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Association between Liver Enzymes and Dyslipidemia in Yemeni Patients with Type Two Diabetes Mellitus

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Abstract

The correlation between liver enzymes and lipid profile in T2D patients in the Yemeni population has been evaluated. This is a case-control study comprising 142 T2D patients and 142 healthy control subjects were carried out at the outpatient clinics of Ibn-Sina hospital, Mukalla, during the period from January to May 2020. Serum fasting blood glucose (FBG), total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyltransferase (GGT) were analyzed using the Cobas Integra Plus 400 autoanalyzer. Also, anthropometric and blood pressure measurements were taken from each participant. Independent sample T-test and Pearson correlation coefficient were used. T2D patients had significantly higher FBG ($P \leq 0.0001$), total cholesterol ($P \leq 0.0001$), LDL-C ($P \leq 0.0001$), and GGT ($P \leq 0.0001$) while HDL-C was significantly lower in T2D patients ($P = 0.021$). In correlation analysis, serum GGT was positively associated with FBG ($r = 0.216$; $P \leq 0.0001$), total cholesterol ($r = 0.196$; $P = 0.0001$), triglyceride ($r = 0.123$; $P = 0.038$), and LDL-C ($r = 0.209$; $P \leq 0.0001$). Also, serum ALT was positively associated with FBG ($r = 0.145$, $P = 0.014$) and triglyceride ($r = 0.172$, $P = 0.004$). In conclusion, higher levels of ALT and GGT are used as the predictive biomarkers for NAFLD in T2D patients with hyperlipidemia. Thus, routine screening of liver enzymes and lipid profile in T2D patients is recommended for the early detection of liver abnormalities and diminish diabetes complications.

Keywords

Liver Enzymes, Dyslipidemia, Type 2 Diabetes Mellitus, Yemeni Patients

1. Introduction

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia which results from defective insulin action and secretion or both [1]. World Health Organization projects that the number of diabetic patients will exceed 350 million by 2030 [1]. Previous data have documented liver disease is a major cause of morbidity and mortality of type 2 diabetes patients [2] [3]. It is well known that the liver is a vital organ in the metabolism of carbohydrates and in maintaining glucose homeostasis during fasting and postprandial period [2] [4].

Non-alcoholic fatty liver disease (NAFLD) is the scope of chronic liver disease in T2D patients [5], which is characterized by excess deposition of fat in the liver and associated with hepatic insulin resistance [3] and T2D risk [5]. Serum alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) are good biomarkers of NAFLD. ALT has been considered the specific marker of liver injury, as found in high concentrations in hepatocytes [6], while GGT is present on the surface of most cell types and highly active in the liver, kidneys, and pancreas [7]. Also, GGT is responsible for extracellular glutathione catabolism and may be linked to oxidative stress [8] and chronic inflammation [9]; both oxidative stress and chronic inflammation are important pathways for hepatic insulin resistance (IR) and subsequently T2D development [10].

Hyperinsulinemia and IR play an important role in lipid abnormalities for T2D patients [2] [11]. Also, altered lipoprotein patterns and liver enzymes have been identified as independent risk factors for the development of cardiovascular disease (CVD) [10] [11] [12]. Moreover, higher levels of triglycerides, LDL-C, total cholesterol, and lower levels of HDL-C were reported in T2D patients than normal healthy subjects [13]. However, few studies reported the correlation between liver enzymes and lipid profile in T2D patients; hence this case-control study was conducted to assess the association between liver enzymes and blood lipid profile in a sample of Yemeni patients with T2D.

2. Subjects and Methods

2.1. Study Design and Subjects Selection

This is a case-control study was carried out at the College of Medicine and Health Sciences, Hadhramout University, and the subjects were selected from the diabetic outpatient clinic of Ibn-Sina hospital, Mukalla during the period from January to May 2020. A total of 284 Yemeni adult subjects, randomly selected, and recruited into this study. At recruitment, an in-person interview was conducted using a structured questionnaire to collect health-related information. The study group was subdivided into two groups: 142 healthy control subjects composed of 51 males and 91 females (age: 46.0 ± 7.94 yr.), and 142 T2D patients composed of 64 males and 78 females (age: 54.0 ± 8.29 yr.). T2D patients were those who reported being diagnosed with T2D. Healthy control subjects were selected from the remaining participants who were free of T2D and were matched for age, sex, and dialect group with cases on a 1:1 ratio. Moreover, the selected healthy control subjects were screened for the presence of undiagnosed T2D at the time of blood donation by measuring fasting blood glucose (FBG). Written consent was obtained from each participant entered into the study. The study was approved by the Ethics Committee of the Medicine and Health Sciences College, Hadhramout University, Mukalla, Yemen. Patients with co-morbidities such as chronic liver disease, chronic renal disease, cardiovascular disease, and malignancy were excluded.

2.2. Data Collection

A questionnaire form focusing on demographic information and diabetes history was given to all subjects. The patient's demographic information, clinical presentation, medical history, and physical findings were taken from each subject. This included the patient's age, sex, smoking status (never, current or past), hypertension status (yes or no), diabetes status (yes or no) diabetes duration (years), diabetes medication, and diabetes complications. Patients were diagnosed with diabetes based on medical history, present intake of diabetes medications, or according to the American Diabetes Association (ADA) criteria [14]. Patients with T2DM were defined as fasting blood glucose level ≥ 126 mg/dl (≥ 7.1 mmol/L), 2-hour postprandial plasma glucose level ≥ 200 mg/dl (≥11.1 mmol/L) or HbA1c ≥ 6.5% [14]. Classification of Body Mass Index (BMI) was based on the World Health Organization [15].

2.3. Anthropometric and Blood Pressure Measurements

Weight and height were measured following measured according to WHO guidelines [15]. Body mass index (BMI) was calculated as weight/height^2 (Kg/m^2). Obese subjects were defined as BMI ≥ 30 kg/m^2 and normal-weight subjects having a BMI of 18-25 according to WHO guidelines [15]. Patients who had a blood pressure of ≥ 140/90mmHg or were taking antihypertensive medications were diagnosed with hypertension [16]. A true healthy normal ALT level ranges from 29 to 33 IU/l for males, and 19 to 25 IU/l for females and levels above this should be assessed as described by the American College of Gastroenterology (ACG) [17].

2.4. Biochemical Investigations

Ten milliliters of the venous blood sample was obtained from consenting subjects. The blood samples were collected by vein puncture in tubes without anticoagulant. The blood samples were then transported to the laboratory immediately. The serum was separated and stored at −20˚C freezers till analyses. The serum samples of matched case–control pairs were randomly placed next to each other with the case/control status blinded to the laboratory personnel and were processed, and tested in the same batch. All laboratory equipment was calibrated. Thawing freezing was avoided by dividing the samples into aliquots. Plasma fasting blood glucose (FBG), total cholesterol, triglycerides, and HDLcholesterol (HDL-C) were determined enzymatically using a chemical autoanalyzer (Cobas Integra 400 Plus, Roche diagnostic GmbH, Mannheim, Switzerland), following the standard procedures as described by the manufacturer. Concentrations of LDL-cholesterol (LDL-C) were calculated using Friedwald's formula [18]. All biochemical investigations were analyzed in the National Center for Public Health Labs-Mukalla, Yemen.

2.5. Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences for Windows (version 24) and are expressed by mean ± standard deviation (SD) for continuous variables (normally distributed). Non-continuous variables are expressed by median (inter-quartile range) and n (percentage) for categorical variables. Independent Student's t-test used for normally distributed continuous variables and Wilcoxon signed-rank test for skewed continuous variables. The Pearson correlation test was performed with ALT, AST, and GGT as the dependent variables. The statistical analysis was conducted at a 95% confidence level and a P-value < 0.05 was considered statistically significant.

3. Results

Descriptive statistics of anthropometric and biochemical data of the study population are presented in **Table 1**. T2D patients had significantly increased BMI (P = 0.008), systolic BP ($P \le 0.0001$), diastolic BP ($P \le 0.0001$), FBG ($P \le 0.0001$), total cholesterol ($P \le 0.0001$), LDL-C ($P \le 0.0001$), and GGT (P = 0.016) as compared to healthy control subjects. No significant difference was found in serum triglyceride (P = 0.097) and ALT (P = 0.07). Healthy control subjects had significantly increased HDL-C (P = 0.021) and AST (P = 0.001) as compared to T2D patients. On the other hand, 31.7% of T2D patients had hypertension, whereas, 6.3% of healthy control subjects had hypertension. Besides, in T2D patients, the current smokers were 4.2% and the former smokers were 3.5%. According to BMI criteria, 38.7% of T2D patients had overweight and 24.6% with obese as compared to healthy control subjects (40.1%, 14.1%) respectively.

Pearson correlation using ALT, AST, and GGT as dependent variables is presented in **Table 2**. Serum ALT was positively associated with FBG (r = 0.145, P = 0.014), triglyceride (r = 0.172, P = 0.004), AST (r = 590, $P \le 0.001$), and GGT (r = 0.507, $P \le 0.001$) respectively. Serum GGT was positively associated with systolic BP (r = 0.134, P = 0.024), diastolic BP (r = 0.218, $P \le 0.001$), FBG (r = 0.216, $P \le 0.0001$), total cholesterol (r = 0.196, P = 0.0001), triglyceride (r = 0.123, P = 0.038), LDL-cholesterol (r = 0.209, $P \le 0.0001$), and AST (r = 0.366, $P \le 0.0001$) across the combined group.

Using partial correlation analysis (**Table 3**), controlling for age and BMI, significant positive association between ALT with AST (r = 0.589, $P \le 0.0001$) and ALT (r = 0.514, $P \le 0.0001$) remained significant across the combined group, whilst, the association between ALT with FBG and triglyceride was no longer significant. Using the same analysis, the association between GGT with systolic BP (r = 0.124, $P = 0.038$), diastolic BP (r = 0.213, $P \leq 0.0001$), FBG (r = 0.213, $P \leq 0.0001$), total cholesterol (r = 0.199, $P = 0.001$), triglyceride (r = 0.127, $P = 0.033$), and LDL-C (r = 0.208, $P \leq 0.0001$) remained significant before and after age and BMI as adjustment.

Table 1. Anthropometric and biochemical data of healthy controls and T2D patients.

Variables	Healthy controls	T2D patients	*P*-value
N	142	142	
Age (years)	46.0 ± 7.94	54.0 ± 8.29	<0.0001
Sex: male/female	51 (35.9)/91 (64.1)	63 (44.4)/78 (54.9)	
Weight (kg)	71.12 ± 10.67	69.61 ± 13.83	<0.0001
Height (cm)	164.57 ± 8.47	159.97 ± 10.04	<0.0001
BMI (kg/m^2)	26.31 ± 3.95	27.21 ± 4.94	0.008
SBP (mmHg)	115.28 ± 13.11	128.80 ± 20.92	<0.0001
DBP (mmHg)	70.45 ± 9.02	79.47 ± 9.90	<0.0001
BMI classification:			
Normal weight	65 (45.8)	52 (36.6)	
Overweight	57 (40.1)	55 (38.7)	
Obese	20 (14.1)	35 (24.6)	
History of hypertension:			
Yes/no	9 (6.3)/133 (93.7)	45 (31.7)/97 (68.3)	
Smoking status:			
Never Smoker	142 (100)	131 (92.3)	
Current Smoker	0 (0)	6 (4.2)	
Former Smoker	0 (0)	5 (3.5)	
FBG (mmol/L)	5.18 ± 0.91	8.91 ± 2.89	<0.0001
Total cholesterol (mmol/L)	4.70 ± 0.77	5.16 ± 1.20	<0.0001
Triglyceride (mmol/L)	1.24 ± 0.37	1.16 ± 0.42	0.097
HDL-C (mmol/L)	1.67 ± 0.42	1.57 ± 0.34	0.021
LDL-C (mmol/L)	2.77 ± 0.80	3.35 ± 1.17	0.001
ALT (IU/L)	13.1 (8.37 - 19.3)	11.6 (7.3 - 16.8)	0.07
AST (IU/L)	21.2 (17.8 - 28.7)	16.4 (13.3 - 21.7)	0.001
GGT (IU/L)	25.1 (16.8 - 34.7)	29.2 (18.4 - 49.7)	<0.0001

Data were presented as mean ± SD for normal continuous variables and median (interquartile range) for continuous non-normal variables. Independent sample T-test for normally distributed continuous variables and Mann-Whitney U test for skewed continuous variables. *P*-value < 0.05 was considered statistically significant. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase.

Table 2. Pearson correlation using ALT, AST and GGT as dependent variables in the combined study group.

N = 284	ALT		AST		GGT	
	r	*P*-value	r	*P*-value	r	*P*-value
Age (years)	−0.046	0.443	0.010	0.860	0.047	0.433
Sex (M/F)	0.119*	0.046	0.116	0.050	0.016	0.789
Weight (kg)	−0.001	0.989	−0.008	0.895	−0.004	0.945
Height (cm)	0.098	0.101	0.071	0.235	−0.058	0.334
BMI (kg/m^2)	−0.070	0.241	−0.059	0.326	0.033	0.538
SBP (mmHg)	−0.037	0.533	−0.058	0.334	0.134*	0.024
DBP (mmHg)	0.013	0.830	−0.080	0.178	0.218**	<0.001
FBG (mmol/L)	0.145*	0.014	−0.067	0.260	0.216**	<0.0001
Total cholesterol (mmol/L)	0.027	0.653	0.081	0.176	0.196*	0.0001
Triglyceride (mmol/L)	0.172**	0.004	0.087	0.141	0.123*	0.038
HDL-C (mmol/L)	−0.091	0.124	−0.023	0.699	−0.064	0.285
LDL-C (mmol/L)	0.047	0.429	0.082	0.170	0.209**	<0.0001
ALT (IU/L)			0.590**	<0.0001	0.507**	<0.0001
AST (IU/L)	0.590**	<0.0001			0.366**	<0.0001
GGT (IU/L)	0.507**	<0.0001	0.366**	<0.0001		

Pearson correlation coefficient with corresponding *p*-value ($p < 0.05$ is considered a significant). ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase.

Table 3. Pearson correlation using ALT, AST and GGT as dependent variables in the combined groups studied after Age and BMI adjustment as a covariance.

N = 284	ALT		AST		GGT	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value
Sex (M/F)	0.116	0.051	0.114	0.055	0.017	0.772
SBP (mmHg)	−0.018	0.764	−0.053	0.377	0.124*	0.038
DBP (mmHg)	0.024	0.686	−0.078	0.194	0.213**	0<0.0001
FBG (mmol/L)	0.161	0.007	−0.074	0.213	0.213**	<0.0001
Total cholesterol (mmol/L)	0.027	0.652	0.085	0.155	0.199	0.001
Triglyceride (mmol/L)	0.171	0.004	0.090	0.130	0.127	0.033
HDL-C (mmol/L)	−0.104	0.081	−0.026	0.668	−0.056	0.351
LDL-C (mmol/L)	0.052	0.388	0.087	0.147	0.208	<0.0001
ALT (IU/L)			0.589**	<0.0001	0.514**	<0.0001
AST (IU/L)	0.589**	<0.0001			0.368**	<0.0001
GGT (IU/L)	0.514**	<0.0001	0.368**	<0.0001		

Pearson correlation coefficient with corresponding *p*-value ($p < 0.05$ is significant). ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase.

4. Discussion

Despite the incidence of diabetes is increasing worldwide and its prevalence is higher in developing countries, no studies have examined the relationship between elevated liver enzymes and T2D risk in Yemeni patients. Our study, therefore, was focused on the liver as the vital organ contributing to glucose homeostasis during fasting and postprandial stage. Serum ALT, AST, and GGT were taken from each participant and used for this work. Additionally, most people aged ≥ 45 years in developing countries suffer from diabetes [19]. These findings were convenient with our study showed that T2D patients had significantly higher mean age compared to healthy control subjects (**Table 1**).

Besides, our present findings also observed significantly increased BMI, systolic BP, and diastolic BP in T2D patients than healthy control subjects. Besides, the present study also showed that serum FBG, total cholesterol, and LDL-C were significantly higher in T2D patients than healthy control subjects, while, no significant difference was found among both groups for serum triglyceride. In contrast, HDL-C was significantly lower in T2D patients. Our study further revealed higher levels of GGT in T2D patients. While AST was significantly lower in T2D patients. Besides, no significant difference was found among both groups for ALT. Such a positive relationship between liver enzymes and blood lipids profile in T2D patients has been observed in previous studies [2] [20] [21] [22] [23].

This finding supports the role of hepatic insulin resistance in the pathogenesis of NAFLD in patients with T2D [24] [25]. Moreover, Cho *et al.* reported a correlation between ALT activity and increased fatty liver [26]. The impairment of the normal process of synthesis and elimination of triglycerides may progress to fibrosis, cirrhosis, and hepatocellular carcinoma [27] [28].

In addition to its effect on lipid metabolism, insulin also contributes a proinflammatory effect to liver abrasion [12]. Thus, inflammation contributes to IR. Pro-inflammatory cytokines and transcription factors are highly expressed in white adipose tissue and liver. Obesity, which is a state of chronic low-grade inflammation and a risk factor for IR and NAFLD, is induced by the overnutrition and is a primary cause of decreased insulin sensitivity. Obesity leads to lipid accumulation and activates the c-Jun N-terminal kinase (JNK) and nuclear factor-kappa B (NF-κB) signaling pathways, which consequently increase the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [29]. Besides, various adipose tissue-derived proteins, such as adiponectin and leptin, are considered to be major links between obesity, IR, and related inflammatory disorders [30].

GGT is known as a marker of hepatobiliary disorders and is associated with other pathological conditions like diabetes. Free radicals generated by diabetes consume glutathione which induces the increased expression of GGT in hepatocytes. Various studies have suggested the association of GGT concentrations with T2D [31] [32] [33] [34], and hyperlipidemia [35]. These findings are in agreement with our study; GGT was significantly associated with the hyperglycemic and hyperlipidemia profile. We observed ALT and GGT together were positively correlated. Moreover, some data also reported elevated GGT levels with ALT in T2D patients with dyslipidemia [32] [33] [36]. Although we did not confirm the presence of fatty liver by ultrasound techniques, we showed the relationship of ALT, AST, and GGT with the predictors of diabetes and lipid profile parameters, presenting hepatocellular injury.

A study of male Korean workers found that AST was independently associated with diabetes [37], while in a study of male Japanese office workers AST was not associated with T2D risk [33]. Some studies also reported that ALT is a significant predictor of diabetes while AST is not [38]. These findings are in agreement with our findings as AST does not show considerable relationship with the studied parameters. Besides, Clark *et al.* also suggested that mild or chronic elevations of these aminotransferases may be due to NAFLD [39] [40].

The strength of the present study included adjustment for well-established diabetes risk factors including BMI, blood lipids, and hypertension. However, there are some limitations. First, our sample size may be small and thus underpowered to detect the interaction with ALT and GGT. Second, we measured liver enzymes only once and may not represent a long-term profile. Third, we did not measure hepatitis B and C infection, which could result in elevated liver enzymes. Fourth, we did not measure insulin, CRP, leptin, and, adiponectin as the predictive biomarkers links between obesity, hepatic IR, and related inflammatory disorders in T2D patients. Thus, a further large sample size with measurement of insulin, CRP, leptin, adiponectin, and interleukins are required to confirm these correlations. We conclude that higher levels of ALT and GGT are used as the predictive biomarkers for NAFLD in T2D patients with hyperlipidemia.

5. Conclusion

Higher levels of ALT and GGT may be used as the predictive markers for NAFLD in T2D patients with hyperlipidemia. Thus, routine screening of liver enzymes and lipid profile in T2D patients is recommended for the early detection of liver abnormalities and diminish diabetes complications.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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