Obesity Medicine 16 (2019) 100137

Contents lists available at ScienceDirect

Obesity Medicine

journal homepage: www.elsevier.com/locate/obmed

Association between abnormal serum hepatic enzymes, lipid levels and glycemic control in patients with type 2 diabetes mellitus

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ARTICLE INFO

Keywords:
Type 2 diabetes
Liver function
Glycemic control
ALT
AST
NAFALD

ABSTRACT

Aims: To assess the association between abnormal hepatic enzyme, lipid levels and glycemic control in patients with type 2 Diabetes Mellitus. As Liver biomarkers serve as an effective indicator of liver injury in patients whom liver functions are somewhat above average. The abnormality of these markers acts as an alarming sign to the liver function. Since type 2 diabetes can negatively affect the liver via insulin resistance, these biomarkers maybe linked with the severity of the disease.

Materials and methods: A cross-sectional study was carried out at private health care center. A total of 453 diabetic patients. Socio-demographic, clinical, and laboratory data were obtained from the medical records of patients. Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS, version 23).

Results: A total number of 453 patients with T2DM were included in this study. Of the 453 patients, 366 (80.8%) had only one abnormal hepatic profile parameter (ALT, AST & Albumin), 29 (6.4%) had two abnormal hepatic parameters and 11 (2.4%) had more than two abnormal hepatic profile parameters. The results of statistical modeling showed that mean Albumin, mean ALT, and mean AST are jointly highly associated with poorly controlled diabetes mellitus (HbA1c ≥ 7). Lipid profiles (TC, LDL-C and TG) were significantly associated with abnormal hepatic findings.

Conclusion: Current study revealed significant association in liver biomarkers among type 2 diabetic patients.

1. Introduction

Liver is an essential organ for metabolites detoxification, synthesis of proteins, and production of biochemical for digestive functions in the gastrointestinal tract. The liver is also important in the degradation of red blood cells, storage of glycogen, and hormonal production (Mustafa, Mansoor, and Babker, 2016).

Liver plays a vital role in the maintenance of glucose level in the blood. Glycogen storage allows removal of too much glucose, store it, and replenish it when the level falls below the normal. Thus, the liver buffers the blood glucose level. A person whose liver is not functioning the right way may experience an astronomic rise in blood glucose level after having a high-carb meal compared to a person whose liver is functioning optimally. Another way by which the liver maintains normal blood-glucose level is by gluconeogenesis. It involves the production of glucose from glycerol and amino acids (Kumar et al., 2014). The physiology of the liver is determined by the liver function tests. Also known as the hepatic panel, the liver function tests allow the clinician to know the exact state of the patient's liver (Tolman et al., 2007).

The relationship between type 2 diabetes millets (T2DM) & non-alcoholic fatty liver disease (NAFLD) has been established. NAFLD features a macrovesicular hepatocellular steatosis, in the absence of other risk factors such as chronic hepatitis, drugs, and alcohol (Brunt, 2001) which may result in fibrosis, steatohepatitis, and cirrhosis. A well-known biochemical marker of liver damage is serum alanine transferase. The serum level of ALT increases in about 20 percent in diabetic adolescents and children and in many cases, it is linked to NAFLD (Shahwan et al., 2019). Research by Westerbacka et al. (2004) has established a link between ALT and liver fat compared to gamma glutamyl transferase (GGT) and Aspartate transaminase. This explains why ALT is the preferred marker for most epidemiological studies (Schindhelm et al., 2006).

A report by the World Health Organization shows that there would

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https://doi.org/10.1016/j.obmed.2019.100137
Received 19 June 2019; Received in revised form 29 August 2019; Accepted 30 August 2019
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be over 380 million diabetic patients by the year 2025 (Tangvarasittichai, 2015). In Palestine, the reported prevalence of type II diabetes in 2017, for the age group ranging from 20 to 79 years, was found out to be 10.6%. However, studies predict the percentage to be as high as 20.8% by 2020. Out of 1000 individuals, 169 were confirmed type II diabetic patients and is expected to be around 489 by 2040 among the same number of populations (Diabetes Atlas, 2017; Abu-Rmeileh et al., 2013). Diabetes comes in number six as the leading cause of deaths in Palestine, as 5.7% of total number of deaths are estimated to be caused by diabetes and its related complications (El Sharif, Samara, Titi, and Awartani, 2015).

There is a very low prevalence of diabetes mellitus in the rural communities of developing nations. In developed nations, the prevalence is intermediate, and is very high in some ethnic groups, especially those that follow the Western culture. The highest prevalence of diabetes occurs in obese communities. Studies have shown that the prevalence of diabetes is four to six-fold higher in African-Caribbean in the United Kingdom, and South Asians, compared with the White populations in Europe (Kumar et al., 2012). The global gender difference of diabetes is quite small, with the number of diabetic men surpassing the women by just 14 million in 2013. There is a sharp increase in prevalence with age in both gender (Elizabeth and Harris, 2005; Diabetes Atlas, 2017).

There are many reports showing that hepatic disease plays a major role in morbidity and mortality of diabetic patients (Forouhi et al., 2006; IDF Diabetes Atlas, 2013). The role of the liver in glucose homeostasis, both at fasting and in the post-prandial period is fully understood (Shahwan et al., 2019). Liver disease as seen in type 2 diabetes includes non-alcoholic fatty liver disease, abnormal hepatic enzymes, acute liver failure, hepatocellular carcinoma, and cirrhosis (Hanley et al., 2004). Chronic increases in transaminase levels is usually seen in cases of type II diabetes mellitus. Aspartate transaminase and alanine transaminase are hepatic injury markers while serum gamma glutamyl transferase serves as a marker of hepatic at accumulation, one that may result in chronic hepatic insulin resistance and ultimately type 2 diabetes mellitus (King, 2008).

The main goal of this study is to establish the association between abnormal serum hepatic enzymes, lipid levels, and blood-sugar control in T2DM patients.

2. Subjects, materials and methods

A cross-sectional study was conducted in health care center in Ramallah district, Palestine. It comprised a systematic sample of 453 type 2 diabetic patients of which 220 and 233 were males and females respectively from March 2018 through Januray 2019. The study was approved by the health and ethics committee of the health center, and all the participants gave their informed consent in accordance with the Declaration of Helsinki (Declaration of Helsinki, 2009). Relevant sociodemographic, clinical and laboratory data were obtained from the medical records of the patients including: age, gender, BMI, hepatic profile parameter (ALT, AST and albumin), lipid profile (LDL, HDL, TC, TG) and HbA1c.

2.1. Inclusion and exclusion criteria

Male and female patients diagnosed with type 2 diabetes mellitus age 18 and above were included, having a regular monitoring check-up including clinical laboratory finding data in 2018.

The study excluded Type 2 diabetic patients who have high hepatic transaminases, but consume alcohol, or who are positive for hepatitis C or hepatitis B, or those whose history or available laboratory tests suggested diseases which are associated with elevation in liver enzymes like autoimmune hepatitis, malabsorption syndrome, hemochromatosis or Wilson's disease.

Table 1
Basic characteristics, anthropometric and serum lipid profile parameters result for patients with T2DM.

Parameters	All patients (n = 453)			
	Mean	SD	Median	Inter quartile Range (Q1-Q3)
Age(years)	54.5	10.6	56	48–62
Height (cm)	166.5	10.2	163	157–177
Weight (Kg)	81.3	13	81	72–90
BMI (kg/m2)	29.4	4.5	28.8	26.2–31.2
HbA1c (%)	7.8	1.3	7.6	6.8–8.3
FBS (mg/dl)	192.8	78.2	171	143–212
TC (mg/dl)	212.6	75	203	189–228
TG (mg/dl)	275.7	174.9	207	161–331
HDL-C (mg/dl)	40.6	21.2	39	32–43
LDL-C (mg/dl)	124.2	35.2	120	101–141
ALT (U/L)	20	12.8	16	11.8–23.5
AST (U/L)	19.2	13.4	16	21–21.5
Albumin (g/dL)	4.6	2	4.3	4.1–4.8

Abbreviations: HbA1c, hemoglobin A1c; FBS, fasting blood sugar HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride, BMI, Body mass index, ALT, Alanine transaminase, AST; Aspartate transaminase.

2.2. Statistical analysis

Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS, version 23). Chi-square tests and multivariate logistic regression were used to assess the correlation between overweight/obesity and serum calcium among patients with diabetes and other related risk factors. Separate regression models were used, and stepwise method was used for variable selection and model building.

3. Results

3.1. Sociodemographic, anthropometric and biochemical characteristics of the participants

The demographic, anthropometric and biochemical characteristics of patients' is shown in Table 1. A total number of 453 patients with T2DM were included in this study. Among these patients 48.6% (n = 220) were male and 51.4% (n = 233) were female. The mean age ± S.D of the patients was 54.47 ± 10.56. The mean age ± S.D of height, weight, BMI, HbA1c, FBS, TC, TG, HDL-C and LDL-C, ALT, AST and albumin were 166.5 ± 10.6, 81.3 ± 13, 29.4 ± 4.5, 7.8 ± 1.3, 192.8 ± 78.2, 212.6 ± 75, 275.7 ± 174.9, 40.6 ± 21.2 and 124.2 ± 35.2, 20 ± 12.8, 19.2 ± 13.4, 4.6 ± 4.3 respectively.

3.2. Prevalence of abnormal serum hepatic enzymes level in patients with type 2 diabetes mellitus

Prevalence of different types of abnormal serum hepatic enzymes in all the patients and in males and females are shown in Table 2. Overall, 13.9% (95% CI: 10.7%–17.1%) of patients with type 2 diabetes had abnormal ALT levels (ALT $>$ 33 U/L) and 3.8% (95% CI: 2%–5.5%) had abnormal AST levels (AST $>$ 37 U/L). Abnormal albumin levels (albumin $<$ 3.5 g/dL & albumin $>$ 5 g/dL) were found in 84.5% (95% CI: 81.2%–87.9%) of patients. Of the 453 patients, 366 (80.8%) had only one abnormal hepatic profile parameter, 29 (6.4%) had two abnormal hepatic parameters and 11 (2.4%) had more than two abnormal hepatic profile parameters. There were no significant differences between male and female according to abnormal serum hepatic enzymes.

Prevalence of different types of abnormal serum hepatic enzymes stratified by patients' glycemic are shown in Table 3. Patients were divided into two groups as per their glycemic index (HbA1c); the first group consisted of patients with HbA1c $<$ 7.0% and the second group consisted of patients with HbA1c values ≥ 7.0%. There was an increase

Table 2
Prevalence of Abnormal serum hepatic enzymes in male and female patients with type 2 diabetes mellitus.

Abnormal serum hepatic enzymes	All (n = 453)	Male (n = 220)	Female (n = 233)	P.val
ALT (U/L)				
≤33	390 (86.1%)	184 (83.6%)	206 (88.4%)	0.142
> 33	63 (13.9%)	36 (16.4%)	27 (11.6%)	
AST (U/L)				
≤37	436 (96.2%)	209 (95%)	227 (97.4%)	0.175
> 37	17 (3.8%)	11 (5%)	6 (2.6%)	
Albumin (g/dL)				
3.5–5	70 (15.5%)	39 (17.7%)	31 (13.3%)	0.193
< 3.5 & > 5	383 (84.5%)	181 (82.3%)	202 (86.7%)	

ALT; Alanine transaminase, AST; Aspartate transaminase, p value < 0.05.

Table 3
Prevalence of abnormal serum hepatic enzymes categorized by patients' glycemic.

Abnormal serum hepatic enzymes	Glycated Hemoglobin (HbA1c) (n = 453)		P.val
	HbA1c < 7 (n = 131)	HbA1c ≥ 7 (n = 322)	
ALT (U/L)			
≤33	120 (30.8%)	270 (69.2%)	0.031
> 33	11 (17.5%)	52 (82.5%)	
AST (U/L)			
≤37	131 (30%)	305 (70%)	0.007
> 37	0	17 (100%)	
Albumin (g/dL)			
3.5–5	20 (28.6%)	50 (71.4%)	0.944
< 3.5 & > 5	111 (29%)	272 (71%)	

Abbreviations: HbA1c, hemoglobin A1c; ALT; Alanine transaminase, AST; Aspartate transaminase, p value < 0.05.

in frequency of abnormal ALT (P = 0.031) and abnormal AST (P = 0.007) in patients with HbA1c values ≥ 7.0% Fig. 1.

3.3. Abnormal serum hepatic enzymes associated with poorly controlled type 2 diabetes mellitus diabetes (HbA1c ≥ 7)

Table 4 displays the results of logistic regression analysis applied to each abnormal hepatic enzyme. This table shows the results for poorly controlled diabetes mellitus (HbA1c ≥ 7). The odds ratios in this table show the magnitude of the association and their corresponding p-values

Table 4
Odds ratios of HbA1c ≥ 7 by abnormal serum hepatic enzymes before and after adjusting for the effect of all other factors.

Abnormal serum hepatic enzymes	HbA1c ≥ 7							
	Unadjusted				Adjusted			
	OR	95% CI		P.value	OR	95% CI		P.value
ALT (U/L)	1.030	1.010	1.049	0.002	1.028	1.006	1.051	0.014
AST (U/L)	1.041	1.013	1.070	0.003	1.080	1.040	1.121	< 0.001
Albumin (g/dL)	0.551	0.349	0.870	0.011	0.769	0.478	1.237	0.280

Notes: Adjustment for age, BMI, TC, TG, LDL-C, HDL-C, FBS, Height, Weigh. P < 0.05 was considered statistically significant.
Abbreviations: OR, odds ratio; CI, confidence interval; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride, BMI, Body mass index, ALT; Alanine transaminase, AST; Aspartate transaminase.

indicate whether the association is statistically significant or not by using the cut-off values of 0.05 as mentioned in the method section. In this model poorly-controlled diabetes mellitus (HbA1c ≥ 7) were significantly associated with mean ALT and mean AST even after adjustment for age, Height, Weigh, BMI, total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol and fasting blood sugar. To select the set of factors that jointly influence poorly controlled diabetes mellitus (HbA1c ≥ 7), we used the stepwise procedure applied to the multivariate logistic regression model. In Table 5 the results of this procedure showed that mean Albumin, mean ALT, and mean AST are jointly highly associated with poorly controlled diabetes mellitus (HbA1c ≥ 7). If serum albumin increases by 1 g/dL, then the odds of having HbA1c ≥ 7 will be decreases 52.7%. If serum ALT increases by 10 U/L, then the odds of having HbA1c ≥ 7 will be increases by 36%. If serum AST increases by 10 U/L, then the odds of having HbA1c ≥ 7 will be increases by 53%.

3.4. Association between abnormal serum hepatic enzymes, lipid levels and glycemic control

Table 6 shows the results of stepwise logistic regression analysis for the factors associated with abnormal hepatic ALT (> 33 U/L). HBA1c, BMI, TG and TC were significantly associated with abnormal hepatic ALT.

If HBA1c increases by 1%, then the odds of having abnormal ALT

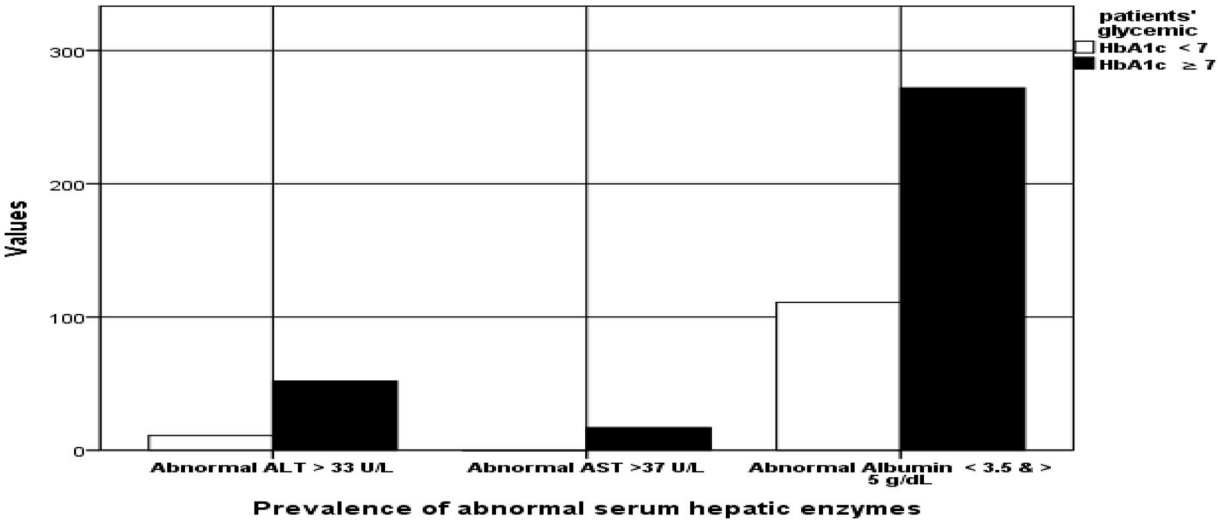

Fig. 1. Bar chart for abnormal serum hepatic enzymes categorized by patients' glycemic.

Table 5
Multivariate logistic regression model for factors associated with poorly controlled diabetes (HbA1c ≥ 7).

Abnormal serum hepatic enzymes	HbA1c ≥ 7			
	OR	95% CI		P.value
Albumin (g/dL)	0.473	0.299	0.748	0.001
ALT (U/L)	1.036	1.016	1.057	< 0.001
AST (U/L)	1.053	1.022	1.084	0.001
Age	1.018	.998	1.039	0.072

Abbreviations: OR, odds ratio; CI, confidence interval; HbA1c, hemoglobin A1c; ALT; Alanine transaminase, AST; Aspartate transaminase.

Table 6
Multivariate logistic regression model for factors associated with abnormal hepatic ALT (> 33 **U/L**).

Parameters	ALT > 33 (U/L)			
	OR	95% CI		P.value
HBA1c	1.30	1.04	1.625	0.021
BMI	1.192	1.119	1.269	< 0.001
TG (mg/dl)	1.003	1.001	1.005	0.002
TC (mg/dl)	1.021	1.003	1.038	0.019
LDL-C (mg/dl)	0.980	0.957	1.003	0.083

Notes: P < 0.05 was considered statistically significant. **Abbreviations:** OR, odds ratio; CI, confidence interval; HbA1c, hemoglobin A1c; FBS, fasting blood sugar, HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride, BMI, Body mass index, ALT; Alanine transaminase, AST; Aspartate transaminase.

will increases by 30%. If BMI increase by one unit, then the odds of having abnormal ALT will increases by 19%. If TG increases by 10 mg/dl, then the odds of having abnormal ALT will increases by 3%. If the TC increases by 10 mg/dl, then the odds of having abnormal ALT will increases by 21%.

Table 7 shows the results of stepwise logistic regression analysis for the factors associated with abnormal hepatic AST (> 37 U/L). HBA1c, TC, LDL-C and TG were significantly associated with abnormal hepatic AST.

If HBA1c increases by 1%, then the odds of having abnormal AST will increases by 83.7%. If TC increases by 10 mg/dl, then the odds of having abnormal AST will decrease by 26%. If LDL-C increases by 10 mg/dl, then the odds of having abnormal AST will decrease by 50% If TG increases by 10 mg/dl, then the odds of having abnormal AST will decrease by 10%.

Table 8 shows the results of stepwise logistic regression analysis for the factors associated with abnormal serum albumin (< 3.5 & > 5 g/dL). BMI, HDL-C and TG were significantly associated with abnormal hepatic albumin.

If BMI increases by 10 unites, then the odds of having abnormal albumin will increase by 75%. If HDL-C increases by 10 mg/dl, then the odds of having abnormal albumin will decreases by 27%. If TG increases by 10 mg/dl, then the odds of having abnormal albumin will decrease by 5%.

Table 7
Multivariate logistic regression model for factors associated with abnormal hepatic AST (> 37 **(U/L)**.

Parameters	AST > 37 (U/L)			
	OR	95% CI		P.value
H BA1c (%)	1.837	1.157	2.918	0.010
FBS (mg/dl)	1.005	1.000	1.011	0.061
TC (mg/dl)	0.974	0.956	0.993	0.008
LDL-C (mg/dl)	0.950	0.922	0.980	0.001
TG (mg/dl)	0.990	0.981	0.999	0.025

Table 8
Multivariate logistic regression model for factors associated with abnormal hepatic albumin.

Parameters	Albumin < 3.5 & > 5 (g/dL)			
	OR	95% CI		P.value
BMI	1.075	1.004	1.151	0.037
HDL-C (mg/dl)	0.973	0.951	0.995	0.019
TG (mg/dl)	0.995	0.992	0.998	0.001
HBA1c (%)	1.256	0.987	1.598	0.064
TC (mg/dl)	0.990	0.979	1.002	0.102

4. Discussion

The results of statistical modeling of our study showed that Albumin, ALT, and AST are highly associated with poorly controlled T2DM. The association remained significant even after adjustment for age, height, weight, BMI, total cholesterol (TC), triglyceride (TG), LDL cholesterol, HDL cholesterol and fasting blood sugar.

Although previous epidemiological studies have associated male gender with a higher risk of elevated ALT readings (Liu et al., 2005; Di Bonito et al., 2009), our study showed no significant differences among both sexes in the prevalence of abnormal serum hepatic enzymes. Other studies demonstrated a relationship between liver markers and T2DM. A study done by Hanly et al. (Hanley et al., 2004) is in line with our findings in that the increase in the liver serum hepatic enzymes levels were significant in patients with T2DM.

Our study has demonstrated abnormal levels of ALT, AST and Albumin, with the ALT showing the highest prevalence among our studied population, which has been also pointed out by Harris (2005) in that the ALT was found out to be the most common abnormality. Our study revealed at least one abnormal hepatic profile parameter in 366 (80.8%) out of the 453 patients. The ALT was elevated in 13.9% (ALT > 33 U/L) of the participants, while the AST and Albumin showed abnormal readings at 3.8% (95% CI: 2%–5.5%) and 84.5% (AST > 37 U/L) respectively. These results are consistent with a study by Mandal et al. (2018) in which a statistically significant increase in ALT levels was reported in the diabetic population. Likewise, Ni et al. demonstrated a similar pattern in the diabetic patients [Ni et al. (2012).

The manifestation of T2DM related complications may include obesity, peripheral resistance to insulin, hyperinsulinemia, hypertension, or hypertriglyceridemia, and all have been pointed as contributing to NAFLD (Cazzo et al., 2016; Moyad et al., 2019). This study therefore is in line with the with the current knowledge of NAFLD pathogenesis, as increased ALT is common in T2DM patients, suggesting that the onset of NAFLD may precede T2DM diagnosis.

Our results showed a significant association between poorly controlled T2DM (HbA1c ≥ 7) and ALT and AST even adjusting other confounding factors. The present study found a positive ALT relation with incident T2DM, this was consistent with previous meta-analysis study that reported a relative risk in 17 out of the 24 studies for ALT (Kunutsor et al., 2013). Also, our study demonstrated an increase frequency of AST in patients with poorly controlled HbA1c levels, which is in line with previous studies (Nannipieri et al., 2005; Shahwan et al., 2019). However, one study by Saligram (Saligram et al., 2012) showed an insignificant association between glycemic control and elevated ALT, and this may be attributed to the fact that the study covered only a newly diagnosed patients rather than ones who have been diagnosed with T2DM for a rather long period of time where insulin resistance is more probable.

There are strong therapeutic, biochemical, and epidemiological evidences to back up the premise that the major anomaly in most NAFLD patients are insulin resistant (Polyzos et al., 2009). With insulin

resistance, the affected patient experiences increased lipolysis, pooling of hepatic triglycerides, synthesis of triglycerides, and increased uptake of free fatty acids (Ali et al., 2013; Willner et al., 2001). A study by Asegonkar et al. (2013) pointed out to ALT having a positive correlation with total cholesterol (TC), triglycerides (TG) and LDL. Our study partially agrees with the previous study in that it also demonstrated a statistically significant ALT levels with TC and TG, however, the LDL was found out to be statistically insignificant, which agrees with another study reported by Saligram et al. (Saligram et al., 2012) which resulted in a positive correlation of TC and TG with an elevated ALT, but a negative correlation with LDL and HDL.

5. Conclusion

Current study revealed significant association in liver biomarkers among type 2 diabetic patients as it demonstrated that high ALT is characteristic of T2DM patients, there was an increase in frequency of abnormal ALT ($P = 0.031$) and abnormal AST ($P = 0.007$) in patients with HbA1c values $\geq 7.0\%$. pointing to the fact that the development of hepatic anomalies with poor glycemic control attendants could indicate unfavourable evolution of T2DM.

Conflicts of interest statement

Authors declare no conflict of interest.

Authors' contributions

All authors helped to perform the research; Moyad Jamal Shahwan conception, study design and manuscript writing and drafting; Ahmed H. Khattab manuscript writing, drafting and editing; Mohammed H. Khattab conceptualization, Methodology, Writing - review & editing; Ammar A. Jairoun conceptualization, Methodology, Validation, Statistical analysis, Data curation. All authors contributed in data collection and entry.

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