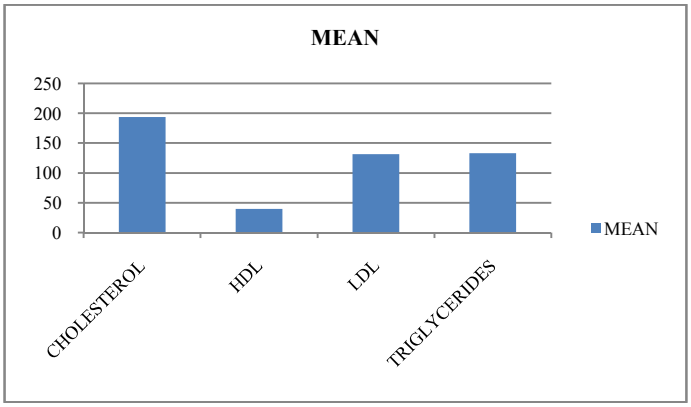


Table 9 Age Group and Mean Lipid Profile

Age Group	Cholesterol mg/dl	HDL mg/dl	LDL mg/dl	Triglycerides mg/dl
30-39	187.12	48.72	121.92	119.12
40-49	201.79	39.29	130.14	138.76
50 - 59	189.04	39.85	136.35	130.68

As shown in Table – 9, the mean cholesterol levels increased as the age increased and so did the LDL and triglycerides when compared to the age group 30-39 years with that of 40-49 years.

The mean HDL decreased as the age increased.

There is a slight decrease in the mean cholesterol and triglyceride level when compared to the age group 40-49 years with that of 50-59 years.

This may be due to small number of subjects in that group when compared to the other two age groups and also may be

due to the acceptance of life style modification measures at this age as they were already having risk factors or may be due to the reason that they are being treated for the co-morbid conditions like hypertension or ischemic heart disease.

Table 9 Mean FBS and PPBS Levels at One Year

Blood Glucose (mg/dL)	Mean	SD
FBS	97.21	± 6.90
PPBS	122.80	± 11.62

The mean FBS at one year follow up was 97.21 mg/dl and a SD ± 6.90

The mean PPBS at one year follow up was 122.80 mg/dl and a SD of ± 11.62.

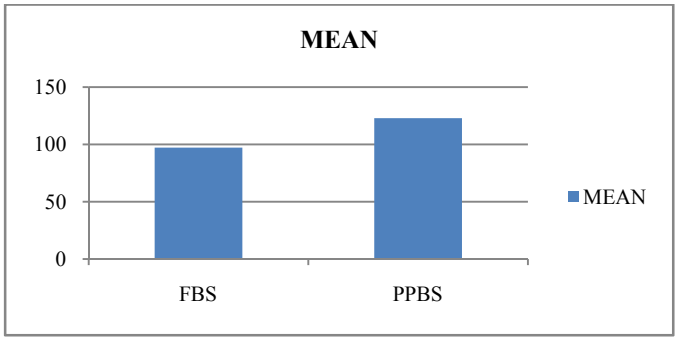


Table 10 Percentage Increase in FBS and PPBS at One Year

mg/dl	Mean at Baseline	Mean at 1 year	% increase at 1 year	Z score	P value
FBS	91.89	97.21	5.78	5.16	< 0.001
PPBS	114.90	122.80	6.87	4.67	< 0.001

The mean FBS at baseline and at one year in the study increased.

Z = 5.16 and P < 0.01 (significant)

The mean PPBS at baseline and at one year in the same group also increased

Z = 4.67 and P < 0.01 (significant)

Correlation Co-efficient (r) was calculated to know the association between the enzymes namely ALT, AST, GGT and ALP and the fasting blood sugar and PostPrandial blood sugar.

DISCUSSION

Insulin resistance is a central feature in the pathogenesis of type 2 diabetes. It is present in subjects at high risk for diabetes and it is found to predict the development of diabetes in prospective studies. Aminotransferases are considered indicators of hepatocellular health. ALT is found primarily in liver, AST and GGT are also found in other tissues. The liver plays an important role in maintaining normal glucose concentrations during Fasting as well as Post Prandial state. It is also a major site of insulin clearance.

A number of recent studies have suggested that abnormal hepatocellular function is associated with obesity, insulin resistance and type2 diabetes. Non alcoholic fatty disease is also associated with elevation of liver enzymes, raising the possibility of relationship between elevated liver enzymes and type2 diabetes.Direct measurement of liver fat requires imaging modalities like ultrasound, computed tomography or proton spectroscopy and such techniques are unlikely to be recommended for routine clinical practice. Though ultrasound is easily available and cheap among them, the sensitivity and specificity is about 65% and also observer dependent. Measurement of insulin resistance requires the use of techniques (including clamps and intravenous glucose tolerance tests) that are far too costly, time consuming and invasive for clinical studies. A number of studies have been reported that ALT, AST and GGT levels independently predict incident type2 diabetes, metabolic syndrome and cardiovascular disease. Thus these liver markers which are inexpensive and routinely collected in clinical settings may provide a simple and accurate enhancement to models currently used to identify subjects with insulin resistance. Though all the studies done earlier were long term prospective studies and involved general population we wanted to know the association between liver enzymes and incident type 2 diabetes in high risk individuals, in relation to shorter duration of time i.e., one year. Hence this study was undertaken with the objective of testing the hypothesis that elevated liver enzymes can predict the onset of type2 diabetes mellitus in high risk individuals.

In our study, among 100 non diabetic subjects at baseline 3 subjects (3%) had become impaired glucose tolerant (IGT). This is in conjunction with the studies conducted by Naveed Sattar, Olga S.*et al*[5] (2.33%) and Perry IJ, *et al*[6]. Thus the hypothesis that elevated liver enzymes are the predictors of type2 diabetes mellitus cannot be ruled out. Further when individual enzymes are evaluated we found that Gamma-Glutamyl Transferase gives a stronger prediction of Impaired Fasting Glucose / Impaired Glucose Tolerance and also type2 diabetes. This is in conjunction with the findings of the studies conducted by Monica Nannipieri *et al*[3]., Sasiwarang GW. *et al*(RR:ALT-2.72,GGT-3[7].), Matteo M. *et al*.(2.54%), Perry IJ. *et al*[6]., N. Nakanishi *et al* and Andre P. *et al*[9]. Studies conducted by Anthony JG. *et al*[8]., Barbora Vozarova *et al*[4]., Naveed ,Sattar *et al* [5]have also shown that elevated levels of ALT also predicts IGT/ Type2 diabetes and our study also predicts the same.

Other enzymes like AST also showed prediction but the strength of association was not as much as seen for the GGT and ALT. The same was noted by Monica Nannipieri *et al* (OR:AST-1.9,GGT-1.8,ALT-1.6). In our study we did not find any association between ALP levels and the prediction of type2 diabetes. This corresponds with the study done by Barbora Vozarova *et al*[4]. And also when the mean enzyme levels were studied according to the risk factors, the levels were found to be higher in obese risk group followed by hypertensive group.

As most of the studies have included general population unlike in our study, where we had selected subjects with high risk factors for the development of type2 diabetes, there was no evidence for comparison of mean liver enzyme levels in each risk group.

The mean fasting blood glucose was raised from baseline by 5.78% at one year (P < 0.001) and mean post prandial blood glucose was raised by 6.87% (P < 0.001) at one year when

compared to baseline sugar levels. This increase was statistically significant.

Our study also showed a positive correlation of liver enzymes with BMI which is an important risk factor for the development of type2 diabetes mellitus. The association being more for GGT and ALT, the same was seen by AJG Hanely *et al*., and Ian Perry *et al*[6].

Limitations of our study

- The first being the duration of the study. If studied for a longer period of time, it can predict onset of type2 diabetes.
- The second is that the laboratory reference ranges for liver enzymes are not standardized as they are in the western world.

CONCLUSION

In our study we were able to conclude the following:

- Elevated liver enzymes at baseline predict the onset of IGT. Hence the hypothesis that elevated liver enzymes predict the onset of type2 diabetes in high risk individuals cannot be ruled out.
- GGT had the highest association for prediction of IGT. Elevated ALT also had positive association for prediction of IGT.
- Elevated AST and Alkaline Phosphatase did not predict IGT/ type2 diabetes.
- Elevated liver enzymes in our study also have association with BMI; hence these can be the markers of obesity.
- There is definite association between GGT, ALT and incident diabetes and the strength of association can be increased by longer duration of the study.
- Thus elevated liver enzymes especially GGT and ALT act as an independent risk factors in prediction of Impaired Glucose Tolerance and hence they can be used as reasonable, cheap, surrogate markers in high risk individuals. This will help in early detection of insulin resistant states and appropriate intervention contributing to decrease the burden of this global pandemic.

Summary

About 100 non-diabetic subjects aged between 30-59 years who had one or more risk factors according to ADA and elevated liver enzymes, who had attended outpatient department at Santhiram Medical College, Nandyal during December 2011 to May 2012 were included and studied.

During the follow up, 3 subjects, who had elevated liver enzymes, had increased FBS/ PPBS to IFG/ IGT levels, predicting the occurrence of diabetes. The liver enzymes mainly GGT and ALT were positively associated with body mass index, systolic and diastolic blood pressure and triglycerides and negatively associated with HDL.

In our study, GGT was found to have positive association with FBS ($r = 0.58$ and $P < 0.001$) and PPBS ($r = 0.43$ and $P < 0.001$) and ALT was also found to have positive association with FBS ($r = 0.53$ and $P < 0.001$) and PPBS ($r = 0.48$ and $P < 0.001$). These enzymes were also found to have positive correlation with BMI (GGT: $r = 0.22$ and $P < 0.05$ and ALT: $r = 0.20$ and $P < 0.05$) Systolic Blood Pressure (GGT: $r = 0.34$ and $P < 0.01$ and ALT: $r = 0.32$ and $P < 0.01$). There was a negative correlation with HDL (GGT:$r = -0.23$ and $P < 0.05$ and ALT: $r = -0.20$ $P < 0.05$) and positive with Triglyceride levels(GGT: $r = 0.52$ and $P < 0.001$ and ALT: $r = 0.48$ and $P < 0.001$).

Thus elevated liver enzymes especially GGT and ALT act as independent risk factors in prediction of impaired glucose tolerance and hence they can be used as reasonable, cheap, surrogate markers in high risk individuals.

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