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ASSOCIATION OF LIVER ENZYMES WITH INSULIN RESISTANCE IN PREDIABETIC YOUNG ADULT SUBJECTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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Conflicts of Interest: Nil

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Abstract:

Background: Insulin resistance had been associated with altered metabolism in prediabetics. This transient insulin resistance causes disturbance in the metabolism of carbohydrates, lipids and proteins. Liver is the main organ for most of the metabolic reactions. In the current decades the prevalence of NAFLD has been increased in prediabetics and metabolic syndrome patients.

Objective: To study the association of liver enzymes with insulin resistance in prediabetic young adult subjects with non-alcoholic fatty liver disease.

Methods: 100 prediabetic young adult subjects of age 18-35 had been selected via screening. The C-peptide was measured by ELISA methods. Fasting blood sugar (FBS), impaired Glucose tolerance (IGT), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-Glutamyl Transferase (GGT) and triglycerides were estimated by Mindray BS-400 fully autoanalyzer. FLI was calculated with the help of GGT, Triglycerides (TG), waist circumference and body mass index (BMI). HOMA-IR was calculated by HOMA2 calculator.

Results: Prediabetics had elevated liver enzymes on the higher side of normal range. Significant positive correlation was found between GGT, ALT with insulin resistance in these subjects.

Conclusion: Prediabetic subjects have NAFLD and the altered metabolism is responsible for varying degrees of insulin resistance in these subjects. Altered liver enzymes (ALT, GGT) can be used as a marker for diagnosis of prediabetes with NAFLD.

Keywords: Prediabetes, Liver enzymes, GGT, NAFLD, insulin resistance.

Introduction

Prediabetes is a condition characterized by slightly elevated blood glucose levels, but not yet enough to be diagnosed as diabetes [1]. Diagnosis of prediabetes is based on the presence of IFG and/or IGT and/or HbA1C 5.7% to 6.4% (39–47 mmol/mol) [2]. The fasting plasma glucose ranges from 6.1 to 6.9 mmol/L (110 to 125 mg/dL) is called impaired fasting glucose (IFG). Similarly 2 hrs plasma glucose, after intake of 75 g of oral glucose ranges from 7.8-11.0 mmol/L (140-200 mg/dL) is called impaired glucose tolerance (IGT) [3]. Numerous research studies revealed the prevalence of non-alcoholic fatty liver disease (NAFLD) in prediabetic subjects [4-8]. NAFLD is defined by disproportionate accumulation of lipids (lipid content >5% in hepatocytes or a lipid content >5% of liver weight) [9, 10]. NAFLD causes accumulation of lipid molecules in liver [11] and altered the liver architecture [12]. The intracellular lipid aggregation induces inhibition of insulin signal transduction pathways related to glucose metabolism in liver and muscle [13, 14]. It is already established that the intra-hepatic and intra-myocellular lipid accumulation are strongly associated with hepatic and peripheral and IR respectively [15]. Many studies suggested that the insulin resistance and fat infiltration in hepatocytes could induce

abnormal *liver enzymes [16, 17].* Therefore, this study was intended to determine the association of liver enzymes with insulin resistance in prediabetic young adult subjects with non-alcoholic fatty liver disease.

MATERIALS AND METHODS

This study was conducted on prediabetic young adult subjects, selected via screening through survey in the Gwalior (M.P.) and in the Department of Biochemistry, G.R. Medical College & J.A. group of hospitals, Gwalior (M.P.). The inclusion criteria included 100 prediabetic young adult subjects selected via screening for this study. We had excluded the subjects with hepatic disorders, type I diabetes mellitus (DM), type II DM, other diseases and agents that altered glucose metabolism and pregnant women. The screening questionnaires and written consents were taken from all subjects. The study proforma which includes the anthropometric parameters like age, sex, height, weight etc. were noted during screening time. Ethical approval was taken from Institutional Ethical Committee, G.R. Medical College Gwalior. The C-peptide was measured by ELISA method. Fasting blood sugar (FBS), impaired Glucose tolerance (IGT), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-Glutamyl Transferase (GGT) and triglycerides were estimated by Mindray BS-400 fully autoanalyzer. FLI was calculated with the help of GGT, Triglycerides (TG), waist circumference and body mass index (BMI). HOMA-IR was calculated by HOMA2 calculator.

STATISTICAL ANALYSIS:

All the data of overall status of anthropometric and biochemical parameters of prediabetic young adult subjects with non-alcoholic fatty liver disease were expressed as mean ± standard deviation (SD). Linear regression analyses were used to estimate the significance of liver enzymes including ALT, AST, ALP, GGT and HOMA-IR. All analyses were performed using Statistical Package for the Social Sciences, version 23.0 (SPSS software). The graphs were prepared by using Excel and graph pad prism7. The p-value < 0.01 was considered significant.

RESULTS: A total of 100 patients aged 18-35 years old were taken in the analysis with mild to moderate NAFLD. Patients had elevated liver enzymes on the higher side of normal range. Table 1 showing the overall status of anthropometric and biochemical parameters of prediabetic young adult subjects with non-alcoholic fatty liver disease. Table no. 2 and figure no. 1-4 showing the correlation of liver enzymes with insulin resistance (HOMA-IR). Significant positive correlation was found between GGT and ALT with insulin resistance shown in figure no. 2 and 4.

Table 1: Overall status of anthropometric and biochemical parameters of prediabetic young adult subjects with non-alcoholic fatty liver disease.

Parameters	Mean ± SD
Age (Yr)	25.66 ± 5.03
Weight (Kg)	69.45 ± 5.61
Height (mt)	1.63 ± 0.1
BMI (Kg/m2)	26.3 ± 2.54
Waist (cm)	84.5 ± 4.96
Hip (cm)	99.36 ± 4.68
W/H Ratio	0.85 ± 0.03
FBS (mg/dl)	115.39 ± 7.03
IGT (mg/dl)	155.54 ± 8.24
Triglycerides (mg/dl)	148.45 ± 16.00
AST (IU/L)	28.76 ± 3.75
ALT (IU/L)	32.74± 4.34
ALP (IU/L)	70.98 ± 8.74
GGT (IU/L)	34.9 ± 4.01
Fatty liver Index (FLI)	42.26 ± 8.18
C-peptide (ng/ml)	1.96 ± 0.37
HOMA-IR	1.56 ± 0.31

Table 2: Showing the correlation of liver enzymes with insulin resistance (HOMA-IR) of prediabetic young adult subjects with non-alcoholic fatty liver disease.

	Coefficients	Standard Error	T-statistics	P-value
Intercept	1.48	0.18	8.04	0.00
AST (IU/L)	0.00	0.01	0.44	0.66^{NS}
Intercept	0.94	0.17	5.39	0.00
ALT (IU/L)	0.02	0.01	3.58	0.00**
Intercept	1.37	0.19	7.11	0.00
ALP (IU/L)	0.00	0.00	0.94	0.35^{NS}
Intercept	0.23	0.18	1.25	0.21
GGT (IU/L)	0.04	0.01	7.43	0.00**
** Correlation is significant at p-value < 0.01				

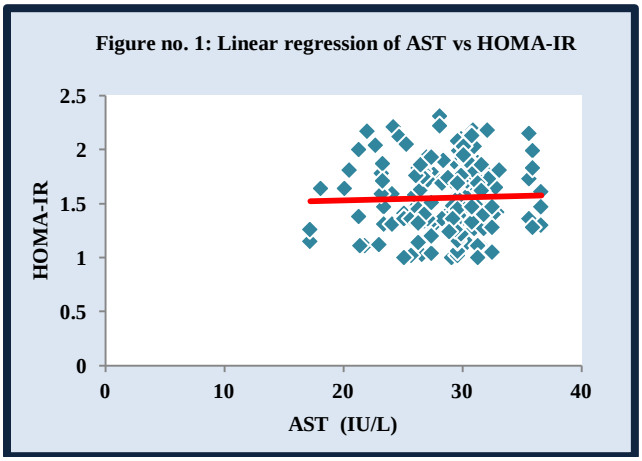

Figure no. 1: Linear regression of AST vs HOMA-IR

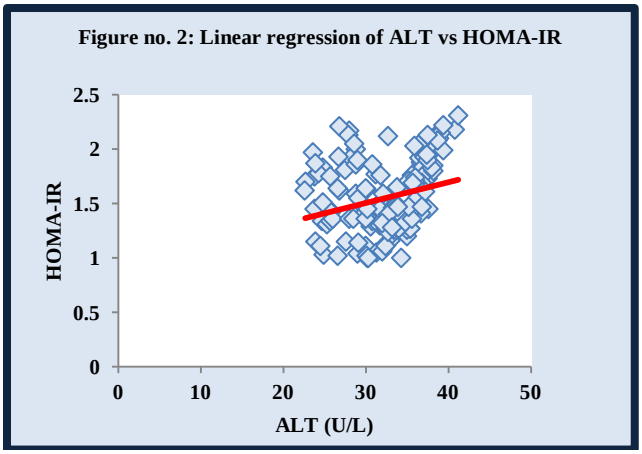

Figure no. 2: Linear regression of ALT vs HOMA-IR

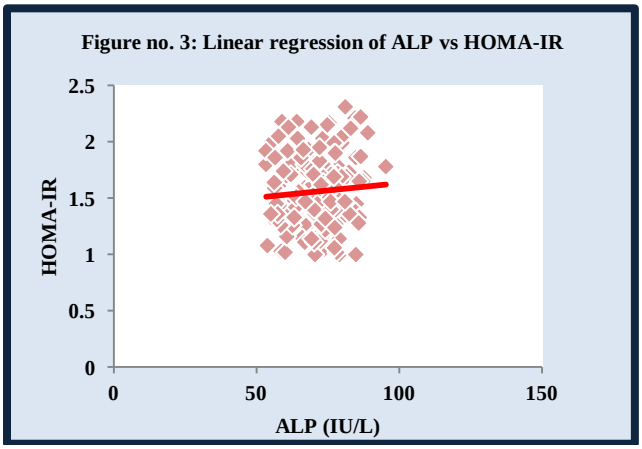

Figure no. 3: Linear regression of ALP vs HOMA-IR

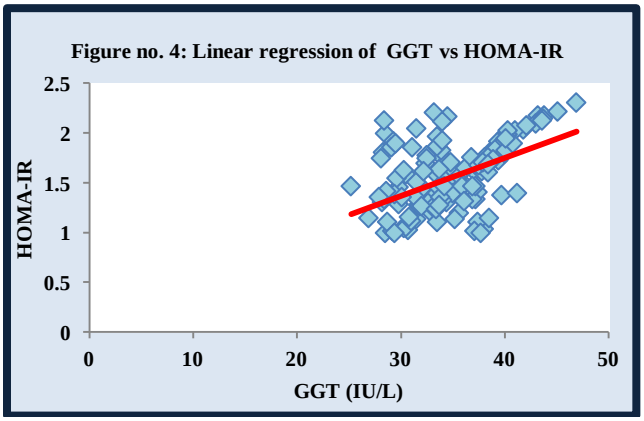

Figure no. 4: Linear regression of GGT vs HOMA-IR

DISCUSSION AND CONCLUSION:

Strong positive correlation was found between ALT and GGT with insulin resistance in prediabetic young adult subjects with non-alcoholic fatty liver disease. Similar findings were quoted by Burgert TS et al., 2006 [18]; Hwang ST et al., 2010 [19]; Nguyen QM et al., 2011[16]. One of the study conducted by Hsiao JY et al., 2007 in Taiwan showed that the ALT and GGT were associated with insulin resistance as the glycemic status progressed in the prediabetic subjects [20]. GGT is used as a sensitive diagnostic marker for alcohol intake [21]. However, both GGT and ALT can predict T2DM even in the exclusion of excessive alcohol [22-24] as well as in those statistically adjusting for alcohol intake [25-27]. In prediabetes, NAFLD is closely linked to the pathogenesis of insulin resistance syndrome [28]. In a large Korean populations without clinical evidence of diabetes, the risk of NAFLD increased with an increasing level of HbA1c [29].

In prediabetes, the altered metabolism is responsible for NAFLD [30]. Specially, altered lipid metabolism is the possible mechanism of NAFLD in prediabetes. The imbalance between lipid accumulation and lipid export is because of the effects of insulin resistance and the subsequent states of hyperinsulinemia and unstable level of relative insulin deficiency. The key regulatory enzymes involved in fatty acid uptake, *de novo* lipogenesis, transport from the liver and lipid oxidation are often measured as surrogate markers of lipid metabolism [31]. These methods show that in insulin-resistant states, both uptake of exogenously derived fatty acid and *de novo* hepatic synthesis of fatty acid; exacerbated by decreased lipid export, lead to an increase in lipid synthesis and hepatic lipid content in NAFLD [32]. The altered metabolism is also responsible for increased liver enzymes (ALT and GGT).GGT is a marker of oxidative stress. Oxidative stress causes the rise of GGT levels [33]. Moreover, recent studies [34, 35] suggested that, the GGT is involved in the generation of reactive oxygen species (ROS). This increased ROS generation could exceed the capacity of the antioxidant system and induce oxidative stress to cells. Because of oxidative stress with the attendant low-grade inflammation is responsible for mild elevations of GGT [36, 37].

From the above results, it may conclude that prediabetic subjects have NAFLD and altered metabolism is responsible for varying degrees of insulin resistance in these subjects. Altered liver enzymes can be used as a marker for diagnosis of

prediabetes with NAFLD. The screening of NAFLD can be made in prediabetic subjects with FLI along with liver enzymes specially ALT and GGT. These enzymes and FLI and liver enzymes are cost effective, non-invasive procedure and can be performed in small set up also.

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