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Association of Abnormal Serum Bilirubin and Liver enzymes in Iraqi Patients with Metabolic Syndrome (A cross-sectional study)

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ABSTRACT

Background: *Metabolic syndrome is a multifaceted risk factor associated with insulin resistance and abnormal accumulation and functioning of adipose tissue. Hypertension, insulin resistance, central obesity, dyslipidemia, and pro-inflammatory state are cardiometabolic risk factors. Bilirubin is produced from the breakdown of haemoglobin. Recent studies show that small bilirubin elevations can protect tissue and control oxidative stress and inflammation. Alanine aminotransferase (ALT) is primarily located in the liver but also in the heart, kidneys, and muscles. Aspartate aminotransferase (AST) is present in the liver, kidneys, skeletal and cardiac muscles, and brain.*

Objectives*: The study aims to assess the impact of bilirubin and liver enzymes on the components and severity of metabolic syndrome(Obesity, fasting blood glucose, Triglycerides, HDL, and blood pressure).*

Materials and methods: *This cross-sectional study was conducted at the diabetes center in Al-Najaf City, Iraq, from October 2023 to February 2024. Age, gender, blood pressure, height, weight, fasting blood glucose, bilirubin, ALT&AST, triglycerides, and HDL were examined in 122 Mets patients.*

Results: *The study results show a significant difference ($P<0.05$) in the levels of bilirubin(0.9280±0.03783), ALT(12.8934±0.40234), and AST(22.0410±0.89667)among individuals with metabolic syndrome. Also, the study found a significant difference in ALT levels between overweight (19.8409±1.17134), obese (24.0192±.96722), and normal BMI persons (13.7692±.84909). A significant difference in AST levels was observed between those with normal BMI (16.0000±1.29970) and those with overweight (21.3182±1.72740) or obesity (22.4615±.93791). Between BMI groups, bilirubin levels were not substantially different. The study found a positive correlation between ALT and AST with fasting blood glucose and triglyceride.*

Conclusion: *Metabolic syndrome may lead to diabetes and/or fatty liver, liver steatosis, or cirrhosis, any of which may result in leakage of liver enzymes and an increase in ALT and AST. ALT and AST are liver enzymes, they are active in liver cells and used as a markers of liver cell injury*

Keywords: **Metabolic Syndrome, Body Mass Index, Bilirubin. Alanine Aminotransferase, Aspartate Aminotransferase.**

Article Information

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INTRODUCTION

Metabolic syndrome (MS) is a complex risk factor characterized by insulin resistance and irregular adipose tissue deposition and function. It is also known as Syndrome X, Insulin Resistance Syndrome[1].The prevalence rate as high as 30% in specific populations[2]. multiple diagnostic criteria for MS exist, but most of them incorporate cardiometabolic risk factors, including central obesity, dyslipidemia, hypertension, insulin resistance, and pro-inflammatory state[3]. Each of these correlated risk factors has a separate impact; nevertheless, when combined, they result in a significant rise in the incidence and death rate of cardiovascular disease [4]. Metabolic syndrome arises in an individual depending on lifestyle, genetic predisposition, and age. Insulin resistance is regarded as a primary metabolic abnormality responsible for various other symptoms of MS [5]). Individuals with MS have a fivefold chance of acquiring type 2 diabetic mellitus compared to healthy individuals; additionally, they have a threefold higher risk of experiencing a stroke and myocardial infarction compared to those without MS[6].

The metabolic syndrome, characterized by insulin resistance and glucose intolerance, is closely linked to the development of steatosis, fibrosis, and cirrhosis of the liver in extremely obese adults[7]. Metabolic syndrome encompasses several conditions such as hypertension, elevated fasting blood glucose (above 100mg/dL) or type 2 diabetes mellitus, reduced level of high-density lipoprotein cholesterol (below 40mg/dL in men or 50mg/dL in women), high concentration of triglycerides (above 150 mg/dL) and waist circumference exceeding 40 inches in men or 50 inches in women[8].

Bilirubin is generated by the breakdown of haemoglobin. There are two forms of bilirubin: unconjugated and conjugated. However, the majority of tests assess the overall levels of bilirubin. The liver metabolizes the insoluble unconjugated form into a soluble conjugated form for elimination. Unconjugated hyperbilirubinemia commonly arises from either hemolysis or defective conjugation. In contrast, conjugated hyperbilirubinemia typically occurs due to liver parenchymal disease or bile duct obstruction [9]. Bilirubin has been primarily regarded as a detrimental chemical, especially for the central nervous system, or as a negligible consequence of heme metabolism. Recent research suggests that even a slight elevation in bilirubin levels has significant benefits in protecting tissues and regulating oxidative stress and chronic inflammation in individuals with MS[10]. However, it is essential to note that excessive accumulation of bilirubin can be detrimental to newborns. Studies suggest that central obesity, insulin resistance, dyslipidemia, and hypertension, all of which are potential contributors to the development of type 2 diabetes mellitus and cardiovascular disease, are inversely correlated with total blood bilirubin([11].

Alanine aminotransferase (ALT) is primarily located in the hepatocyte but can also be found in minor quantities in cardiac, renal, and muscular tissue. Therefore, it is limited to damage specifically to hepatocytes. ALT promotes the synthesis of pyruvate and glutamate within hepatocytes, which is crucial for energy production. The typical range for ALT in males is 29-33IU/L, whereas, in females, it is 19-25IU/L[12].

Aspartate aminotransferase (AST), similar to ALT, is an enzyme found in the liver, although it is also present in other parts of the body in less quantities compared to ALT. The primary sites of occurrence are skeletal muscle, heart muscle, renal tissue, and the brain. AST facilitates amino acid metabolism. Because AST is widely distributed in several tissues, caution should be used when interpreting aberrant AST levels. The established reference range for AST is less than 35 IU/L(13). The most accurate biomarker of liver disease is ALT. Every individual aspect of MS, including heightened triglyceride level, elevated blood sugar level, expanded waist circumference, increased diastolic blood pressure, and reduced level of high-density lipoprotein cholesterol, is directly linked to elevated levels of ALT[(13)].

Aims of study

1- To assess the impact of bilirubin and liver enzymes on the components of metabolic syndrome.

2- To investigate the correlation between the severity of metabolic syndrome and the levels of the above parameters.

MATERIALS AND METHODS

Patients' collection and study design

This cross-sectional study was conducted at Al-Sadr Teaching Hospital/diabetic center in Al-Najaf City, Iraq, from 1 October 2023 to 30 February 2024. The study had a total of 122 participants, with 55 being male and 67 being female, all of whom were diagnosed with metabolic syndrome. The study group consisted of individuals between 30 and 77 years old. Essential data, including age, gender, family history, length of illness, medication history, blood pressure, height, and weight, are collected to calculate the body mass index(BMI) of the patients, along with measuring their waist circumference. Serum samples were collected to evaluate the following parameters: total bilirubin, liver enzymes (ALT&AST), fasting blood glucose, and lipid profile (triglycerides and HDL).

The sample size of a study was determined according to this equation:

N=Z2 P (1-P)/d2

Where:

N: Sample size.

Z: Statistics correspond to the confidence level, which equals 1.96, as the level of trust is 95%.

P: Expected prevalence of metabolic syndrome (%).41.8% in 2017–2018(Liang et al., 2023).

d: Precision, which equals 5%, as the prevalence of the disease is between 10% and 90%.

All cases will be subjected to complete history taking and subsequent laboratory investigations.

Inclusion and exclusion criteria

The inclusion participants include:

-Aged between (30-77years old).

-Patients with metabolic syndrome

While exclusion criteria include**:**

-Age < 18 or > 80 years old.

-Have liver disease.

-Patients taking iron supplements

-Smoker & Alcoholic patients.

Body Mass Index Calculation (BMI)

All participants' weight and height were calculated using a sensitive balance after removing excessive things (e.g., shoes, bags, coats, and jackets). After that, the BMI is calculated by using this equation:

BMI weight (Kg)/ height (m^2).

The participants were divided into four categories according to their body mass index (WHO, 2020) as shown in (table 1).

Table 1: Body mass index value

Classification	BMI (kg/m2)
Underweight	BMI< 18.5 kg/m^2
Normal	18.5-24.9 kg/m^2
Overweight	25-29.9 kg/m^2
Obese	≥30 kg/m^2

Materials

Kit of total bilirubin (Spinreact/Spain), kit of ALT (Spinreact/Spain), kit of AST (Spinreact/Spain), kit of blood glucose assay (Spinreact/Spain), kit of HDL cholesterol (Spinreact/Spain), kit of triglycerides (Spinreact/Spain), spinreact 200 / automated analyzer (Spinreact / Spain).

Statistical analysis

The data was analyzed using the statistical package for Social Sciences (SPSS) software (version 25 IBM SPSS, Inc., Chicago, Illinois, USA) and Microsoft Excel 2019. the ANOVA test was used to examine numerical variables that were normally distributed across the groups. The data was provided using the mean value together with the standard error. The graphical depiction of nominal variables included both the frequency and percentages (%). The analysis of the correlation coefficient was conducted using Pearson's Eta square. At a significance threshold of $P < 0.05$, the differences were determined to be statistically significant.

Ethical considerations

The study was founded on the ethical principles outlined in the Declaration of Helsinki. Prior to extracting the sample, the patient's explicit and cognitive permission was acquired. The local ethics committee granted authority for the study protocol, subject information, and consent form in October 2023, under document number 64, after evaluation and approval.

RESULTS

Distribution of study population according to gender:

The research had a total of 122 patients, with 55 being male (45.1%) and 67 female (54.9%), as seen in Figure 1.

Distribution of study population according to age :

The population of this study was categorized into three categories based on their age. The age group was categorized as follows: G1 (30-45 years), G2(46-61 years),G3(62-77 years) as shown in (Table 2).

Impact of some hepatic parameters on the study population

The research results demonstrate a significant difference ($P<0.05$) in the levels of hepatic parameters (bilirubin, ALT, AST) among individuals with metabolic syndrome, when comparing their levels with the normal value of each parameter as seen in (Table 3).

Distribution of total bilirubin level according to different BMI groups in the metabolic syndrome populations

The findings indicated that there were no significant differences ($P>0.05$) in the bilirubin concentration when comparing various BMI categories, as shown in (Table 4).

Distribution of ALT levels according to different BMI groups in the metabolic syndrome population

The study's results showed a significant difference (P<0.05) in the ALT levels when comparing among various BMI categories. Individuals with a normal BMI have a considerable difference when compared to individuals who are overweight or obese. Furthermore, a significant difference in the ALT level was seen between patients who were overweight and those who were obese, as shown in (Table 5).

Distribution of AST level according to different BMI groups in metabolic syndrome population

The findings from (Table 6) indicated a significant difference (P<0.05) in the levels of AST between individuals with a normal BMI and those who were overweight or obese. There was no statistically significant difference (P>0.05) seen between overweight and obese patients.

Correlation between the liver enzyme

(ALT&AST) and metabolic syndrome components (fasting blood glucose, and triglycerides):

According to the findings of the study, there is a positive correlation between the levels of ALT and AST and the levels of fasting blood glucose and triglycerides. This is seen in (Figures 2, 3, 4, and 5).

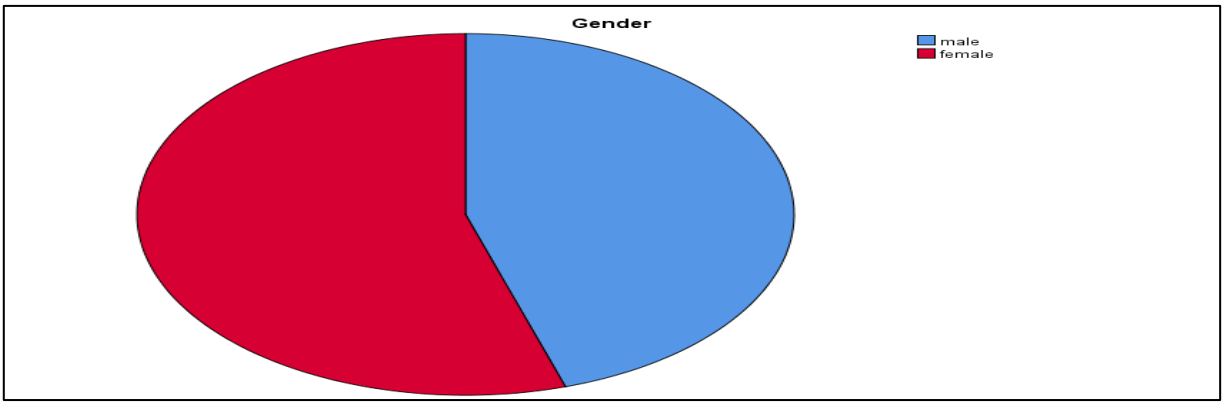


Figure 1: Distribution of the study population according to gender.

Table 2: Distribution of the study population according to their age.

Age groups	Frequency	Percentage
G1 (30-45 years)	8	6.6%
G2 (46-61 years)	76	62.3%
G3 (62-77 years)	38	31.1%

Table 3: Impact of bilirubin and liver enzymes (ALT, AST) on the study population.

Parameters	No. of patients	Mean ± St. Error	P value
Bilirubin mg/dL	122	0.9280±0.03783	0.000**
ALT U/L	122	12.8934±0.40234	0.000**
AST U/L	122	22.0410±0.89667	0.001*

ALT= alanine aminotransferase; AST= Aspartate aminotransferase ; **= highly significant; *= significant

Table 4: Distribution of total bilirubin level according to different BMI groups in the metabolic syndrome population

Dependent Variable: bilirubin			
Parameters	Groups of BMI	Mean ±S.Error	P value
Bilirubin mg/dL	Normal	.9654±.08375	.7300
	Overweight	1.0009±.07323	
	Normal	.9654±.08375	.2400
	Obese	.8477±.04684	
	Overweight	1.0009±.07323	.0740
	Obese	.8477±.04684	

Table 5: Distribution of ALT levels according to different BMI groups in the metabolic syndrome population

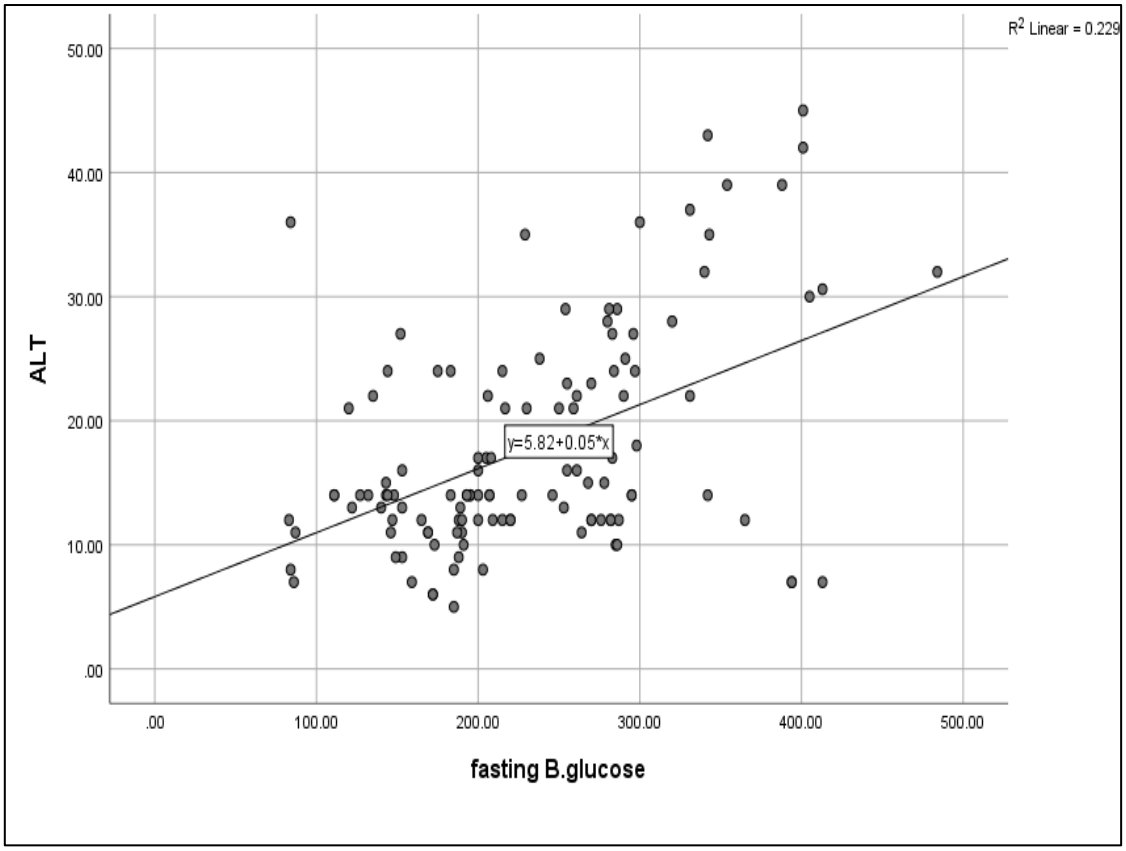
Parameters	Groups of BMI	Mean ±S.Error	P value
ALT U/L	Normal	13.7692±.84909	0.000**
	Overweight	19.8409±1.17134	
	Normal	13.7692±.84909	0.000**
	Dependent Variable: ALT		
	Obese	24.0192±.96722	
	Overweight	19.8409±1.17134	.003*0
	Obese	24.0192±.96722	

**= highly significant; *= significant

Table (6): Distribution of AST level according to different BMI groups in the metabolic syndrome population

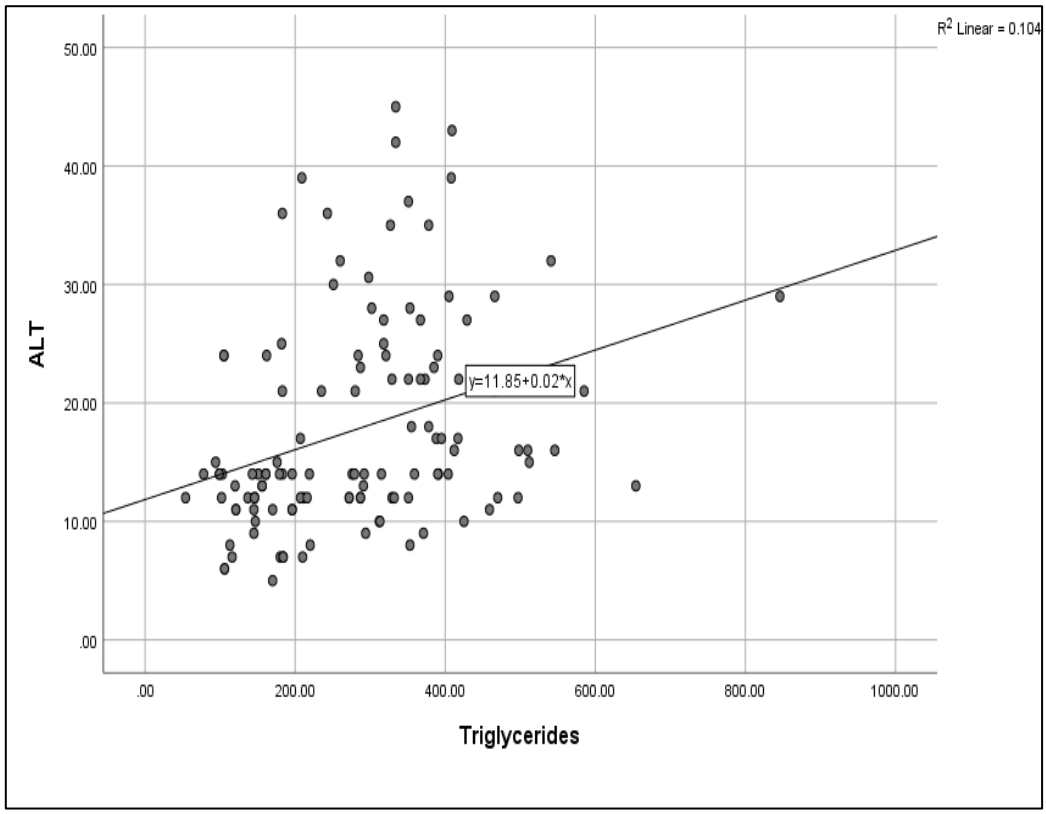
Dependent Variable: AST			
Parameters	**Groups of BMI**	**Mean ±S.Error**	**P value**
AST U/L	**Normal**	16.0000±1.29970	**0.015***
	Overweight	21.3182±1.72740	
	Normal	16.0000±1.29970	**0.003***
	Obese	22.4615±.93791	
	Overweight	21.3182±1.72740	**0.524**
	Obese	22.4615±.93791	

*= significant



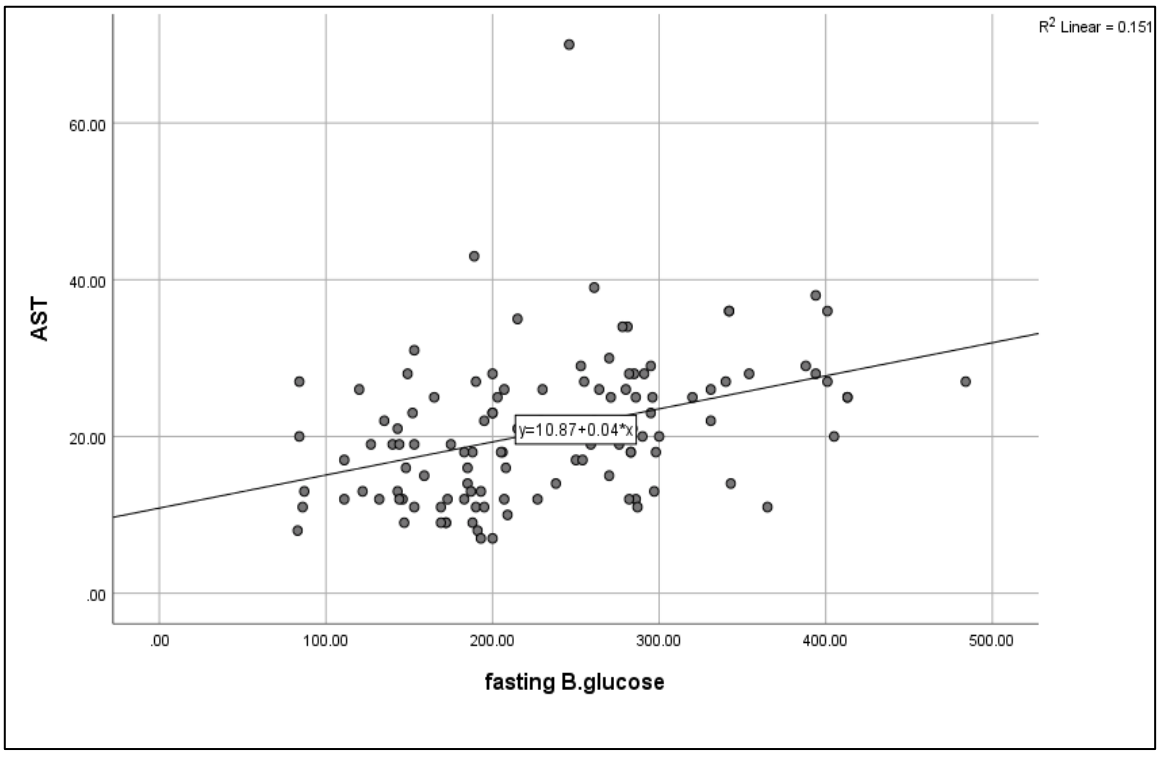
R= 0.5 P<0.00

Figure (2): Correlation between the ALT level and the level of fasting B. glucose.



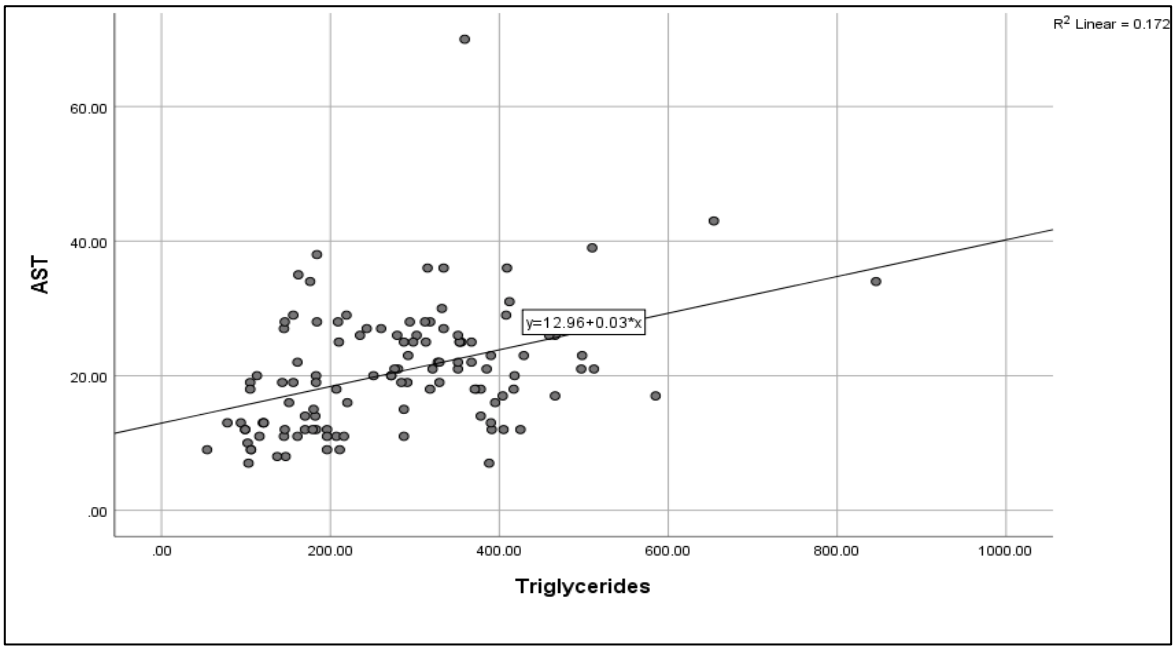
R =0.37 P<0.000

Figure (3): Correlation between the ALT level and triglycerides level.



R= 0.4 P< 0.001

Figure (4) Correlation between the AST and fasting Blood glucose levels.



R= 0.41 p<0.000

Figure (5): Correlation between the AST level and triglycerides level .

DISCUSSION

Biochemical markers like serum bilirubin can diagnose hepatobiliary and metabolic diseases. It mostly comes from senescent erythrocyte haemoglobin degradation. Bilirubin has long been considered a metabolic waste product of iron porphyrin complexes; hence, it has no benefits. Research suggests that modestly elevated bilirubin levels, such as in Gilbert's syndrome (GS), may act as an endogenous tissue protector[11]. The study's results indicate that there is no statistically significant disparity (P>0.05) in the amount of total bilirubin when comparing the BMI groups, as demonstrated in Table(3). Additional research conducted by Vieira et al.2018[15] and Liang et al.2022[16] indicates a negative correlation between levels of blood total bilirubin (TBIL) and direct bilirubin (DBIL), specifically in relation to serum DBIL levels and metabolic syndrome.

The study results show a significant difference (P<0.05) in the levels of ALT and AST when compared between BMI groups. The study results match research by Pirola, 2012 [17]. In many studies, ALT levels have been found to interact significantly with body mass index. In another study by Kim & Han, 2018 [18]), elevated ALT levels were connected to MS and its components even in the normal range. He et al. 2015 [19] also found links between MS, ALT, AST, and the AST/ALT ratio. Both men and women with MS showed lower AST/ALT ratios and higher ALT and AST levels. In addition, Zhang et al.2015[20] found that metabolic syndrome patients had considerably higher liver enzyme levels than the general population.

The rationale for these findings is that the majority of the patients exhibited impaired glucose tolerance, insulin resistance, and central obesity and were diagnosed with either diabetes or heart disease. Excessive accumulation of visceral fat can promote the increased secretion of lipoproteins high in triglycerides and the production of fat in the liver. In addition, central obesity can worsen insulin resistance due to decreased expression of insulin-sensitizing and anti-inflammatory

adiponectin, as well as increased synthesis of proinflammatory adipocytokines. Therefore, the increase in oxidative stress may be associated with elevated levels of liver enzymes[21].

The results of the study demonstrate a favorable link between the study population's fasting blood glucose level and their ALT and AST values, as seen in Figures(2,4). These findings align with those of a previous investigation by Lan et al., 2022[22]. The results of this investigation demonstrated a significant relationship between the onset of type-2 diabetes mellitus and the initial blood levels of AST and ALT. Furthermore, research by Islam et al. 2020[23] showed that those with type 2 diabetes had higher liver enzyme activity than people without type 2 diabetes.

Elevated liver aminotransferases were associated with an increased risk of diabetes. Fatty liver disease is indicated by liver cell lipid accumulation[24]. One theory is that lipid buildup and insulin resistance cause hepatic fat formation. Elevated blood aminotransferases indicate this mechanism. High insulin levels and glucose production raise the risk of diabetes [25]. Another theory is that the disease increases oxidative stress and inflammation caused by fatty acid buildup, promoting pro-inflammatory adipocytokines and systemic inflammation. Several studies show that moderate, persistent inflammation precedes atherothrombotic and diabetic symptoms. Inflammation may impair insulin signaling [26].

As seen in Figure (3,5), the study's findings indicate a positive correlation between the population's triglyceride levels and ALT and AST levels. In line with our findings, a survey by Kashinakunti et al. 2017[27] shows a significant positive correlation between TG, LDL, cholesterol, ALT, AST, and very low-density lipoprotein This resulted from the presence of fat particles that stimulate inflammation in the liver and produce free radicals. These free radicals then cause liver tissue to undergo fibrosis or cell death. Furthermore, because of the thinning brought on by the buildup of lipid residues, the liver cells may release higher concentrations of hepatic enzymes and become more permeable [28].

CONCLUSION

Metabolic syndrome may lead to diabetes and/or fatty liver, liver steatosis, or cirrhosis, any of which may result in leakage of liver enzymes and an increase in ALT and AST. ALT and AST are liver enzymes, they are active in liver cells, but in plasma, they do not perform their function and cannot lead to any disease, they are used as a marker of liver cell injury.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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