Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

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

Lotfi S. Bin Dahman (lotfydahman@hu.edu.ye)
College of Medicine and Health Sciences, Hadhramout University https://orcid.org/0000-0002-1526-4955

Mariam A. Humam
College of Medicine and Health Sciences, Hadhramout University

Omar H. Barahim
College of Medicine and Health Sciences, Hadhramout University

Mohammed A. Balfas
College of Medicine and Health Sciences, Hadhramout University

Research Article

Keywords: liver enzymes, dyslipidemia, type 2 diabetes mellitus, Yemeni Patients

Posted Date: March 15th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-148386/v4

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

The current study was aimed to assess the association between liver enzymes and blood lipid profile in a sample of Yemeni patients with T2D. This is a case-control study comprising 142 T2D patients and 142 healthy control subjects at the Ibn-Sina hospital's outpatient clinics in Mukalla, Yemen. Fasting blood glucose (FBG), total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-cholesterol), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyltransferase (GGT) were determined using 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*= <0.0001), total cholesterol (*P*= <0.0001), LDL-cholesterol (*P*= <0.0001), and GGT (*P*= <0.0001) while, HDL-cholesterol was significantly lower in T2D patients (*P*= 0.021). In correlation analysis, serum GGT was positively associated with FBG (r= 0.216; *P*= <0.0001), total cholesterol (r= 0.196; *P*= 0.0001), triglyceride (r= 0.123; *P*= 0.038), and LDL-cholesterol (r= 0.209; *P*= <0.0001). Also, serum ALT was positively associated with FBG (r= 0.145, *P*= 0.014) and triglyceride (r= 0.172, *P*= 0.004). We conclude that higher ALT and GGT are used as the predictive biomarkers for NAFLD in T2D patients with hyperlipidemia. Therefore, routine screening of liver enzymes and lipid profile in T2D patients is recommended to detect liver abnormalities and diminish diabetes complications.

1. Introduction

Diabetes mellitus is defined as a metabolic disorder characterized by chronic hyperglycemia, which results from defective insulin action and secretion or both [1]. World Health Organization (WHO) projects that the number of diabetic patients will exceed 350 million by 2030 [1]. Previous data have documented liver disease is a significant cause of morbidity and mortality of type 2 diabetes patients [2] [3]. It is 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 promising biomarkers of NAFLD. ALT has been considered the specific liver injury marker, as found in high concentrations in hepatocytes [6]. At the same time, 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 essential pathways for hepatic insulin resistance (IR) and subsequently T2D development [10].

Accordingly, hyperinsulinemia and IR play an essential 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-cholesterol, total cholesterol, and lower HDL-cholesterol levels were reported in T2D patients than normal healthy subjects [13]. However, few studies reported the correlation between liver enzymes and lipid profiles in T2D patients; hence, this case-control study was conducted to assess the association between liver enzymes and blood lipid profiles 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 carried out at the College of Medicine and Health Sciences, Hadhramout University. 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 consisting 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 free of T2D and matched for age, sex, and dialect group with cases on a 1:1 ratio. Moreover, the chosen 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 current 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 gave questionnaire form focusing on demographic information, and diabetes history was given to all subjects. The patient's demographic data, clinical presentation, medical history, and physical findings were taken from each participant. These data are 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. Participants were diagnosed with diabetes according to medical history, present intake of diabetes medications, or the American Diabetes Association (ADA) criteria [14]. Patients with T2DM were defined as fasting blood glucose level ≥126 mg/dl (≥7.0 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 WHO [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/height2 (Kg/m^2). Obese subjects were defined as BMI ≥30 kg/m2 and normal-weight subjects having a BMI of 18–25 according to WHO guidelines [15]. Patients who had

a blood pressure of ≥140/90 mmHg 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 then 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 HDL-cholesterol 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 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 by 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 represented 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 And Discussion

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*= <0.0001), diastolic BP (*P*= <0.0001), FBG (*P*= <0.0001), total cholesterol (*P*= <0.0001), LDL-cholesterol (*P*= <0.0001), and GGT (*P*= 0.016) as compared to healthy control subjects. We found no significant difference in serum triglyceride (*P*= 0.097) and ALT (*P*= 0.07). Healthy control subjects had significantly increased HDL-cholesterol (*P*= 0.021) and AST (*P*= 0.001) 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 compared to healthy control subjects (40.1%, 14.1%).

Pearson correlation using ALT, AST, and GGT as dependent variables is presented in table 2. ALT was positively associated with FBG (r= 0.145, *P*= 0.014), triglyceride (r= 0.172, *P*= 0.004), AST (r= 590, *P*= <0.001), and GGT (r= 0.507, *P*= <0.001) respectively. Serum GGT was positively associated with systolic BP (r= 0.134, *P*= 0.024), diastolic BP (r= 0.218, *P*= <0.001), FBG (r= 0.216, *P*= <0.0001), total cholesterol (r= 0.196, *P*= 0.0001), triglyceride (r= 0.123, *P*= 0.038), LDL-cholesterol (r= 0.209, *P*= <0.0001), and AST (r= 0.366, *P*= <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*= <0.0001) and ALT (r= 0.514, *P*= <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*= <0.0001), FBG (r= 0.213, *P*= <0.0001), total cholesterol (r= 0.199, *P*= 0.001), triglyceride (r= 0.127, *P*= 0.033), and LDL-cholesterol (r= 0.208, *P*= <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
Systolic BP (mmHg)	115.28±13.11	128.80±20.92	<0.0001
Diastolic BP (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-cholesterol (mmol/L)	1.67±0.42	1.57±0.34	0.021
LDL-cholesterol (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
Systolic BP (mmHg)	-0.037	0.533	-0.058	0.334	0.134*	0.024
Diastolic BP (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-cholesterol (mmol/L)	-0.091	0.124	-0.023	0.699	-0.064	0.285
LDL-cholesterol (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
Systolic BP (mmHg)	-0.018	0.764	-0.053	0.377	0.124*	0.038
Diastolic BP (mmHg)	0.024	0.686	-0.078	0.194	0.213**	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-cholesterol (mmol/L)	-0.104	0.081	-0.026	0.668	-0.056	0.351
LDL-cholesterol (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

Although 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 research, therefore, was focused on the liver as the vital organ contributing to glucose homeostasis during the fasting and postprandial stage. Also, most people aged ≥45 years in

developing countries have 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).

Our present findings also observed significantly increased BMI, systolic BP, and diastolic BP in T2D patients than healthy control subjects. The present study also showed that serum FBG, total cholesterol, and LDL-cholesterol were significantly higher in T2D patients than healthy control subjects. At the same time, there is no significant difference found among both groups for serum triglyceride. In contrast, HDL-cholesterol was significantly lower in T2D patients. Our study further revealed higher levels of GGT in T2D patients. In contrast, 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 NAFLD's pathogenesis 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 pro-inflammatory effect to liver abrasion [29]. Thus, inflammation contributes to IR. Moreover, Pro-inflammatory cytokines and transcription factors are highly expressed in white adipose tissue and the liver. In contrast, obesity, a state of chronic low-grade inflammation and a risk factor for IR and NAFLD, is induced by overnutrition. It 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) [30]. Besides, various adipose tissue-derived proteins, such as adiponectin and leptin, are considered significant links between obesity, IR, and related inflammatory disorders [31].

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 [32] [33] [34] [35], and hyperlipidemia [36]. These findings agree 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 [33] [34] [37]. Even though 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 [38], while in a study of male Japanese office workers, AST was not associated with T2D risk [34]. Some studies also reported that ALT is a significant predictor of diabetes while AST is not [39]. Our data agree with our findings as AST does not show considerable relationship with the studied parameters. Besides, Clark et

al. also suggested that these aminotransferases' mild or chronic elevations may be due to NAFLD [40] [41].

The present study's strength included adjustment for well-established diabetes risk factors, including BMI, blood lipids, and hypertension. However, there are some limitations: Our sample size may be small and thus underpowered to detect the interaction with ALT and GGT. We measured liver enzymes only once and may not represent a long-term profile. We did not measure hepatitis B and C infection, resulting in elevated liver enzymes. 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 is required to confirm these correlations. We conclude that higher 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.

Declarations

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

The authors are grateful to Al-Huda Medical Agency, Mukalla, Yemen, for funding the study and the Ibn-Sina Hospital, Mukalla, Yemen for technical support. Also, we are thankful to the physicians and nurses who recruited and collected the data of the participants. Also, thanks to the National Center for Public Health Laboratories – Mukalla for the biochemical investigations performance. Special thanks to Students of Medical Laboratory Sciences Department (Ebrahim Al-Muhamedi, Ali Alqaaiti, Saleh Daiban, Sabri Barafah, Afaf Aldibani, Safa Basawaid, and Noor Zahfan) for the performance of data and sample collection, data entry, and biochemical investigations. Special thanks to Ms. Nasiba Al-Aidros for the statistical analysis.

References

1. World Health Organization (1999) Definition, diagnosis and classification of diabetes mellitus and its complications: Report of a WHO consultation. Geneva: *World Health Organization*, 1999. https://apps.who.int/iris/handle/10665/66040.

2. Al-Jameil, N., Khan, F. A., Arjumand, S., *et al*. (2014) Associated liver enzymes with hyperlipidemic profile in type 2 diabetes patients. *Int J Clin Exp Pathol*, 7, 4345-4349. [PubMed].
3. Hanley, A.J., Williams K., Festa, A., *et al*. (2004) Elevations in marker of liver injury and risk of type 2 diabetes-The insulin resistance atherosclerosis study. *Diabetes,* 53, 2623-2632. https://doi.org/10.2337/diabetes.53.10.2623.
4. Gavin, N. and Levinthal, A.S.T. (1999) Liver disease and diabetes mellitus. *Clin Diabetes*, 17.
5. Ballestri, S., Zona, S., Targher, , *et al*. (2016) Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. *J Gastroenterol Hepatol*, 31, 936–44. https://doi.org/10.1111/jgh.13264.
6. Giannini, E.G., Testa, R. and Savarino, V. (2005) Liver enzyme alteration: a guide for clinicians. *CMAJ*, 172, 367–379. https://doi.org/10.1503/cmaj.1040752.
7. Hanigan, M.H. and Frierson, H.F., Jr. (1996) Immunohistochemical detection of gamma-glutamyl transpeptidase in normal human tissue. *J Histochem Cytochem*, 44, 1101–11108. https://doi.org/10.1177/44.10.8813074.
8. Turgut, O. and Tandogan, I. (2011) Gamma-glutamyltransferase to determine cardiovascular risk: shifting the paradigm forward. *J Atheroscler Thromb*, 18, 177–181. https://doi.org/10.5551/jat.6189.
9. Lee, D.H. and Jacobs, D.R., Jr. (2005) Association between serum gamma-glutamyltransferase and C-reactive protein. *Atherosclerosis*, 178, 327–330. https://doi.org/10.1016/j.atherosclerosis.2004.08.027.
10. Ye-Li, W., Woon-Puay, K., Jian-Min, Y. and An, P. (2016) Association between liver enzymes and incident type 2 diabetes in Singapore Chinese men and women. *BMJ Open Diabetes Research and Care*, 4, e000296. https://doi.org/10.1136/bmjdrc-2016-000296.
11. Ginsberg, H.N., Zhang, Y.L. and Hernandez-Ono, A. (2006) Metabolic syndrome: focus on dyslipidemia. *Obesity (Silver Spring)*, 14 Suppl 1:41S-49S. https://doi.org/10.1038/oby.2006.281.
12. Balaji, A.S. (2014) Serum alanine transaminases and lipid profile in type 2 diabetes mellitus Indian patient. *J Diab Res*, [Epub ahead of print]. https://doi.org/10.5171/2013.613176.
13. Rajeswari, S., Kumar, A., Gandhi, M. and Swaminathan, S. (2014) Association between Lipid Profile and Liver Function Tests in Diabetic Patients. *Int J Pure App Biosci*, 2(4):26-31.
14. American Diabetes Association (2016) Standards of medical care in diabetes-2016. *Diabetes Care*, 39, 101–106. https://doi.org/10.2337/dc16-S003.
15. World Health Organization (1995) Physical status: the use and interpretation of anthropometry (1995) Report of WHO expert committee. WHO Technical Report Series, no. 854. Geneva: *WHO*, 321–344. https://apps.who.int/iris/handle/10665/37003.
16. Chobanian, A.V., Bakris, G.L., Black, H.R., *et al.* (2003) Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*, 42, 1206–1252. https://doi.org/10.1161/01.HYP.0000107251.49515.c2.

17. Kwo, P.Y., Cohen, S.M. and Lim, J.K. (2017) ACG clinical guideline: evaluation of abnormal liver chemistries. *Am J Gastroenterol*, 112, 18–35. https://doi.org/10.1038/ajg.2016.517.
18. Friedewald, W.T., Levy, R.I. and Fredrickson, D.S. (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*, 18, 499–502. https://doi.org/10.1093/clinchem/36.1.15.
19. Nwarfor, A. and Owhoji, A. (2001) The prevalence of diabetes mellitus in port-Harcourt correlates with the socio-economic status. *J Appl Sci Environ Mgt*, 5, 75-77. [Google Scholar].
20. Jain, H.R., Shetty, V., Singh, G.S. and Shetty, S. (2016) A Study of Lipid Profile in Diabetes Mellitus. *Int J Sci Stud*, 4, 56-61. [Google Scholar].
21. Han, N., Soe, H.K. and Htet, A. (2012) Determinants of Abnormal Liver Function Tests in Diabetes Patients in Myanmar. *Int J Diab Res*, 1, 36-41. https://doi.org/10.5923/j.diabetes.20120103.02.
22. Belay, Z., Daniel, S., Tedla, K. and Gnanasekaran, N. (2014) Impairment of liver function tests and lipid profiles in type 2 diabetic patients treated at the diabetic center in Tikur Anbessa specialized teaching hospital (Tasth), Addis Ababa, Ethiopia. *J Diabetes Metab*, 5, 454. https://doi.org/10.4172/2155-6156.1000454.
23. Adeniran, S.A., Dolapo, P.O., Oluwole, A.B., *et al*. (2013) Liver Enzymes and Lipid Profile Among Type 2 Diabetic Patients in Osogbo, Nigeria. *Greener J Med Sci*, 3, 174-178. https://doi.org/10.15580/GJMS.2013.5.011313373.
24. Tolman, K.G., Fonseca, V., Dalpiaz, A., *et al*. (2007) Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. *Diabetes Care*, 30, 734-743. https://doi.org/10.2337/dc06-1539.
25. Nannipieri, M., Gonzales, C., Baldi, S., *et al*. (2005) Liver enzymes, the metabolic syndrome, and incident diabetes: The Mexico City diabetes study. *Diabetes Care*, 28, 1757-1762. https://doi.org/10.2337/diacare.28.7.1757.
26. Cho, N.H., Jang, H.C., Choi, S.H., *et al*. (2007) Abnormal liver function test predicts type 2 diabetes: a community-based prospective study. *Diabetes Care*, 30, 2566–2568. https://doi.org/10.2337/dc07-0106.
27. Tolman, K.G., Fonseca, V., Tan, M.H. and Dalpiaz, A. (2004) Hepatobiliary disease in type 2 diabetes mellitus. *Ann Intern Med*, 141, 946-956. https://doi.org/10.7326/0003-4819-141-12-200412210-00011.
28. Chatila, R. and West, A.B. (1996) Hepatomegaly and abnormal liver tests due to glycogenesis in adults with diabetes. *Med Balt*, 75, 327-333. https://doi.org/10.1097/00005792-199611000-00003.
29. Balaji, A.S. (2014) Serum alanine transaminases and lipid profile in type 2 diabetes mellitus Indian patient. *J Diab Res*, [Epub ahead of print]. https://doi.org/10.5171/2013.613176.
30. Sharma, M., Vikram, N.K., Misra, A., et al. (2013) Assessment of 11-beta hydroxysteroid dehydrogenase (11-betaHSD1) 4478T> G and tumor necrosis factor-alpha (TNF-alpha)-308G>A polymorphisms with obesity and insulin resistance in Asian Indians in North India, *Mol Biol Rep*, 40, 6261–70. [PubMed].

31. Chen, Z., Yu, R., Xiong, Y., et al. (2017) A vicious circle between insulin resistance and inflammation in nonalcoholic fatty liver disease, *Lipids in Health and Disease*, 16, 203-211. [PubMed].
32. Lee, D.H., Silventonein, K., Jacobs, D.R., *et al*. (2014) Gamma glutamyltransferase, obesity and the risk of type 2 diabetes observational cohort study among 20,158 middle aged men and women. *J Clin Endocrinol Metab*, 89, 5410-5414. https://doi.org/10.1210/jc.2004-0505.
33. Lee, D.H., Ha, M.H., Kim, J.H., *et al*. (2003) Gamma glutamyltransferase and diabetes-a four year follow up study. *Diabetologia*, 46, 359-364. https://doi.org/10.1007/s00125-003-1036-5.
34. Nakanishi, N., Suzuki, K. and Tatara, K. (2004) Serum gamma glutamyltransferase and risk of metabolic syndrome and type 2 diabetes in middle aged Japanese men. *Diabetes Care*, 27, 1427-1432. https://doi.org/10.2337/diacare.27.6.1427.
35. Lee, D.H., Jacobs, D.R., Gross, M., Kiefe CI, *et al*. (2003) Gamma glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Clin Chem*, 49, 1358-1366. https://doi.org/10.1373/49.8.1358.
36. Sakuta, H., Suzuki, T., Yasuda, H. and Ito, T. (2005) Gamma glutamyltransferase and airflow obstruction in middle-aged men. *Eur J Intern Med*, 16, 348-351. https://doi.org/10.1016/j.ejim.2005.06.005.
37. Marchesini, G., Brizi, M., Bianchi, G., *et al*. (2001) Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes*, 50, 1844-1850. https://doi.org/10.2337/diabetes.50.8.1844.
38. Ahn, H.R., Nam, H.S., Park, K.S., *et al*. (2014) The association between liver enzymes and risk of type 2 diabetes: the Namwon study. *Diabetol Metab Syndr*, 6, 14. https://doi.org/10.1186/1758-5996-6-14.
39. Vozarova, B., Stefan, N., Lindsay, R.S., *et al*. (2002) High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. *Diabetes*, 51, 1889–1895. https://doi.org/10.2337/diabetes.51.6.1889.
40. Clark, J.M. and Diehl, A.M. (2003) Nonalcoholic fatty liver disease: an underrecognized cause of cryptogenic cirrhosis. *JAMA*, 290, 3000-3004. https://doi.org/10.1001/jama.289.22.3000.
41. Clark, J.M., Brancati, F.L. and Diehl, A.M. (2003) The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol, 98, 960-967. https://doi.org/10.1111/j.1572-0241.2003.07486.x.