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Association Of C-Peptide Based Insulin Resistance With Liver Biomarkers In Type 2 Diabetes Mellitus.

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ABSTRACT

Objectives of our study were to compare liver markers in type 2 diabetic patients with that in non-diabetic healthy volunteers and also to find the correlation between insulin resistance and liver markers.We also aimed to find out whether PON1 can be an alternative liver marker. The cross sectional study was conducted in the Clinical Biochemistry laboratory. 114 type 2 DM patients in the age group 18-65 years, diagnosed as per ADA guidelines were included in the study.100 age and gender matched non diabetics,healthy volunteers or those having health packages were chosen as controls.Blood sample was collected and fasting blood glucose, AST,ALT and Alkaline phosphatase, total bilirubin, ,direct bilirubin,total protein , albumin and insulin were estimated. HOMA-IR was calculated.Statistical analysis was carried out using SPSS 16. A significant elevation was seen in AST, ALT, ALP, GGT, TB, DB, TP, A:G ratio in diabetics. A lowered albumin and A:G ratio were observed in diabetics compared to controls.Fasting C-peptide levels were 1.26 times higher in controls compared to diabetics. Homeostatic model for assessment of insulin resistance (C-peptide based) was 3.5 times higher in T2DM compared to controls.20/(fasting C peptide x fasting plasma glucose) levels was 1.45 times higher in controls. C-pepide based HOMA-IR had a significant negative correlation with albumin (r=-0.230 and P=0.035). We conclude that diabetic patients had high liver enzymes as compared to non-diabetics. An association was found between type 2 diabetes mellitus, liver markers and insulin resistance.

Keywords: insulin resistance, diabetes mellitus, liver markers

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INTRODUCTION

Liver disease is reported to be one of the important causes of death in diabetes mellitus (DM). A population-based diabetes study by De Marco et al reported that cirrhosis accounted for 4.4% of diabetes related deaths (1). In a study Balkau B et al suggested that cirrhosis accounted for 12.5% of deaths in DM(2). Various reports suggest that diabetes is becoming one of the commonest causes of liver disease. A spectrum of liver disorders can occur in DM. Trombetta et al suggests that prevalence of diabetes in cirrhotics is 12.3 - 57%(3). These suggest higher prevalence of DM in liver diseases. The cause and effect relationship between diabetes mellitus and liver disease are yet to be established in our settings. Since this is a less explored area,we would like to find an association between liver markers and insulin resistance, which are associated with type 2DM.

Rationale of the study:As insulin resistance (IR) is associated with DM as well as liver disorders,it is justifiable to measure liver markers in diabetics. As traditional liver markers proved to be nonspecific in identifying liver disorders,a better non invasive marker needs to be explored. Hence This is an attempt to find out whether paraoxanase 1(PON1) can be a better marker compared to traditional liver markers. It is very much essential to find out the relationship between insulin resistance, liver markers and diabetes mellitus.

Insulin resistance and DM

Insulin resistance is a condition where cells are non-responsive to insulin. IR is associated with type 2 diabetes mellitus(4).IR measured by HOMA-IR, is found to have certain limitations in patients with low BMI, decreased β cell function and high fasting blood glucose (5). C-peptide and insulin are secreted in equimolar ratios.C-peptide has a longer half life as it is not cleared by liver. Studies suggest that C-peptide based index, 20/ (Fasting C-peptide x FPG) is a better index for IR compared to HOMA-IR (6).

IR and liver disorders

IR is independently associated with NAFLD and a close association was found between NAFLD and metabolic syndrome (7).NAFLD is in turn consistently associated with DM.

Since IR is associated with both DM and liver disorders, liver markers could be elevated in DM.

DM & Liver markers

Clinical trials report suggests that serum ALT, AST or alkaline phosphatase were 1-2.5 times higher in type 2 DM (8). In a retrospective study, we found ALT and AST were 1.3 and 1.4 times respectively higher in diabetes patients . It has been suggested that diabetics have an inclined tendency towards alterations of liver enzymes (9). Increased activity of the liver enzymes is associated with Insulin resistance.

From literature review, association between IR &DM, DM & liver disorders ,Liver disorders and IR is evident. However the cause and effect relationship among these is not well established . This necessitates a study which explores an association between insulin resistance and liver markers. It has been widely accepted that standard biochemical tests which assess liver functions have low sensitivities. Histo-pathological study of liver biopsy sample is the gold standard. Invasive procedure and complications are its limitations. Hence, a reliable, accurate and noninvasive hepatic biomarker is needed. Under such circumstances parameter of choice appears to be paraoxanase1(PON1), which originates from liver and its gene expression is confined to liver.
It is interesting to note that PON1 is antioxidant enzyme ,associated with DM,IR as well as liver disorders.

PON1 , IR and DM

PON1 is HDL bound antioxidant ,found to be significantly reduced in diabetics with insulin resistance.It has also been suggested that PON1 activity is positively correlated to IR, as assessed by HOMA index(10).

PON1 & liver disorders

PON1 has been reported to be reduced significantly in acute viral hepatitis, chronic hepatitis , cirrhosis and sepsis (11).Theses findings suggest that PON1 activity assay may serve as an useful additional test in evaluation of liver conditions.

All the published data are international, there are a few national studies which focus on IR, liver markers and PON1 to the best of our knowledge.

Research hypothesis

We hypothesize that

- liver biomarkers are positively associated with C-peptide based insulin resistance in diabetics
- possibility of elevation of liver markers is high in diabetics
- PON1 is a sensitive liver marker compared to routine markers in DM.

Objectives

Aims of our study were to

- compare liver markers in type 2 diabetic patients with that in non-diabetic healthy volunteers
- find the correlation between C-peptide based insulin resistance and liver markers
- find out effectiveness of PON1 activity as a liver biomarker as compared to traditional liver parameters

METHODOLOGY

Study design

The cross sectional study was conducted in the Department of Biochemistry. Institutional ethics committee approval was sought before starting the study. Informed consent was obtained from the subjects.

Inclusion criteria

Hundred and fourteen type 2 DM patients (18-65 years), diagnosed as per ADA 2016 guidelines were included as cases. Hundred age and gender matched non diabetics, healthy volunteers or those having health packages undergoing surgery were considered as controls.

Exclusion criteria

Alcoholics, diagnosed cases of acute and chronic hepatitis, other liver disorders.

Sample collection and analysis

Five ml of fasting venous blood sample was collected using aseptic precaution. Blood sample was centrifuged at 3000 rpm for 20 min and serum was separated. Fasting blood glucose , AST,ALT , Alkaline phosphatase, GGT, total bilirubin, direct bilirubin, total protein and albumin were estimated using fully automated chemistry analyzer, Cobas C-311. Fasting C-peptide was assayed by using ELISA.

Insulin resistance was calculated by the formula,

$$20/ (\text{Fasting C-peptide} \times \text{FPG}) \quad \text{and}$$

$$\text{HOMA –IR by C-peptide} = \text{fasting glucose} \times \text{fasting C-peptide} / 22.5$$

C-peptide expressed in µ U/L ,glucose in mmol/l.

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PON1 activity was assayed using spectrophotometric method (12).

Statistical analysis

Statistical analysis was done using the software, SPSS version 16.

Mann Whitney U test was used to compare liver markers in diabetics and non-diabetics. Spearmann's correlation coefficient was used to find the correlation liver markers and insulin resistance. Receiver Operative characteristic curve (ROC) was constructed to find out the whether PON1 can be used as an alternative liver marker.

RESULTS

Fasting C-peptide levels were 1.26 times in controls compared to diabetics. In liver profile, total bilirubin, direct bilirubin, liver enzymes like AST, ALT, ALP, GGT were higher 1.2, 1.12, 1.63, 1.43, 1.09, 1.59 times respectively in cases compared to controls. Albumin levels were decreased and total protein and globulins were increased significantly in cases compared to control. Homeostatic model for assessment of insulin resistance (C-peptide based) was 3.5 times higher in T2DM compared to controls.20/(fasting C peptide x fasting plasma glucose) levels was 1.45 times higher in controls.

There was no significant correlation was found between C-peptide levels and liver function tests. C-pepide based HOMA-IR had a significant negative correlation with albumin (r=-0.230 and P=0.035). 20/(fasting C peptide x fasting plasma glucose) had a significant positive correlation with albumin (r=0.261, P=0.016).

Table 1 Comparison of Liver markers and insulin resistance in diabetics and non-diabetics

	CASES(T2DM)	CONTROLS (Non diabetics)	P VALUE
C -peptide (NMOL/L)	0.94±0.07	1.1862±0.079	0.046*
TP (G/dl)	7.47±0.06	7.22±0.06	0.01*
ALB(G/dl)	4.1±0.04	4.2±0.057	0.026*
Globulin (G/dl)	3.2 ± 0.78	1.4± 0.49	0.000**
A:G ratio	1.29±0.03	1.48±0.03	<0.0001**
TB (mg/dl)	0.94±0.066	0.78±0.96	0.026*
DB (mg/dl)	0.37±0.03	0.33±0.05	0.016*
AST (U/L)	52.28±5.75	32.1±3.6	0.0179*
ALT (U/L)	40.17±3.74	28.1±3.845	0.0001***
ALP (IU/L)	94.54± 2.96	86.5± 3.91	0.04*
GGTP(U/L)	68.09±13.44	42.89±5.2	0.011*
GLU (mg/dl)	192.7±9.12	105.97±2.29	0.000***
GLU (mmol/l)	10.69±0.50	5.88±0.12	0.000***
HOMA-IR(C-peptide based)	1.27±0.14	0.36±0.038	0.000***
20/ (Fasting C-peptide x FPG)	4.99±0.65	7.25±1.39	0.041*
PON 1 (nmol/ml/min)	0.84±0.03	0.69±0.04	0.003**

*P<0.05 is significant
**P< 0.01 highly significant
***P<0.001 very highly significant

When the utility of PON1 as a biomarker of liver disease, it was observed that ,PON1 was not a good liver marker in T2DM.Liver transaminases, especially ALT and AST were good markers (AUC =1 and 0.908 respectively whereas that for PON1 was 0.472).GGT was a better marker compared to ALP (AUC 0.848 VS 0.720) .

A significant positive correlation was observed between PON1 and HOMA-IR (P=0.000), PON and insulin (P=0.015).

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Fig 1: ROC for PON 1 and Liver Markers

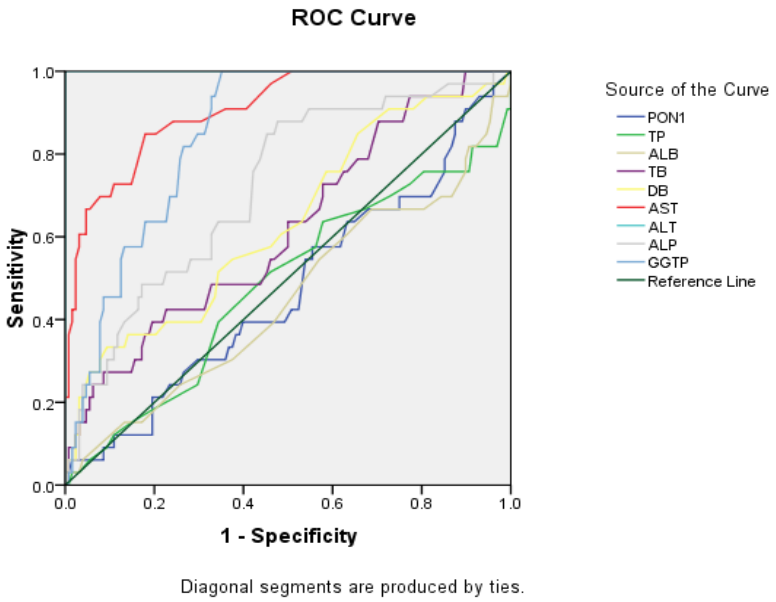

Table 2: Area under the curve for PON1 and liver markers

Test variable	Area under the curve
AST	0.908
ALT	1
ALP	0.720
GGT	0.848
TB	0.617
DB	0.634
TP	0.484
Albumin	0.450
PON1	0.472

DISCUSSION

A significant increase in Bilirubin, liver enzymes and total proteins were observed in diabetics compared to non-diabetics (Table 1).

Elevation of ALT, while uncommon in apparently normal subjects is common in patients with type 2 diabetes (7). A clinical trial report suggests that 2- 24% of screened type 2 DM patients had liver enzyme tests above the upper limit of normal (13). Another report involving multiple clinical trials with type 2 diabetes suggests that diabetics had higher levels of serum alanine amino transferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase than the normal limits (8). Liver has an important role in the carbohydrate metabolism and regulation of blood glucose. It is the major site for glycogenesis and gluconeogenesis. This function of liver makes it susceptible in diabetes mellitus (14).

The cause and effect relationship between diabetes mellitus and liver diseases are yet to be well documented. This is the less explored area in the field of research in our settings.

In our previous study, ALT and AST levels were in the normal range, but AST levels were 1.3 times high in diabetes patients as compared to normal controls. ALT levels were 1.4 times high in diabetes patients. This suggests that diabetes patients have an inclined tendency towards alterations of liver enzymes(9).But the limitation of the previous study was insulin resistance was not studied.

Apart from this, there are several studies which report that there is an elevation in liver enzymes in diabetics. In a report involving clinical trials with type 2 diabetes patients, serum ALT, AST or alkaline phosphatase were 1-2.5 times higher than the upper normal. 5.6% had serum ALT values between 1 and 2.5 times upper normal limit (10). Asymptomatic individuals with mild elevations of ALT and AST revealed that 98% had liver disease, fatty liver disease and chronic hepatitis (15). The most common cause of a mild elevation of serum ALT is non-alcoholic fatty liver disease (16), which is the most prevalent liver disease in type 2 diabetes. Our study is supported by a recent review report by Paola et al suggests that patients with type 2 DM are at the highest risk of non-alcoholic steatohepatitis (NASH) , even in the setting of normal plasma aminotransferases (17).Comparatively high liver enzymes suggest a probable risk of chronic liver disease in future. Since we have not assessed the histopathology of liver biopsy specimens, we cannot specify whether there is a fatty change or to which liver disorder they are prone.

An increase in total proteins and decrease in albumin levels in diabetics observed in our study could be due to reduced fractional synthetic rate of albumin in insulin deficiency . Lowered albumin levels are widely reported by study by Rehman et al (18). Total proteins are reported to be elevated in diabetics (19).

Our own study suggests that, A significantly high (p= 0.0013) total protein level was found in diabetics as compared to the control group. Globulin was extremely significantly elevated (p =0.0001) in type 2 DM. However an insignificantly lowered albumin levels were noted in patients. A/G ratio was lowered in extremely significant (p=0.001) manner in patient group in comparison to the control group(20).

Comparatively high total proteins found in our study is supported by findings of various studies (18,21). This elevation could be attributed to the elevation of various acute phase proteins, fibrinogen and globulins in DM which contribute to the elevation in plasma proteins. In diabetics, reports are available which suggest an elevation in acute phase proteins CRP,α1-acid glycoprotein ,plasminogen ,complement C3, ceruloplasmin etc (22-25). Fibrinogen levels are reported to be increased in type 2 DM due to increased synthesis (19,26). Study by Ardavi and colleagues suggests that diabetics might exhibit hypergamma globulinemia (27).

Significant negative correlation was observed between albumin levels and C-peptide based insulin resistance in our study. This is supported by a study by Cheol Bae et al reported that increased serum albumin level was associated with insulin resistance(28).

Insulin resistance is a principal cause of type 2 diabetes and serum albumin has been associated with insulin resistance (29-33). However, in our study, serum albumin did not have independent effect on the development of diabetes. Although it is not clear whether there is causal relationship between insulin resistance and serum albumin levels, our results indicate that insulin resistance may affect serum albumin levels. Insulin resistance is by definition linked to hyperinsulinemia (34). However C-peptide based insulin resistance was assayed in the present study.Meier et al. reported that C-peptide-based index was more closely correlated than insulin-based index with β-cell mass [6-igmm].C-peptide doesn't undergo hepatic extraction, so C-peptide may more accurately reflect pre-hepatic β-cell secretion. Pre-hepatic β-cell insulin secretion can be estimated by plasma C-peptide level (35,36). C-peptides has more steady clearance than insulin [8].C-peptide has lower within subject and between subject variation than insulin, so C-peptides were more reproducible for the determination of β-cell function (37,38).

ROC curve is the graphical plot that illustrates the diagnostic ability of a binary classifier system as its discrimination threshold varies. AUC is equal to the probability that a classifier will rank a randomly chosen positive instance higher than a randomly chosen negative one. An ROC curve that follows the left hand border and top border of ROC space, implies that the test is accurate. A perfect test will have area under the curve (AUC) equal to 1.The test is considered excellent if AUC lies between 0.9 -1.The value of 0.80-0.90 implies good accuracy.

Based on our results, ALT and AST have excellent area under the curve implying that they are the better markers of liver disease compared to PON1 which has the AUC of 0.472.AUC for GGT is in the acceptable range (AUC = 0.848).

Our finding is in contradictory to the reports by Pyati et al , which compared the diagnostic accuracy of PON1 versus routine liver markers. The study showed that PON1 had an area under the curve 0.990 which was in accordance with the other parameters like, ALT (AUC = 0.999) , total bilirubin (AUC = 0.977) and ALP (AUC = 0.904)(39).

However a significant increase (1.25 times) in PON1 levels was observed in diabetics compared to non-diabetics. Our results are in accordance with the study by Suvarna et al , which reported an elevated PON1 in uncomplicated diabetes mellitus patients compared to non-diabetics(40). PON1 is an antioxidant enzyme, it's elevation could be an compensatory increase so as to fight the enhanced oxidative stress in diabetics.

Yamada et al. have shown that there was a positive correlation between the Homeostasis Model Assessment (HOMA) index and HDL-corrected PON1 activity in non-diabetic Japanese subjects (10). In another study on Turkish population, PON1 activities were not different between non-diabetic subjects with and without metabolic syndrome(41).

Beer et al found that PON1 activities and concentrations were not different in diabetic patients compared to subjects with impaired fasting glucose and controls, although postprandial hyperlipemia was associated with changes in serum PON1 in diabetic subjects(42). In the same study, significantly low serum PON1 concentrations in the postprandial period were demonstrated, attributed to postprandial hypertriglyceridemia, whereas the decrease in PON1 activity was not statistically significant. There was no difference in the postprandial PON1 response between diabetic and nondiabetic groups. In another study, PON1 activity was not significantly altered compared with normoglycemic controls compared to glucose-intolerant and newly diagnosed diabetic subjects(33). All these studies suggest that PON1 activity loss may occur later in the course of diabetes mellitus and hyperglycemia, rather than in the stage of insulin resistance. Serum PON1 activity is significantly decreased in type 1 and type 2 diabetics compared to the healthy control subjects (44-46). Ferretti et al. reported significantly lower PON1 activity in type 1 diabetic patients compared to healthy controls(44).

Study by Pyati et al suggests that diagnostic accuracy of serum PON1 activity is better than total bilirubin, total protein, albumin and ALP. It also reports that PON1 activity measurement could significantly improve the current efficiency of a laboratory's evaluation of patients with suspected chronic hepatitis(39). However we could not establish the role of PON1 as an effective liver marker in predicting liver diseases associated with type 2 diabetes mellitus.

CONCLUSION

We conclude that diabetic patients had high liver enzymes,bilirubin and total protein as compared to non-diabetics. An association was found between type 2 diabetes mellitus , liver markers and insulin resistance. Paroxanase 1 activity may not be a good marker to predict liver disease in diabetes mellitus.

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