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Relation between Non-Alcoholic Fatty Liver Disease and Epicardial Fat in Metabolic Syndrome

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is becoming recognized as a component of the metabolic syndrome and insulin resistance. There has been recent interest in the association between epicardial fat and atherosclerotic disease with increased risk of cardiovascular mortality and morbidity.

Aim of the work: In this study we investigated the relationship between the metabolic syndrome with liver involvement and epicardial fat. **Patients and methods**: 85 patients who had the criteria of metabolic syndrome are subjected to thorough clinical evaluation. Abdominal circumference, body mass indexand waist/hip ratio were recorded for all patients. Laboratory investigations including urine, complete blood picture, fasting and postprandial blood glucose, uric acid, blood urea and creatinine,C-reactive protein (CRP) , lipid profile, liver enzymes and bilirubin were done to all patients. Ultrasonography was used to grade fatty liver and measure the thickness of epicardial fat. **Results**: Patients with high ALT levels have significantly higher (p<0.01) AST, fasting blood glucose (FBG), uric acid, triglyceride (TG) level, more epicardial fat and waist circumference (p<0.05) compared to those with normal levels. Patients with high grade of fatty liver have significantly higher total cholesterol, TG, FBG, AST, ALT, uric acid levels, more epicardial fat and waist circumference (p<0.01) compared to those with mild and moderate. ALT, FBG and TG are significantly higher in patients with detectable epicardial fat than those without (p<0.01). There were significant direct correlations between epicardial fat thickness with FBG (r= 0.324; p<0.01), TG (r= 0.217; p<0.05), AST (r= 0.493; p<0.01), ALT (r= 0.561; p<0.01), and grade of fatty liver (r= 0.479; p<0.01). Also there were significant direct correlations between FBG with waist circumference (r= 0.422; p = 0.01), TG level (r = 0.370; p<0.01), HDL-C (r = 0.284; p<0.05) and grade of fatty liver (r = 0.533; p = 0.01). There were significant direct correlations between grade of fatty liver with waist circumference (r= 0.264; p<0.05), TG (r= 0.407; p<0.01), uric acid (r= 0.288; p<0.05), and AST levels (r= 0.642 p<0.01). CRP was found correlated only with liver enzymes (r = 0.481;p<0.05). Simple logistic regression analysis revealed that epicardial fat thickness (mm) showed a trend in patients with NAFLD and metabolic syndrome. **Conclusion:** Echocardiographic assessment of epicardial adipose tissue, abdominal ultrasound assessment of NAFLD and transaminase level might serve as a reliable marker of visceral adiposity and more severe degree of metabolic syndrome.

Key words: Non-alcoholic fatty liver disease (NAFLD), Metabolic syndrome, Epicardial fat.

INTRODUCTION

The metabolic syndrome, which includes diabetes or prediabetes, abdominal obesity, unfavourable lipid profile and hypertension, triples the risk of myocardial infarction or stroke and doubles mortality from these conditions. It also increases the risk of developing type 2 diabetes, if not already present, fivefold.(1) There are several definitions for the metabolic syndrome; The National Cholesterol Education Program (NCEP/ATP III) is the most widely used. Current ATP III criteria define the metabolic syndrome as the presence of any Abdominal obesity, (waist circumference≥102 cm (40 in) in men and ≥88 cm (35 in) in women), Serum TG ≥ 150 mg/dL (1.7 mmol/L) or drug treatment for elevated TG, Serum high density lipoprotein cholesterol (HDL-C)≤ 40 mg/dL (1 mmol/L) in men and ≤ 50 mg/dL (1.3 mmol/L) in women or drug treatment for low density lipoprotein cholesterol (LDL-C), Blood pressure ≥ 130/85 mmHg or drug treatment for elevated blood pressure, Fasting plasma glucose

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(FPG)≥ 100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose.[2]

Non-alcoholic fatty liver disease (NAFLD) is becoming recognized as a component of the metabolic syndrome and insulin resistance. It affects up to 30% of adults and is the most common liver disease in Western nations.It encompasses the entire spectrum of fatty liver diseases from simple steatosis to nonalcoholic steatohepatitis (NASH) withlobular/portal inflammation, hepatocellular necrosis, and fibrosis.NASH is the progressive form of liver injury inmetabolic syndrome. Of those who develop NASH, 15–25% will progress to end stageliver disease and hepatocellular carcinoma over 10–20 years.[3]

Elevations of ALT, AST and ALK are common in individuals with type 2 diabetes as well as the metabolic syndrome.[4,5] Studies suggestedthatthe diagnosis ofinsulin resistance (IR) can be made with measures of obesity, withbody mass index (BMI)> 28.9 kg/m^2 identifying IR as well or better than measures of serum insulin. The addition of other clinical characteristics to the decision tree (including a family history of diabetes or elevated triglycerides) provided an even more sensitive and specific prediction of IR.[6] It was suggested that BMI alone may be a reasonably sensitive predictor of IR.There has been some recent interest in the association between epicardial fat and atherosclerotic disease.[7] The fat cells surrounding coronary arteries may play a central and previously unrecognized role in the development of cardiovascular disease. It has shown that the perivascular adipose tissue that envelops most large blood vessels in humans is involved in promoting coronary artery inflammation and growth of vasa vasorum and collateral coronary vessels in response to ischemia.[8]

Echocardiographic epicardial fat (EF) is identified as a hypoechoic space anteriorly to the right ventricular wall and its thickness is measured between the epicardial surface and the parietal pericardium, identified by the sliding between these two layers.[9] The mean values described for EF thickness in systole during investigation of cardiovascular risk were 6.8 mm.[10] Echocardiographic epicardial fat thickness reflects visceral adiposity rather than general obesity. It correlates with metabolic syndrome, insulin resistance, coronary artery disease, and subclinical atherosclerosis, and therefore it might serve as a simple tool for cardiometabolic risk prediction.[11,12] Epicardial fat thickness is independently correlates with cardiac performance index. Increased epicardial fat thickness may therefore be a predictor of left ventricular dysfunction.[13]

The aim of this study is to define the relation between the metabolic syndrome and non-alcoholic fatty liver diseasewiththe epicardial fat. The correlation between elevated liver function, amount of epicardial fat and the component of metabolic syndromes will be studied.

PATIENTS AND METHODS

This study included 85 patients who had the criteria of metabolic syndrome.They are recruited from Theodor Bilharz Research Institute hospital. All the patients were subjected to thorough clinical evaluation including history taking with special stress on the manifestations of diabetes, cardiovascular diseases and liver affection. Abdominal circumference, BMI and waist/hip ratio were recorded for all patients. Routine laboratory investigations were done including urine, complete blood picture, fasting and postprandial blood sugar, uric acid, blood urea and creatinine, lipid profile and liver enzymes and bilirubin. Estimation of CRP was done to all patients.

The diagnosis of fatty liver was based on the brightness of the liver on abdominal ultrasound (US) in comparison with the kidney, vascular blurring of the hepatic vein trunk, and deep attenuation in the right hepatic lobe.[14]The severity of fatty liver change was classified according to standardized ultrasonographic criteria.[15] Fatty liver was assessed semi-quantitatively on a scale of mild, moderate, to severe on the basis of abnormally intense, high-level echoes arising from the hepatic parenchyma, liver-kidney difference in echo amplitude, echo penetration into the deep portion of the liver, and clarity of the blood vessel structures in the liver.[16] This scale was associated with the metabolic syndrome.[17]

The diagnosis of epicardial fat was based on the use of echocardiography for the direct assessment of epicardial adipose tissue. The thickness of epicardial fat was measured on the free wall of the right ventricle from both parasternal long-axis and short-axis views. Measurements were also made of

M-Mode strips obtained from both two-dimensional views, with longitudinal cursor-beam orientation in each. The maximum values at any site were measured and the average value considered.[18,11]

Inclusion criteria: Patients with criteria of metabolic syndrome.

Exclusion criteria:

1. Patients with endocrinal diseases apart from DM
2. Patients with positive markers for viral hepatitis and autoimmune diseases
3. Patients with alcoholic liver disease
4. Patients with heart failure, renal impairment or other major systemic disease
5. Patients with history of any prior liver disease apart from NAFLD

All patients were provided by informed consent, and the ethical committee of hospital approved this study.

STATISTICS ANALYSIS

Statistical analyses were carried out using the Statistical Package for Social Sciences for Windows version 20.0 (SPSS, Chicago, IL, USA). Descriptive statistics for each variable were determined. Results for continuous variables were demonstrated as data were expressed as Mean±SE and were compared using Kruskal-Wallis in the same group was performed using Friedman's ANOVA with post hoc Wilcoxon matched pairs. Statistically significant differences between groups were determined non-parametrical tests were used due to the distribution of the variables. Associations between the variables were explored using the Pearson correlation and differences among groups were identified by the Mann-Whitney *U* test. A multiple stepwise line regression analysis was used to determine the contribution of various factors to EF. Statistical significance was defined as a *p* value less than <0.05.

RESULTS

This study included 85 patients with mean age of 43.88year. Baseline clinical and laboratory characteristics of all patients are showed in table (1). Patients with high ALT levels have significantly higher CRP ($p< 0.05$), FBG, AST, uric acid, TG levels, more epicardial fat and waist circumference ($p<0.01$) compared to those with normal levels (table 2). Patients with high FBG levels have significantly higher blood pressure, AST, ALT, uric acid, TG levels, more epicardial fat and waist circumference ($p< 0.01$) compared to those with normal levels (table 3).

In table (4) patients with high TG levels have significantly higher diastolic blood pressure, ALT ($p< 0.01$), AST, FBG levels and more epicardial fat ($p< 0.05$) compared to those with normal levels. ALT, FBG and TG are significantly higher in patients with detectable epicardial fat than those without ($p< 0.01$) table (5) and Fig (1). Patients with high grade of fatty liver have significantly higher total cholesterol, TG, AST, ALT, uric acid, FBG levels, more epicardial fat and waist circumference ($p< 0.01$) than those with mild and moderate table (6).

Simple logistic regression analysis revealed that epicardial fat thickness (mm) showed a trend in patients with NAFLD and metabolic syndrome. 91.9% were correctly classified by the model to have epicardial fat and 69 % were correctly classified without epicardial fat (OR = 1.422, 95% CI: 0.915-2.236; $p < 0.01$). Factors affecting the model (best model) are epicardial fat, waist circumference, systolic, diastolic blood pressure and liver enzymes table (7).

There were significant direct correlations between epicardial fat thickness with FBG (r=0.324; $p<0.01$), TG (r=0.217; $p<0.05$),AST (r=0.493; $p<0.01$), ALT (r= 0.561;$p<0.01$), and grade of fatty liver (r= 0.479; $p<0.01$) (Fig.2). Also there were significant direct correlations between FBG with waist circumference (r=0.422; $p = 0.01$), TG level (r=0.370; $p<0.01$), HDL-C(r=0.284; $p<0.05$) and grade of fatty liver (r=0.533; $p= 0.01$). There were significant direct correlations between grade of fatty liver with waist circumference (r=0.264; $p<0.05$), TG (r= 0.407; $p<0.01$), uric acid (r= 0.288; $p<0.05$), and AST levels (r=0.642; $p<0.01$). CRP was found correlated only with liver enzymes (r=0.481; $p<0.05$).

DISCUSSION

Extra-abdominal visceral fat depots, including mediastinal and epicardial fat, have been studied with emerging evidence pointing to a specific role for epicardial adipose tissue, both as a cardiac risk marker and as a potentially active player in the development of cardiac pathology.[19]

In our study, we examined the epicardial fat, in association with all metabolic parameters, in

addition to liver fat and liver function tests trying to correlate these factors together. Patients with fatty liver disease and elevated liver enzymes has statistically higher waist circumference, fasting blood glucose level, uric acid, serum triglyceride, and epicardial fat thickness. Thus, with increasing the liver affection, metabolic parameters and epicardial fat become worse. This was supported also by the finding of significant direct correlations between the same parameters. It means that all these abnormalities could be induced and affected by the same pathogenesis which is insulin resistance; the main cause of metabolic syndrome. Also, it could be possible that NAFLD including steatohepatitis and epicardial fat when found during general examination might be considered as markers of metabolic syndrome.

Another important point in this study is the finding of significant direct correlation between CRP being an inflammatory marker and liver enzymes. This might explain the inflammatory progress of liver disease in metabolic syndrome that can lead to steatohepatitis and even liver cirrhosis with its all complications. In 652 subjects from the Insulin Resistance Atherosclerosis Study (IRAS) who did not have the metabolic syndrome or diabetes at baseline, liver functions were assessed for their role in predicting the development of the metabolic syndrome.[1,20] After 5 years, 131 (20%) of subjects had developed the metabolic syndrome. The levels of ALT and ALK were correlated with the number of metabolic disorders at follow-up. Therefore, evolving abnormalities in liver function tests may portend the eventual development of the metabolic syndrome in high-risk individuals.[4] In another recent study, it was found that patients with metabolic syndrome had a higher global nonalcoholic steatohepatitis (NASH) score based on liver histology than did patients without metabolic syndrome. They had more severe steatosis, hepatocytic ballooning and a higher NASH activity score. The patients with higher NASH scores also were significantly less active than those in the low-score group.[5]

Similarly, other studies showed correlation of liver transaminases with blood pressure, dyslipidaemia, blood glucose and waist circumference as components of the metabolic syndrome.[21-23] There was evidence of association between hepatic steatosis or its marker alanine aminotransferase (ALT) and carotid atherosclerosis[24] and also coronary events.[25]

The directly determined liver fat content was shown to correlate with several features of insulin resistance in normal weight and moderately overweight subjects independent of BMI and intra-abdominal or overall obesity.[26] Also, it was found that ALT appears to be the best marker for liver fat accumulation.[27] Elevated ALT has been shown to predict incident type 2 diabetes.[28] In another study, ALT, but not aspartate aminotransferase levels were found to increase progressively with the increasing number of metabolic syndrome abnormalities.[29] It was suggested that inflammatory cytokines via their ability to enhance *de novo* hepatic fatty acid synthesis, may contribute to both elevated ALT and diabetes. Also, it was found in these studies that elevated CRP was an independent predictor of incident diabetes.

The metabolic syndrome was found to be associated with measures suggestive of low grade inflammation, such as concentrations of CRP and increased proinflammatory cytokines.[4,30-32] This low-grade inflammation, which has been associated with an increased risk for cardiovascular disease and diabetes[18,33] may provide a mechanism for the increased risk of these conditions experienced by individuals who have the metabolic syndrome. The close anatomic relationship of epicardial adipose tissue to the adjacent myocardium and coronary vessels could suggest paracrine regulation by this small fat depot, although the relationship could not exclude systemic control. Also, the epicardial adipose mass might reflect intra-abdominal visceral fat.[34,9,8]

CONCLUSION

Echocardiographic assessment of epicardial adipose tissue, abdominal ultrasound assessment of NAFLD and transaminase level might serve as a reliable marker of visceral adiposity and more severe degree of metabolic syndrome. Further studies of this neglected tissue and its relationship with cardiac function, as well as of its use as a marker of metabolic and cardiovascular risk, should be encouraged.

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Table 1: Baseline Clinical and laboratory characteristics of study population

Characteristics	Mean±SE N= 85
Age (Y)	43.88 ± 1.08
Waist Circumference (cm)	115.32±1.13
Epicardial Fat (cm)	0.47±0.21
Systolic Blood Pressure (mm Hg)	144.12±1.77
Diastolic Blood Pressure (mm Hg)	95.55±1.03
Total Cholesterol (mg/dl)	215.61±3.30
Triglyceride (mg/dl)	235.20±8.67
HDL-C (mg/dl)	38.62±0.85
Uric Acid (mg/dl)	6.98±0.15
AST (IU/L)	41.78±2.04
ALT (IU/L)	62.60±3.58
CRP (mg/L)	6.57±0.49
Fasting Blood glucose (mg/dl)	126.29±4.18

Table 2: Clinical, Laboratory and sonographic parameters according to ALT level.

	Normal ALT (IU/L) level N= 23	High ALT (IU/L) level N= 62
Age (Y)	40.52±1.89	45.00±1.83*
Epic. fat thickness (cm)	0.34±0.04	0.51±0.02**
Waist Circumference (cm)	112.17±1.43	117.55±1.01**
Systolic Blood Pressure (mm Hg)	145.65±3.00	143.36±2.17
Diastolic Blood Pressure (mm Hg)	95.83±1.36	95.45±1.32
Total Cholesterol (mg/dl)	207.78±8.01	218.52±3.38
Triglyceride (mg/dl)	185.91±13.49	253.48±9.86**
HDL-C (mg/dl)	36.30±1.27	39.48±1.04
AST (IU/L)	26.39±0.79	47.48±2.41**
ALT (IU/L)	34.91±1.12	72.87±4.21**
Uric Acid (mg/dl)	6.19±0.26	7.27±0.17**
CRP (mg/L)	4.74±0.99	7.25±0.55*
Fasting Blood Glucose (mg/dl)	103.86±3.46	134.61±5.20**

Normal ALT range 10-40 IU/L; High ALT >40 IU/L

*p<0.05 significant, **p<0.01 highly significant.

Table 3: Clinical, Laboratory and sonographic parameters according to FBG Levels.

	Normal FBGN = 39	High FBGN = 46
Age (Y)	39.79±1.62	47.35±1.24**
Epicardial Fat (cm)	0.38±0.03	0.54±0.02**
Systolic Blood Pressure (mm Hg)	138.21±2.29	149.13±2.42**
Diastolic Blood Pressure (mm Hg)	93.43±1.38	97.35±1.45
Waist Circumference (cm)	111.67±0.93	119.85±1.15**
Total Cholesterol (mg/dl)	209.92±6.18	220.43±3.02
Triglyceride (mg/dl)	196.23±11.18	268.24±10.79**

HDL-C (mg/dl)	38.05±1.05	39.11±1.29
AST (IU/L)	34.41±1.71	48.02±3.21**
ALT (IU/L)	49.49±3.37	73.71±5.50**
Fasting Blood Glucose (mg/dl)	103.86±3.46	134.61±5.20**
Uric Acid (mg/dl)	6.54±0.22	7.35±0.19**
CRP (mg/L)	5.95±0.74	7.10±0.67

#Normal FBG range 65-110; High FBG>110** $p<0.01$ highly significant.

Table 4: Clinical, Laboratory and sonographic parameters according TG level.

	Normal TG Level N=28	High TG level N=57
Age (Y)	39.25±1.91	46.16±1.20**
Epicardial Fat (cm)	0.41±0.04	0.50±0.02*
Systolic Blood Pressure (mm Hg)	139.64±2.69	146.32±2.25
Diastolic Blood Pressure (mm Hg)	91.57±1.76	97.51±1.19**
Waist Circumference (cm)	113.78±1.19	117.23±1.13
Total Cholesterol (mg/dl)	213.14±6.68	216.82±3.71
Triglyceride (mg/dl)	155.00±5.21	274.60±8.80**
HDL-C (mg/dl)	39.29±1.38	38.29±1.07
AST (IU/L)	36.71±3.03	44.26±2.6*
ALT (IU/L)	53.75±5.16	66.95±4.63**
Uric Acid (mg/dl)	6.55±0.28	7.19±0.18
CRP (mg/L)	5.61±0.82	7.05±.61945
Fasting Blood Glucose (mg/dl)	115.18±4.40	131.75±5.73*

#Normal TG range 50-160, High TG >160.
* $p<0.05$significant, ** $p<0.01$ highly significant.

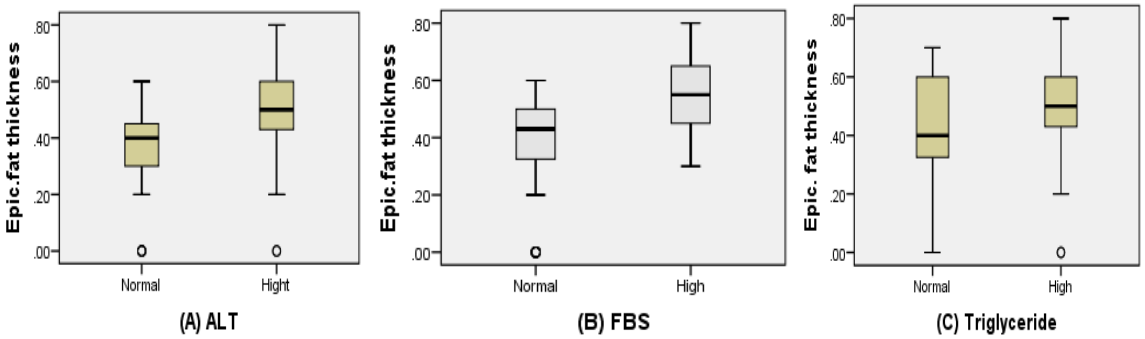

Fig.1: Boxplots of (A) ALT, (B) FBG, (C) Triglyceride with the epicardial fat thickness. The box represents the interquartile range; the line across the box is the median, the top and bottom of the box are the 25th and 75th percentile respectively.

Table 5: Comparison of all parameters with epicardial fat detected by echocardiography.

	Epicardial fat	
	Present N=66	Absent N=19
Age (Y)	43.38±1.24	45.63±2.13
Systolic Blood Pressure (mm Hg)	141.96±1.88	151.58±4.14
Diastolic Blood Pressure (mm Hg)	95.18±1.17	96.84±2.17
Waist Circumference (cm)	115.28±0.99	118.89±1.65
Total Cholesterol (mg/dl)	215.98±3.94	214.32±3.71
Triglyceride (mg/dl)	233.32±10.03	246.74±15.43**
HDL (mg/dl)	38.86±0.90	37.79±2.17
AST (IU/L)	40.92±2.20	44.73±5.05*
ALT (IU/L)	60.41±3.78	72.32±7.23**
Uric Acid (mg/dl)	6.88±0.17	7.34±0.34
CRP (mg/L)	6.48±0.56	6.89±1.08
Fasting Blood Glucose (mg/dl)	124.55±4.86	132.37±8.04**

*p<0.05significant
**p<0.01 highly significant.

Table (6): Clinical, Laboratory and sonographic parameters according to grade of fatty liver.

	Mild N=14	Moderate N=25	Severe N=46
Age (Y)	43.64±2.43	40.20±2.19	45.96±1.35
Epic. fat thickness (cm)	0.40±0.05	0.36±0.04	0.55±0.02**
Waist Circumference (cm)	110.07±1.67	113.72±1.29	119.22±1.16**
Systolic Blood Pressure (mm Hg)	147.86±4.71	140.80±2.44	144.78±2.63
Diastolic Blood Pressure (mm Hg)	96.00±1.97	94.40±1.74	96.04±1.55
Total Cholesterol (mg/dl)	199.14±9.56	206.20±6.64	225.73±3.40**
Triglyceride (mg/dl)	159.21±12.44	205.80±10.71	274.30±11.34**
HDL (mg/dl)	39.57±2.05	36.44±1.25	39.52±1.25
AST (IU/L)	26.86±1.27	36.12±2.33	49.39±3.08**
ALT (IU/L)	34.86±1.97	52.28±4.55	76.65±5.21**
Uric Acid (mg/dl)	5.58±0.30	6.59±0.29	7.62±0.16**
CRP (mg/L)	4.64±1.01	5.84±1.04	7.56±0.63*
Fasting Blood Glucose (mg/dl)	104.35±5.22	108.24±4.09	142.78±6.29**

*p<0.05 significant increase than mild and mild.**p<0.01 highly significant increase than mild and moderate.

Table(7): Logistic regression analysis of epicardial fat thickness.

	Simple regression OR (95% CI)	p-value
Epicardial fat thickness	1.422 (0.915-2.236)	<0.01

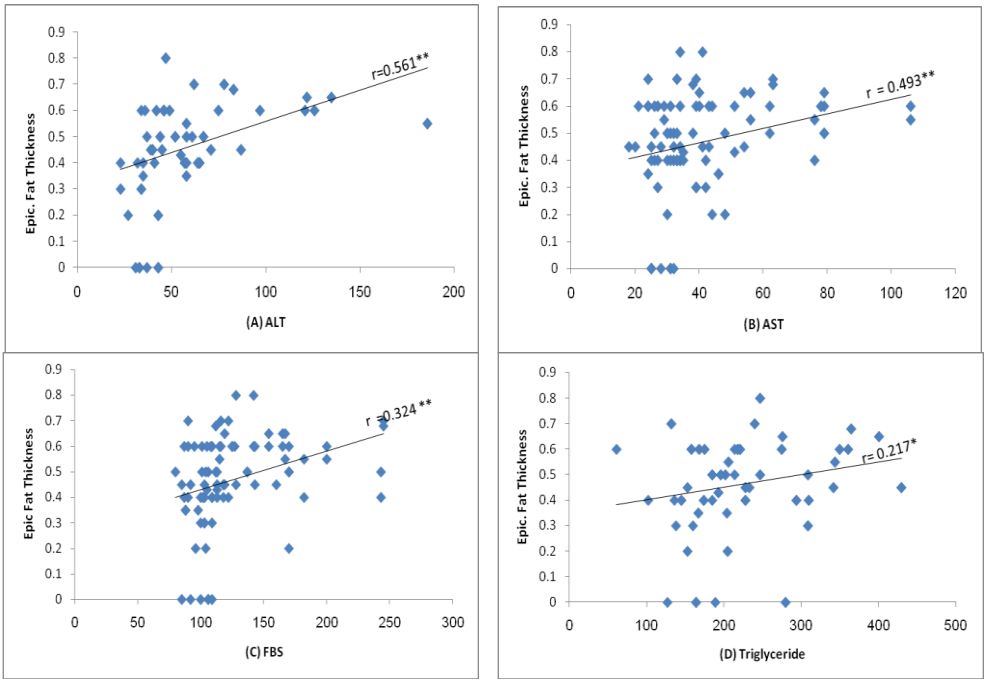

Fig.2:correlation between the epicardial fat thickness and(A) ALT, (B) AST, (C) FBG and (D)triglyceride. $^{*}p<0.05$ significant, $^{**}p<0.01$ highly significant.