The Relation Between Generalized Anxiety Disorder with Blood Liver Enzymes Activity and Lipid Profile Among Ninevah Medical College Students (Case Control Study)

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ABSTRACT

Generalized Anxiety Disorder, liver diseases and atherosclerosis are common problems requiring measures for controlling them. To find possible relation between Generalized Anxiety Disorder among Ninevah Medical College students with the risk of atherosclerosis and liver diseases development. The study, conducted from February to December 2024, involved Ninevah Medical College students in Mosul, Iraq, who were divided into two groups according to the Diagnostic and Statistical Manual of Mental Disorders, control and patient with generalized anxiety disorder, both had negative drug and medical history, including psychiatric problems, which may cause their symptoms or fit with the differential diagnosis. Morning fasting venous blood sample was collected from all for measuring total cholesterol, triglycerides, high density lipoprotein-cholesterol levels, as well as the activities of liver enzymes alanine transaminase, aspartate transaminase, and alkaline phosphatase on automated cobas 6000 machine. Low density lipoprotein-cholesterol, atherogenic index of plasma and atherogenic coefficient were calculated. Statistical analysis was done using Minitab Data analysis. Among patient group, significant elevation of total cholesterol, low density lipoprotein cholesterol and alanine transaminase values. Positive significant correlation was exist between total cholesterol with alanine transaminase, low density lipoprotein, and triglycerides as well as between the number of diagnostic parameters with total cholesterol, low density lipoprotein cholesterol, triglycerides, atherogenic index of plasma, atherogenic coefficient, and alanine transaminase. Patient with generalized anxiety disorder may have increased risk for coronary vascular and liver diseases development and the controlling of disease may help to reduce these risks.

Keywords: Atherosclerosis, Generalized Anxiety Disorder, Lipid profile, and Liver diseases.

INTRODUCTION

Generalized Anxiety Disorder (GAD) is a common mental disorder, while hereditary or genetic factors are thought to be related to condition, the exact relation is not well understood since the environmental factors play more important role in its development[1].

Liver diseases, responsible for two million deaths annually and 4% of worldwide deaths[2]. Standard biochemical blood tests for assessing liver cell damage measure the activities of Alanine transaminase (ALT), Aspartate transaminase (AST), and Alkaline phosphatase (ALP)[3]. As ALT is abundant in liver cells cytosol making its activity is elevated in early stage of liver diseases, AST elevation occurs in more chronic liver diseases as it presents more in mitochondria of liver cells and it is less specific than ALT in diagnosing liver cell damage as it presents in other organs and tissues more than ALT, like heart, muscle, kidney, brain, pancreas, and lungs, ALP found in various organs including the heart, muscle, kidney, brain, pancreas, and lungs in addition to canalicular membrane of bile duct, making its elevation in bile duct obstruction not specific[3].

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, with 19.8 million people died in 2022[4]. It is important to detect the risk of CVDs development and understand the role of lipid profile in its progression, atherogenic indices, such as Atherogenic Index of Plasma (AIP) and Atherogenic Coefficient (AC), are used to predict cardiovascular events and therapy efficacy, especially when

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lipid profile is normal[5, 6] and they are positively correlated with CVDs[5]. Control of dyslipidemia can reduce CVDs morbidity and mortality[7], and even the lipid profile parameters can predict major outcomes in CVDs patients[8].

Although many research study the relation between GAD and lipid profile changes[9] while other, study the relation between psychiatric problems and liver diseases[10], there is no clear correlation between GAD and the risk of liver impairment or both atherosclerosis and liver diseases. This study aims to find any possible relation between GAD among Ninevah Medical College students with the risk for developing atherosclerosis and liver diseases.

MATERIALS AND METHODS

The study, conducted from February to December 2024, involved Ninevah Medical College students in Mosul, Iraq, who were selected after completing research acceptance procedures and obtaining ethical approvals from the College Ethics Committee at 24th November 2024. Participants were divided into two groups based on their answers to Google Form questions and other parameters for diagnosing GAD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[11].

Group I (control group) consisted of 36 (24 males and 12 females) apparently healthy students aged 19-25 years their mean and standard deviation (SD) values were 22.083 and 2.089 respectively, with negative medical or drug history, and did not meet the DSM-5 criteria for GAD.

Group II (GAD group) consisted of 36 students (6 males and 30 females) aged 19-26 years their mean and SD was 21.500 and 2.131 respectively , they diagnosed as GAD patients according to DSM-5 criteria. They experienced excessive anxiety or worry unable to manage it most of the day over six months, with three or more of the six complaints over six months identified by DSM-5 including restlessness, fatigability, problems concentrating, irritability, muscle tension and sleep difficulty. They had significant weakness in their academic performance and had a negative drug and medical history, including psychiatric problems, which may cause their symptoms or fit with the differential diagnosis of GAD.

A morning fasting venous blood sample of 5 mL was collected from all students enrolled in a study. The samples were collected in gel-tube and analyzed in an external lab. to measure total cholesterol (TC), triglycerides (TG), and high-density lipoprotein-cholesterol (HDL-C) levels, as well as the activities of liver enzymes ALT, AST, and ALP.

Serum TC, TG and HDL-C concentrations were estimated on a Cobas 6000 machine by the enzymatic colorimetric methods supplied from Biolabo, France that involve enzymatic reactions between known reagents and an analyte, resulting in a color change, the light absorbance of that color is then measured, reflecting the analyte concentration while Serum HDL-C concentration was estimated by the same procedure of TC estimation after precipitation of LDL, VLDL and chylomicron[12].

The ALT, AST, and ALP activities were measured on Cobas by kinetic method using kits supplied by Biolabo, France, the decrease of absorbance at 340 nm is proportional to ALT and AST activities while the rate of p-nitrophenol formation measured at 405 nm is proportional to ALP activity[13].

The calculation of low-density lipoprotein-cholesterol (LDL-C) was performed using the Friedwald Formula, [(TC(mg/dL) – HDL-C(mg/dL) − TG(mg/dL)/5][14].

The AC was determined by calculating the ratio of non-HDL cholesterol (Non-HDL-C) to HDL-C, the AIP was determined by calculating the logarithm of the molar ratio of TG to HDL-C[15].

The participants' body mass index (BMI) was determined by dividing their weight in kilograms by the square of their height in meters[16].
The study used Minitab Data analysis to calculate mean and SD for each parameter, assessed the statistical significance between group I and group II using student t-test, and determined the degree of correlation between two parameters using Pearson Correlation coefficient, with a *P*-value below 0.05 indicating significance[17].

RESULTS

The participants from Ninevah Medical College students were divided into two groups (I and II) based on DSM-5 criteria for GAD diagnosis. Group I (control group) consisted of 36 students (24 males and 12 females) with ages ranging from 19 -25 Years (mean and SD was 22.083 and 2.089 respectively), who did not meet the criteria for GAD. Group II, (GAD group) consisting of 36 students (6 males and 30 females), with ages ranging from 19-26 years. (mean and SD were 21.500 and 2.131 respectively) who were diagnosed as GAD patients. There are no significant differences in age and BMI between two groups (Table 1).

Comparing group II to group I, the lipid profile parameters showed significant elevation of TC and LDL-C, concerning liver enzymes, the study showed significant increase in ALT activity (Table 2).
The DSM-5 criteria for diagnosing GAD require at least three out of six diagnostic parameters, group II patients demonstrating the following number of these parameters (Table 3).

There is significant positive correlation between the number of diagnostic parameters found in group II and their corresponding values of TC (Figure 1A), AIP (Figure 1B), AC (Figure 1C), LDL-C ((Figure 1D), TG (Figure 1E) and ALT (Figure 1F).

There is a positive significant correlation between TC value and ALT activity in group II (Figure 2A), as well as between TC with LDL-C (Figure 2B) and TG values (Figure 2C).

DISCUSSION

Many reviews worldwide reported high levels of GAD among medical students, therefore, the study involved age-matched students from

Table 1. Age, sex and BMI values in group I and II

Parameter	Group I (n = 36)		Group II (n = 36)		*P*- Value
Age (Years)	Mean	± SD	Mean	± SD	0.245 (NS)
	22.083	2.089	21.500	2.131	
Sex	Male	Female	Male	Female	0.000 (S)
	24	12	6	30	
BMI (Kg/m^2)	Mean	± SD	Mean	± SD	0.056 (NS)
	21.785	3.115	20.339	3.201	

NS: no significant differenc S: significant difference

Table 2. Values of lipid profile parameters and liver enzymes in group I and group II

Analyte	Group I (n = 36)			Group II (n = 36)			*P*- Value
	Mean	± SD	Range	Mean	± SD	Range	
TC (mg/dL)	152.08	38.88	98-205	169.25	31.91	131-223	0.044 (S)
HDL-C (mg/dL)	49.17	6.3	35-55	49.25	5.09	36-55	0.951 (NS)
LDL-C (mg/dL)	85.78	39.31	33.4-140.2	102.55	21.35	73.0-137.0	0.028 (S)
TG (mg/dL)	85.67	46.21	48-167	87.25	61.85	49-249	0.902 (NS)
AIP	-0.1677	0.1997	(-0.148)- (0.139)	-0.1828	0.2195	(-0.376) –(0.297)	0.761 (NS)
AC	2.1457	0.8918	0.782-3.868	2.4409	0.5519	1.735- 3.278	0.096 (NS)
ALT (U/L)	22.67	11.46	11-42	33.58	8.84	20-44	0 (S)
AST (U/L)	26.75	11.06	9-43	23.75	10.28	10-47	0.237 (NS)
ALP (U/L)	230.75	61.13	109-315	207.42	81.39	101-330	0.173 (NS)

NS: no significant difference S: significant higher in group II

Table 3. Diagnostic parameters demonstrated in group II

Diagnostic Parameters							
Restlessness	Fatigability	Concentrating Problems	Irritability	Muscle Tension	Difficulty With Sleep	Number of Positive Diagnostic parameters	Number of Patients in group II
+	+	+	+	+	+	6	3
+	+	+	+	-	+	5	12
+	+	+	-	+	+	5	3
+	+	+	+	+	-	5	3
-	+	+	+	-	+	4	3
+	+	+	+	-	-	4	3
+	-	+	+	+	-	4	3
+	+	-	-	-	+	3	3
-	+	+	-	+	-	3	3

Ninevah Medical College, who were divided into two groups based on DSM-5 criteria for diagnosing GAD[11], group I (control group) with negative family or drug history, and group II (GAD group) with GAD diagnostic criteria according to DSM-5 without any drug or medical history affecting diagnosis. This case control study aims to investigate the possible link between GAD among Ninevah Medical College students and the risk of CVDs and liver diseases development.

The study reveals significant elevations in TC and LDL-C values among individuals with GAD compared to the control (Table 2), the correlation between TC with both LDL-C and TG are positive (Figure 2B and 2C). Although, there are no significant changes in TG, HDL-C, AIP, and AC values between two groups (Table 2), there is a positive correlation between GAD severity (measured by the number of positive diagnostic parameters) (Table 3) and the values of almost all lipid profile parameters including TC (Figure 1A), AIP (Figure 1B), AC (Figure 1C), LDL-C (Figure 1D) and TG (Figure 1E).

The study indicates a significant TC rise in GAD group, consistent with previous study that found significant elevation of both TC and TG among GAD[18], however, unlike this study, not correlate the severity of illness with lipid profile changes. Other study found no significant differences in serum cholesterol levels among the GAD group[19].

The possible explanation of lipid profile changes especially significant elevation of TC and LDL-C among GAD group in this study is that the sympathetic activation increases noradrenergic activity causing a release of epinephrine and corticosteroids into the blood, these two hormones in conjunction with norepinephrine, increase lipoprotein lipase activity leading to an increase of free fatty acids in the serum that may be converted into cholesterol by the liver[18].

A study in adult rats found, high cholesterol levels in their diet led to anxiety-related behaviors due to increased serum corticosterone and decreased hippocampal brain-derived neurotrophic factor, suggesting that high cholesterol may be the cause of anxiety[20].

The study found no significant changes in TG level among GAD patients, despite a positive correlation between TG and both TC and GAD severity, while other studies found high TG levels without a clear cause.

Other studies found the development of CVDs among followed GAD patient[21] and even the anxiety in patients with CVDs is linked to poor health and may lead to heart failure[22].

therefore, this study suggests that patients with GAD may develop CVDs in the future due to alarming lipid profile changes, including

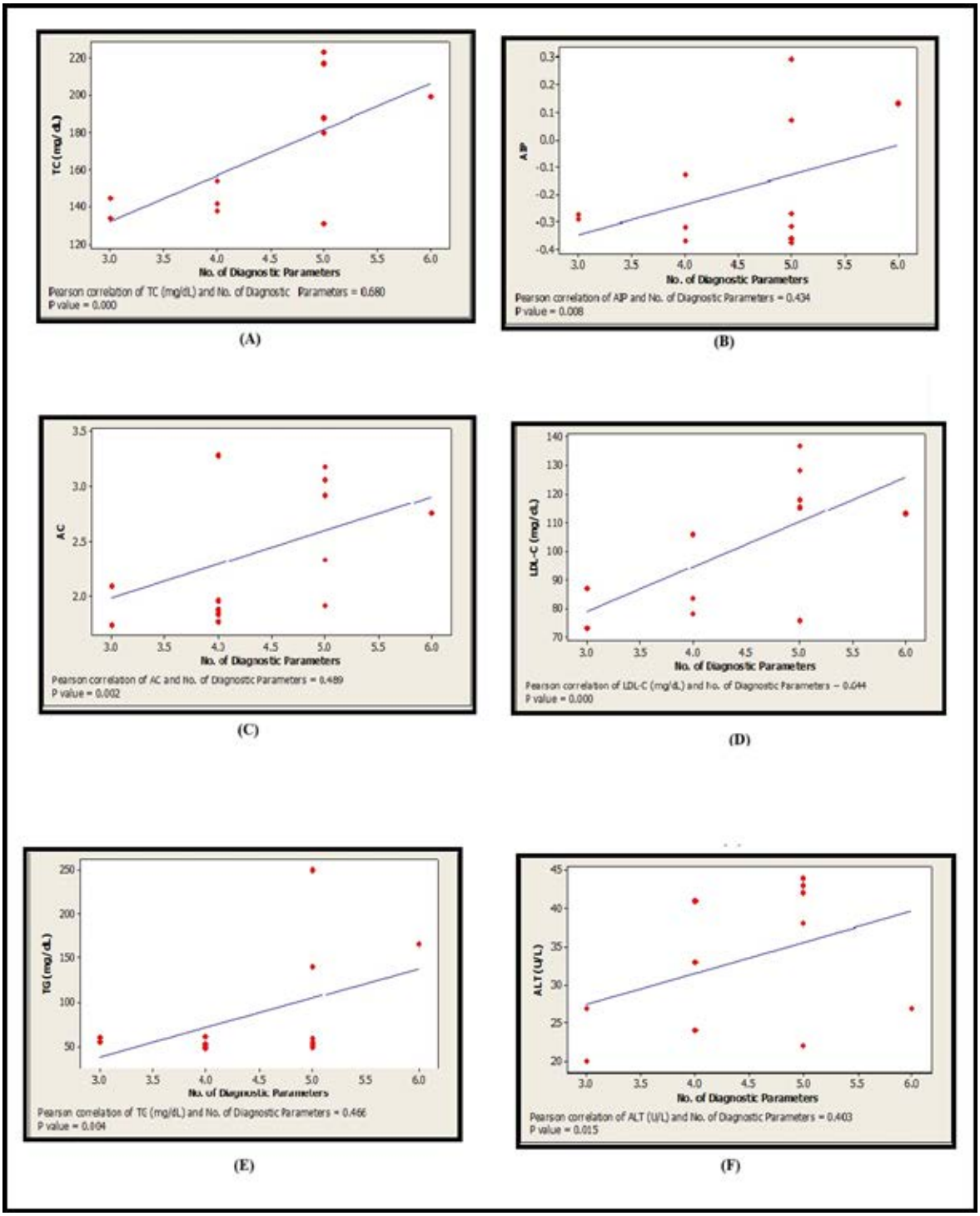

Figure 1. Correlation between number of diagnostic parameters with TC (A), AIP (B), AC (C), LDL-C (D), TG (E) and ALT (F) in group II

high levels of TC and LDL-C, a positive correlation between TG with both TC and GAD severity, and a positive correlation between GAD severity with both AIP and AC indices which are positively correlated with CVDs[5].

The study found a significant increase in ALT activity in GAD patients compared to control group, with a positive correlation between ALT activity and GAD severity (Figure 1F). However, the values of AST and ALP activities in the GAD group are neither significantly differ from the control group nor correlate with GAD severity.

In the study, all students in both groups had no significant medical or drug history that could affect the activities of ALT, AST, and ALP. and as ALT is the most sensitive and specific indicator for liver cell damage located in high concentration in the cytoplasm of liver cells[23,24] compared with both AST and ALP are located mainly in the mitochondria of liver cells and in the canalicular membrane respectively[3].

The increase in ALT activity and its positive correlation with GAD severity suggests an alarming future risk of liver diseases, this finding consistent with previous studies showing that NAFLD is associated

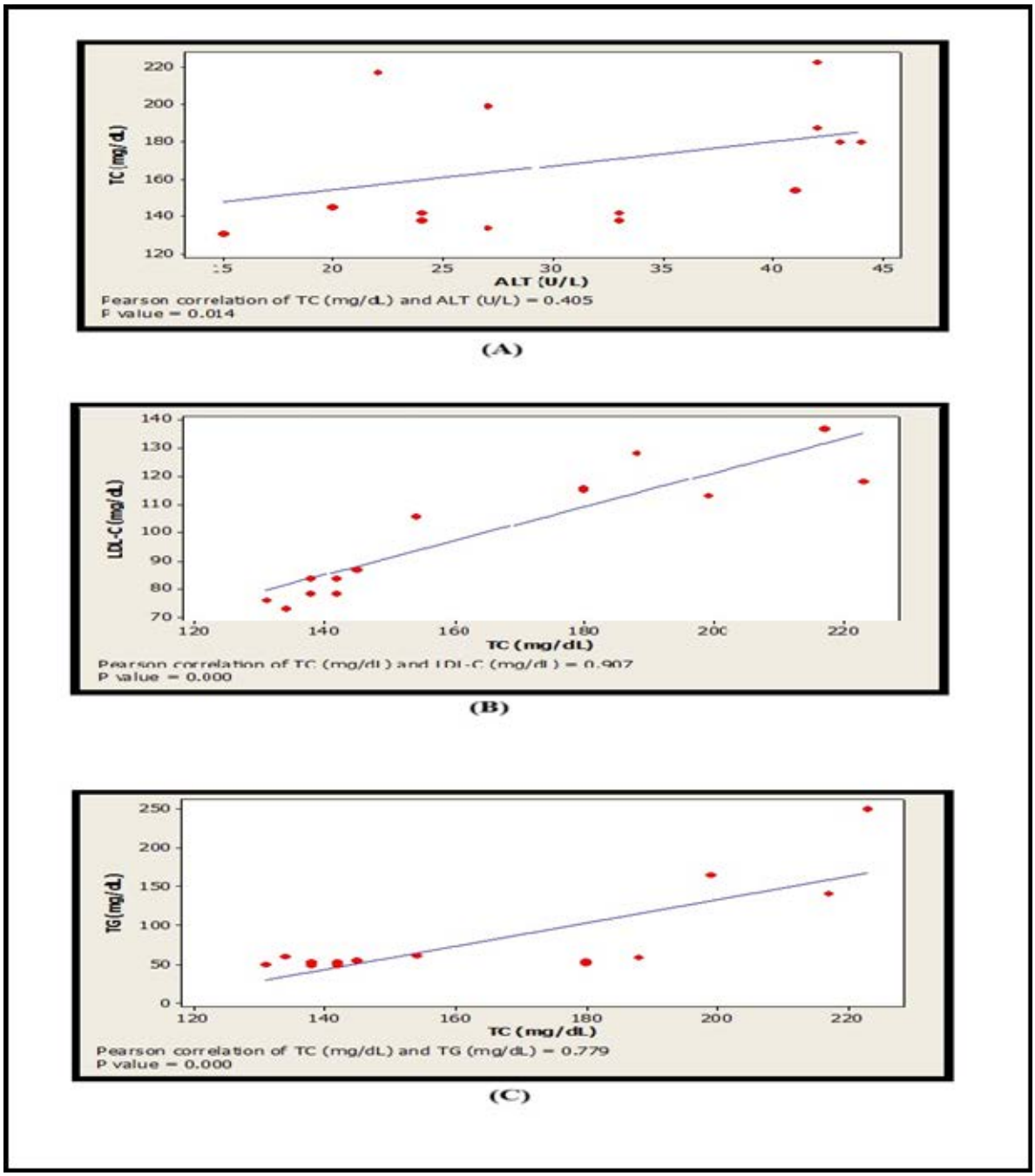

Figure 2. Correlation between TC and ALT (A), LDL-C (B) and TG (C) in group II

with increased prevalence of psychological conditions like depression and anxiety that are linked to insulin resistance and inflammatory states resulting in advancing liver histopathological changes[24]. On another hand, other studies show a positive correlation between psychological stress and liver biochemical parameters, potentially contributing to elevated liver enzymes for unknown reason[25] while other found GAD does not seem to be a risk factor for liver diseases development, but the elevated ALT activity and subsequent liver damage can be attributed to factors like anxiety related insulin resistance, inflammatory states and psychological stress[24]. The study on rats revealed that a 60% reduction in hepatic blood flow due to electric foot shock or psychological stress exposure results in hypoxia of hepatic tissues[26]. Other explanation is that psychological stress decreases intestinal blood flow through sympathetic activation and parasympathetic suppression, releasing stress hormones like norepinephrine to enter the liver and induce Kupffer cells to secrete TNF-α at levels four to sevenfold higher than controls[27].

The study found a significant positive correlation between ALT and TC in GAD group (Figure 2A), consistent with previous research indicating a positive correlation between liver damage and dyslipidemia without clear reason[28], therefore as both TC and ALT are positively correlated with each other and with GAD severity, this suggests that GAD can cause pathological changes in both lipid profile and liver simultaneously, and controlling GAD may eliminate or reduce these changes.

CONCLUSION

The study found that medical students with GAD at Ninevah Medical College showed significant elevations in TC, LDL-C

and ALT compared to those without GAD. There was a positive correlation between the GAD severity with both lipid profile parameters and ALT. These findings suggest that individuals with GAD may be at increased risk for CVDs and liver diseases development. Controlling GAD may help reduce these risks.

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Competing Interest: None

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