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Research Article

Subclinical atherosclerosis and related factors in patients with liver cirrhosis: a case–control study

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ABSTRACT

Background: The atherosclerosis and its complications may be less prevalent in patients with liver cirrhosis. However, the mechanisms underlying this observation remain unclear. This study aimed to evaluate the frequency of subclinical atherosclerosis and associated biochemical factors in patients with cirrhosis.

Methods: This case–control study included 49 patients with liver cirrhosis and 28 age- and sex-matched healthy controls. Subclinical atherosclerosis was assessed by Doppler ultrasonography measuring carotid intima–media thickness (CIMT) and the presence of carotid plaques. Laboratory parameters associated with atherosclerosis, including lipid profile, lipoprotein(a), oxidized low-density lipoprotein (oxLDL), insulin, homocysteine, platelet count, fibrinogen, high-sensitivity C-reactive protein (hsCRP), and bilirubin levels, were analyzed. Statistical analyses were performed using Student's t-test or Mann–Whitney U test as appropriate, with $p < 0.05$ considered statistically significant.

Results: Mean CIMT was significantly lower in cirrhotic patients compared with controls (0.664 ± 0.133 mm vs. 0.749 ± 0.091 mm, $p = 0.002$). Carotid plaque was detected in 18.4% of patients and 14.3% of controls. Cirrhotic patients had significantly higher oxLDL levels, whereas total cholesterol, LDL-cholesterol, triglycerides, lipoprotein(a), platelet counts, and fibrinogen levels were significantly lower compared with controls. hsCRP levels were significantly higher in the cirrhosis group. No significant differences were observed in HDL cholesterol, blood pressure, body mass index, or homocysteine levels between groups.

Conclusion: Despite the presence of potential pro-atherogenic factors such as insulin resistance and elevated oxLDL levels, cirrhotic patients demonstrated lower carotid intima–media thickness, suggesting reduced subclinical atherosclerosis. Decreased lipid levels, thrombocytopenia, and hyperbilirubinemia may contribute to this paradoxical finding.

Keywords: liver cirrhosis, subclinical atherosclerosis, carotid intima–media thickness, oxidized LDL

Introduction

Liver cirrhosis is an irreversible disease characterized by chronic hepatocellular injury accompanied by inflammation, fibrosis, and nodular regeneration, ultimately leading to clinical manifestations of hepatocellular insufficiency and portal hypertension (1). According to the World Health Organization (WHO), liver cirrhosis causes over 1.4 million deaths annually worldwide, accounting for approximately 2.4% of global deaths. The age-standardized death rate due to liver cirrhosis in Türkiye was 7.1 per 100,000 population in 2019

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(2). The major causes of mortality in cirrhotic patients are complications associated with hepatocellular failure and portal hypertension (3).

Interestingly, several metabolic and vascular alterations observed in cirrhosis may influence cardiovascular risk and the development of atherosclerosis. Atherosclerosis is a focal, inflammatory, fibrotic, and degenerative disease affecting the intimal layer of medium- and large-sized elastic arteries. It begins in childhood, progresses slowly over decades, and eventually leads to clinical symptoms (cardiovascular and cerebrovascular diseases) and causes morbidity and mortality due to mechanical obstruction of blood flow (4,5). Major risk factors for atherosclerosis include diabetes mellitus, hypertension, smoking, dyslipidemia, obesity, advanced age, an atherogenic diet, physical inactivity, male sex, hyperhomocysteinemia, and prothrombotic conditions (6,7).

Measurement of carotid intima-media thickness (CIMT) using high-frequency (7–12 MHz) Doppler ultrasonography for detecting subclinical atherosclerosis has become the most widely used technique in clinical studies because of its non-invasive nature, reproducibility, and ease of application (8).

Although cirrhosis is associated with several metabolic abnormalities that may theoretically promote atherosclerosis, previous studies have reported conflicting results regarding the actual burden of vascular disease in these patients (9-11). The relationship between cirrhosis and atherosclerosis has not yet been fully clarified. In this study, CIMT, a reliable marker of subclinical atherosclerosis, was measured using Doppler ultrasonography to compare patients with cirrhosis and healthy control subjects. In addition, clinical and laboratory parameters potentially contributing to the development of atherosclerosis in cirrhotic patients were evaluated before the occurrence of overt cardiovascular complications. The aim of this study was to identify major risk factors associated with atherosclerosis in patients with liver cirrhosis.

Materials and Methods

Study design and ethical approval

This study was conducted at the Department of Gastroenterology, Trakya University Faculty of Medicine, between April 2011 and May 2012. The study was designed to investigate the presence of subclinical atherosclerosis and its associated risk factors in patients with chronic liver cirrhosis. Ethical approval was obtained from the Local Ethics Committee of Trakya University (approval date: April 6, 2011). The study was supported by the Trakya University Scientific Research Projects Unit (TÜBAP; project number: 2011-170). All participants were informed about the study both verbally and in writing, and written informed consent was obtained from each participant before enrollment.

Study population

A total of 49 adult patients with clinically, laboratorial, and radiologically diagnosed liver cirrhosis who were followed in the Gastroenterology outpatient clinic of Trakya University Faculty of Medicine were included in the study.

Patients with cirrhosis were excluded if they had any of the following conditions; diabetes mellitus, hyperlipidemia receiving treatment, hypertension receiving treatment, history of cardiovascular disease or cerebrovascular disease, hepatocellular carcinoma, active bacterial infection or history of esophageal variceal bleeding within the last three months.

The control group consisted of 28 healthy adult volunteers with no known acute or chronic disease. The controls were age- and sex-matched to the patient group and were selected from individuals who presented to the internal medicine outpatient clinic with nonspecific complaints but had no pathological

findings on clinical examination or laboratory evaluation. Individuals with diabetes mellitus, hyperlipidemia, hypertension, cardiovascular or cerebrovascular disease, active bacterial infection, or malignancy were excluded from the control group.

Clinical assessment

Demographic data and detailed medical histories of all participants were recorded. Physical examinations were performed and anthropometric measurements were obtained.

Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared (kg/m²). Waist circumference was measured at the midpoint between the iliac crest and the lower rib margin during normal expiration with the participant standing. Arm circumference was measured at the midpoint between the acromion and the olecranon. Blood pressure measurements were obtained using a calibrated aneroid sphygmomanometer according to World Health Organization guidelines.

Measurement of carotid intima-media thickness

CIMT measurements were performed at the Department of Radiology by an experienced radiologist who was blinded to the clinical and laboratory data of the participants. Measurements were obtained using an Esaote MyLab 60 ultrasound device (Esaote, Saint-Germain, France) with a 7.5 MHz linear transducer in B-mode.

Participants were examined in the supine position with the neck slightly extended and the head turned approximately 45° away from the side being examined. Longitudinal images of the carotid artery were obtained using high-resolution Doppler ultrasonography. CIMT was defined as the distance between the lumen–intima interface and the media–adventitia interface of the arterial wall.

Measurements were performed on the far wall of the common carotid artery over a segment of at least 1 cm, and the highest value obtained was recorded. Both right and left carotid arteries were examined, and the arithmetic mean of the measurements was calculated.

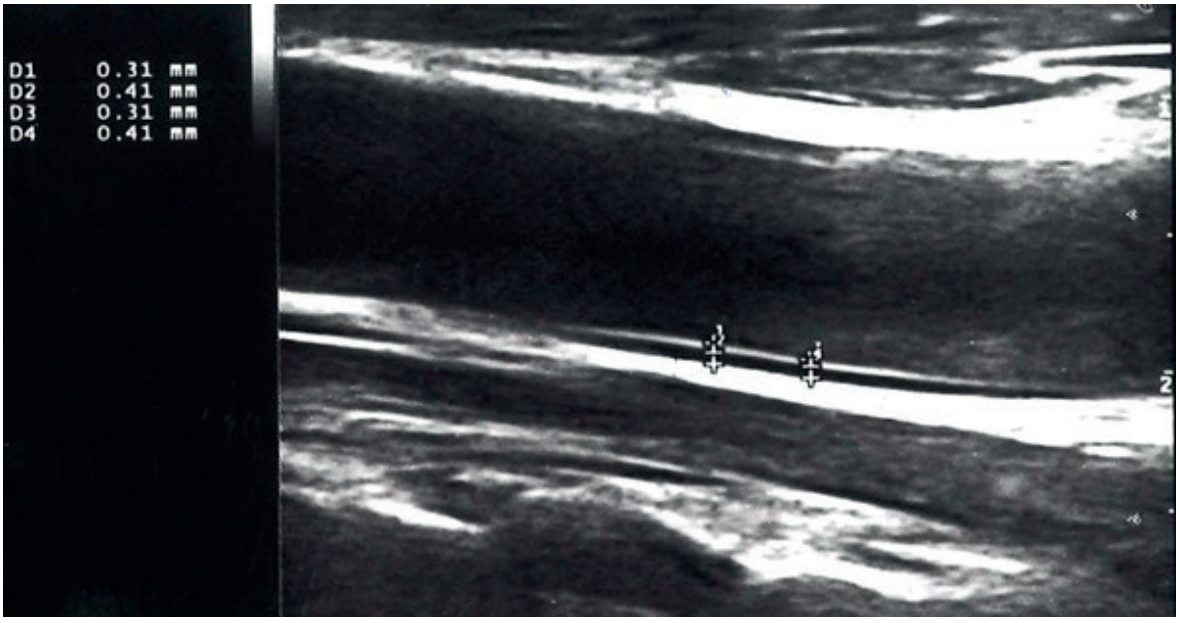

Figure 1. Doppler Ultrasonography image of the thickness of carotid intima media

Carotid plaques were evaluated throughout the common carotid artery and carotid bulb region. A focal protrusion into the lumen greater than 0.5 mm, a thickening exceeding 50% of the surrounding CIMT, or a CIMT measurement greater than 1.5 mm was defined as a plaque. CIMT measurements were not performed at sites where plaques were detected (Figure 1).

Biochemical analysis

Routine laboratory parameters were obtained from hospital medical records or the laboratory information system.

Blood samples were stored at −80°C until the day of study. Homocysteine and insulin levels were measured using the Siemens Immulite 2000 XPi system (Tarrytown, NY, USA). Lp(a) and high-sensitivity C-reactive protein (hsCRP) levels were measured using the Siemens BN2 nephelometric analyzer (Siemens, Tarrytown, NY, USA).

Oxidized low-density lipoprotein (oxLDL) levels were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Immundiagnostik, Bensheim, Germany) according to the manufacturer's instructions, and absorbance was measured at 450 nm using a Biotek ELISA reader (Vermont, USA).

Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) with the following formula:

HOMA-IR = [Fasting insulin (μU/mL) × fasting plasma glucose (mg/dL)] / 405.

Statistical analysis

All statistical analyses were performed using SPSS software version 19 (SPSS Inc., Chicago, IL, USA). The distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± standard deviation or median values where appropriate. For comparisons between the patient and control groups, the Student's t-test was used for normally distributed variables, whereas the Mann–Whitney U test was used for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test where appropriate. A p value < 0.05 was considered statistically significant.

Results

A total of 77 individuals were included in the study, consisting of 28 healthy controls and 49 patients with liver cirrhosis. Among the cirrhotic patients, the etiology was hepatitis B virus (HBV) infection in 13 patients and alcohol consumption in 13 patients. The distribution of cirrhotic patients according to the Child–Turcotte–Pugh (CTP) classification is shown in Figure 2. According to the CTP staging system, 27 patients were classified as stage A, 18 as stage B, and 4 as stage C.

Demographic, anthropometric, and blood pressure characteristics of study groups

In the control group, 17 participants were female and 11 were male, whereas in the cirrhosis group 19 were female and 30 were

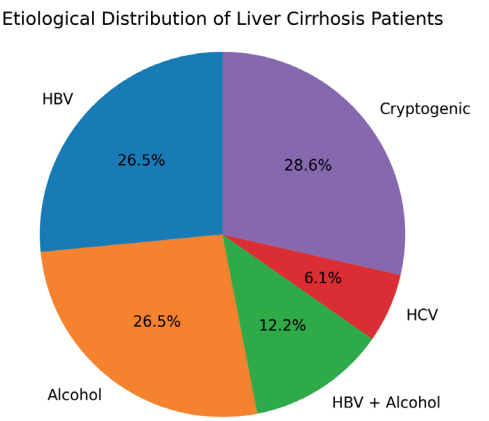

Figure 2. Etiological distribution of liver cirrhosis among the study population. The most frequent causes were cryptogenic cirrhosis (28.6%), hepatitis B virus (HBV) infection (26.5%), and alcohol-related cirrhosis (26.5%), followed by combined HBV and alcohol-related cirrhosis (12.2%) and hepatitis C virus (HCV) infection (6.1%).

male (p=0.06). The mean age was 49.9 ± 7.4 years in the control group and 53.8 ± 10.7 years in the cirrhosis group (p=0.09). Smoking was reported in 32% (n = 9) of the control group and 42% (n = 21) of the cirrhosis group (p=0.35) (Table 1).

The mean body mass index (BMI) was 28.9 ± 4 kg/m² in the control group and 27.3 ± 5.9 kg/m² in the cirrhosis group (p = 0.18). The mean waist circumference was 99.8 ± 10.7 cm in the control group and 101.3 ± 15.4 cm in the cirrhosis group, with no significant difference between the groups (p = 0.99). However, arm circumference was significantly lower in patients with cirrhosis compared with controls (26.5 ± 4.6 cm vs. 29.8 ± 3.2 cm, p = 0.001). The mean systolic blood pressure (SBP) was 115.7 ± 16 mmHg in the control group and 119.2 ± 14 mmHg in the cirrhosis group (p = 0.32). The mean diastolic blood pressure (DBP) was 75.5 ± 12 mmHg and 74 ± 8.8 mmHg, respectively (p = 0.83). No statistically significant differences were observed between the groups regarding blood pressure measurements (Table 1).

Carotid intima–media thickness and carotid plaque findings

The mean carotid intima–media thickness (CIMT) in the healthy control group was 0.75 ± 0.09 mm, whereas the mean CIMT in the patient group was 0.66 ± 0.13 mm (p = 0.002). Carotid plaque was detected in 4 individuals (14.3%) in the control group and 9 individuals (18.4%) in the patient group. (p = 0.65) (Table 2).

Table 1. Comparison of demographic, anthropometric and blood pressure parameters of healthy control and cirrhosis patient groups

Parameter	Control Group (n=28)	Cirrhosis Group (n=49)	p value*
Age (year)	49.9 ± 7.4	53.8 ± 10.7	0.09
Gender (Male/Female)	11/17	30/19	0.06
BMI (kg/m²)	28.9 ± 4	27.3 ± 5.9	0.18
Height (cm)	163.2 ± 10.2	164.9 ± 10	0.50
Weight (kg)	77.5 ± 14.8	75.3 ± 15.7	0.54
Waist circumference (cm)	99.8 ± 10.7	101.3 ± 15.4	0.99
Arm circumference (cm)	29.8 ± 3.2	26.5 ± 4.6	**0.001**
SBP (mmHg)	115.7 ± 16	119.2 ± 14	0.32
DBP (mmHg)	75.5 ± 12	74 ± 8.8	0.83

BMI: Body mass index; SBP: Systolic blood pressure, DBP: Diastolic blood pressure. *Statistical significance level p <0.05.

Table 2. Comparison of doppler ultrasonography parameters of healthy control and cirrhosis patient groups

Parameter	Control Group (n=28)			Cirrhosis Group (n=49)		p value*
CIMT (mm) Mean± SD	0.75 ± 0.09			0.66 ± 0.13		**0.002**
Carotid plaque (n, %)	4 (14.3)			9 (18.4)		0.65
Gender	Male (n=11)	Female (n=17)	p value	Male (n=30)	Female (n=19)	p value
CIMT (mm) Mean± SD	0.75 ± 0.11	0.75 ± 0.08	0.942	0.69 ± 0.14[a]	0.63 ± 0.11[b]	0.138
Carotid plaque (n, %)	3 (27.3)	1 (5.9)	0.114	6 (20)	3 (15.8)	0.711

CIMT: Carotid intima media thickness. *Statistical significance level p <0.05.
[a] p=0.191 vs control male individuals; [b] p=0.0008 vs control female patients.

Table 3. Comparison of biochemical parameters of healthy control and cirrhosis patient groups

Parameters		Control Group (n=28)	Cirrhosis Group (n=49)	p value*
Lipid Parameters	Total Cholesterol (mg/dl)	202.4 ± 33.7	140.2 ± 43.8	**<0.001**
	HDL-Cholesterol (mg/dl)	46.1 ± 9.1	40.6 ± 18.1	0.07
	LDL-Cholesterol (mg/dl)	146.3 ± 31.7	89.2 ± 33.9	**<0.001**
	Triglyceride (mg/dl)	117.5	88	**0.003**
	Lp (a) (mg/dl)	11.5	9.5	**0.005**
	Oxidized LDL (ng/ml)	127.9	588.3	**<0.001**
Glucose Metabolism / Insulin Resistance	FBG (mg/dl)	83 ± 11.8	100 ± 20.4	**<0.001**
	Insulin (μIU/ml)	4.56	14.3	**0.001**
	HOMA-IR	0.96	3.67	**<0.001**
Inflammatory And Thrombotic Markers	hsCRP (mg/dl)	0.33	0.47	**0.009**
	Thrombocytes (x10^3/μL)	244 ± 70.1	106.8 ± 52.4	**<0.001**
	Fibrinogen (mg/dl)	338 ± 73.7	245 ± 86.6	**<0.001**
	Homocysteine (μmol/L)	16.5 ± 8.6	15.7 ± 5.6	0.609
Bilirubin	Total bilirubin (mg/dl)	0.66 ± 0.2	2.47 ± 2.8	**<0.001**
	Direct bilirubin (mg/dl)	0.15 ± 0.7	1.4 ±2	**<0.001**

HDL: High density lipoprotein; LDL: Low density lipoprotein; Lp: Lipoprotein; FBG: Fasting blood glucose; HOMA-IR: Homeostasis model assessment-insulin resistance; hsCRP: High sensitive C reactive protein.
*Statistical significance level p <0.05.

Biochemical parameters

The mean total cholesterol level was 202.4 ± 33.7 mg/dL in the control group and 140.2 ± 43.8 mg/dL in the patient group (Table 3). Total cholesterol levels were significantly higher in the control group than in the patient group ($p < 0.001$). The mean HDL-cholesterol level was 46.1 ± 9.1 mg/dL in the control group and 40.6 ± 18.1 mg/dL in the patient group ($p = 0.07$). The mean LDL-cholesterol level was 146.3 ± 31.7 mg/dL in the control group and 89.2 ± 33.9 mg/dL in the patient group ($p < 0.001$). The mean triglyceride level was 117.5 mg/dL in the control group and 88 mg/dL in the patient group ($p = 0.003$). The mean Lp(a) level was 11.5 mg/dL in the control group and 9.5 mg/dL in the patient group ($p = 0.005$). In contrast other cholesterol levels, the mean oxidized LDL level was 127.9 ng/mL in the control group and 588.3 ng/mL in the patient group, indicating significantly higher oxidized LDL levels in patients with cirrhosis ($p < 0.001$) (Table 3).

The mean fasting blood glucose (FBG) level was 83 ± 11.8 mg/dL in the control group and 100 ± 20.4 mg/dL in the patient group ($p < 0.001$). The mean insulin level was 4.56 μIU/mL in the control group and 14.3 μIU/mL in the patient group ($p = 0.001$). When the HOMA-IR index, used as an indicator of insulin resistance, was evaluated, the mean value was 0.96 in the control group and 3.67 in the patient group ($p < 0.001$). The mean hsCRP level was 0.33 mg/dL in the control group and 0.47 mg/dL in the patient group ($p = 0.009$). The mean platelet count was 244 ± 70.1 ×10^3/μL in the control group and 106.8 ± 52.4 ×10^3/μL in the patient group ($p < 0.001$). Similarly, the mean fibrinogen level was 338 ± 73.7 mg/dL in the control group and 245 ± 86.6 mg/dL in the patient group ($p < 0.001$). The mean homocysteine level was 16.5 ± 8.6 μmol/L in the control group and 15.7 ± 5.6 μmol/L in the patient group ($p = 0.609$). Finally, the mean total bilirubin and direct bilirubin levels were significantly higher in the patient group compared with the control group (both $p < 0.001$) (Table 3).

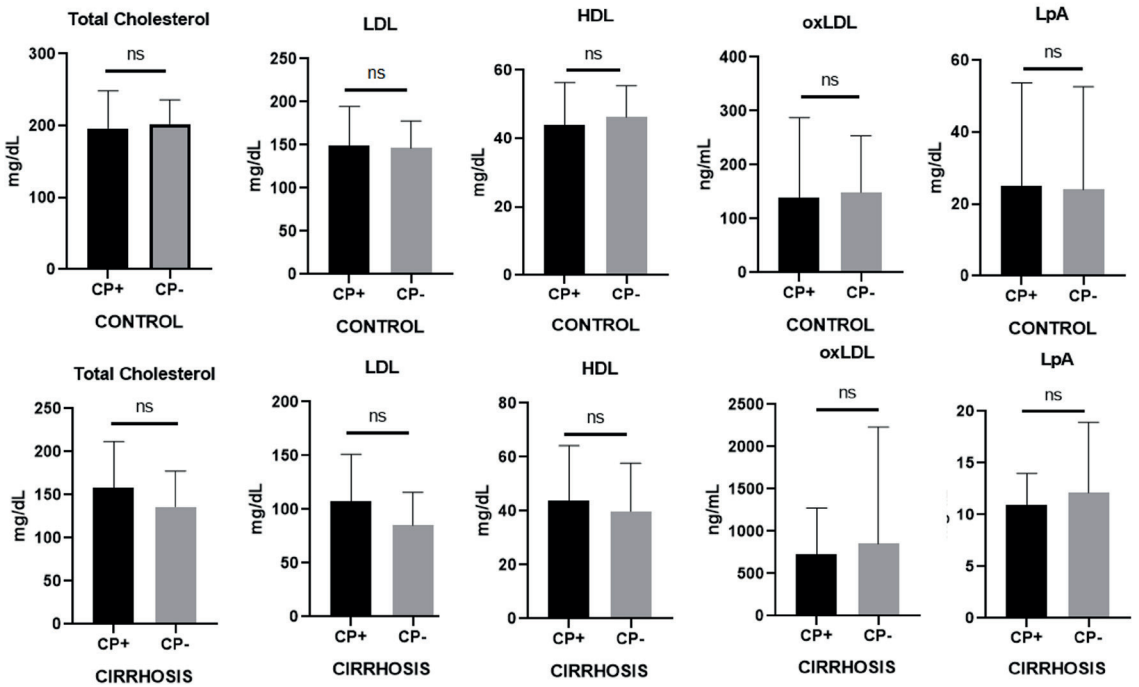

Figure 3. Lipid parameters according to carotid plaque status in control and cirrhosis groups. Comparisons of total cholesterol, LDL-cholesterol, HDL-cholesterol, oxidized LDL (oxLDL), and lipoprotein(a) [Lp(a)] levels according to the presence of carotid plaque (CP+ vs CP−) are shown for both the control group (upper panels) and the cirrhosis patient group (lower panels). Bars represent mean values with standard deviation (ns: not significant).

Comparison of biochemical parameters according to the presence of carotid plaque

Within both the control and patient groups, no statistically significant differences were observed between participants with carotid plaque (CP+) and those without carotid plaque (CP−) in terms of total cholesterol, LDL-cholesterol, HDL-cholesterol, oxidized LDL, and Lp(a) levels (all $p > 0.05$) (Figure 3). In the patient group, neither fasting blood glucose nor insulin levels differed significantly according to carotid plaque status (both $p > 0.05$) (Figure 4).

Platelet and fibrinogen levels according to carotid plaque status are illustrated in Figure 5. As expected, platelet counts were markedly lower in the cirrhosis group than in the control group, regardless of carotid plaque presence. However, no statistically significant differences were observed between CP+ and CP− individuals within either group (all $p > 0.05$). Similarly, fibrinogen levels did not differ significantly according to carotid plaque status in either the control or patient groups.

Discussion

The present case–control study aimed to evaluate subclinical atherosclerosis in patients with liver cirrhosis by assessing CIMT and carotid plaque presence and by examining their relationship with lipid and metabolic parameters. CIMT values which is the main study subject of our study were significantly lower in patients with cirrhosis compared with healthy controls. Beside this, we also found that patients with cirrhosis exhibit metabolic alterations typically associated with increased cardiovascular risk, and the structural markers of subclinical atherosclerosis may remain relatively attenuated in this population.

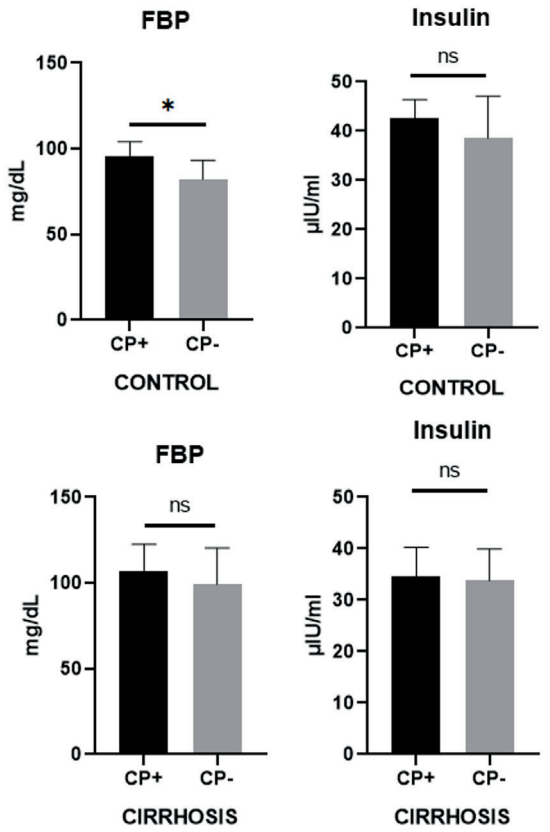

Figure 4. Fasting blood glucose (FBG) and insulin levels according to carotid plaque status. Comparison of FBG and insulin levels according to carotid plaque presence (CP+ vs CP−) in the control group (upper panels) and the cirrhosis patient group (lower panels). Bars represent mean values with standard deviation (ns: not significant).

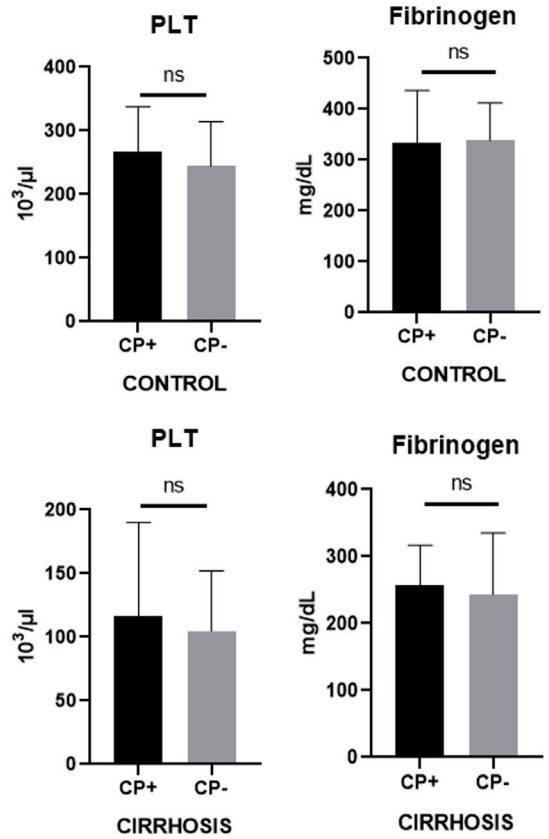

Figure 5. Platelet and fibrinogen levels according to carotid plaque status. Comparison of platelet count (PLT) and fibrinogen levels according to carotid plaque presence (CP+ vs CP−) in the control group (upper panels) and the cirrhosis patient group (lower panels). Bars represent mean values with standard deviation (ns: not significant).

The development of atherosclerosis is strongly influenced by several genetic and environmental risk factors, including dyslipidemia, diabetes mellitus, hypertension, smoking, and metabolic syndrome (12,13). Reduced HDL-cholesterol and elevated triglyceride levels are considered major initiating factors of atherosclerosis, whereas HDL-cholesterol exerts a protective effect (14). Oxidation of LDL particles represents a key step in the initiation of atherosclerosis (15), and a strong inverse association between HDL-cholesterol levels and coronary heart disease has been demonstrated (16). In a study, LDL-cholesterol, HDL-cholesterol, Lp(a), and triglycerides were identified as independent cardiovascular risk factors (17).

Lipid metabolism plays a central role in the pathogenesis of vascular disease, morbidity and mortality worldwide (18). Liver cirrhosis, which represents the final stage of chronic liver disease, profoundly alters lipid metabolism, inflammatory pathways, and hemodynamic regulation (19). Despite the presence of several metabolic abnormalities, numerous studies have reported that atherosclerosis and its clinical complications (cardiovascular and cerebrovascular events) may occur less frequently in cirrhotic patients than in the general

population (10,20,21). These observations have led to the hypothesis that metabolic and hemodynamic alterations associated with cirrhosis—such as hypocholesterolemia, changes in coagulation and fibrinolytic activity, and hormonal or nutritional factors—may modify the development of atherosclerosis. In this context, the present study contributes to the growing body of evidence suggesting that the vascular profile of patients with cirrhosis differs from that of the general population.

Since the cholesterol synthesis largely occurs in the liver, patients with cirrhosis often exhibit reduced lipid levels, and these levels tend to decrease further with disease progression (22). Ghadir et al. reported significantly lower total cholesterol, HDL-cholesterol, and LDL-cholesterol levels in cirrhotic patients compared with controls (23). Kawakami et al. also demonstrated that lipid levels progressively decline with advancing Child–Turcotte–Pugh stages of cirrhosis (24). Consistent with these observations, our study showed that total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels were all lower in patients with cirrhosis compared with healthy controls, with statistically significant differences for total cholesterol, LDL-cholesterol, and triglycerides. These findings support the notion that altered hepatic lipid metabolism and reduced cholesterol synthesis in cirrhosis contribute to the relatively hypolipidemic profile observed in these patients.

Lp(a), a molecule structurally similar to LDL-cholesterol, has well-established atherogenic and prothrombotic properties, and elevated levels are associated with increased risk of ischemic heart disease and cerebrovascular events (25,26). Since Lp(a) is primarily synthesized in the liver, its levels are typically reduced in patients with cirrhosis and tend to decline with worsening liver function (27). Several studies have reported progressively lower Lp(a) concentrations with advancing Child–Turcotte–Pugh stages, suggesting that Lp(a) levels may also reflect hepatic synthetic capacity (28,29). In agreement with these findings, we observed significantly lower Lp(a) levels in cirrhotic patients compared with controls (9.5 mg/dL vs. 11.5 mg/dL, $p < 0.005$). This finding supports the hypothesis that impaired hepatic synthesis contributes to the reduced atherogenic lipid profile observed in cirrhosis.

Elevated oxidized LDL levels have been associated with increased coronary lesion burden and higher risk of coronary artery disease (30). Interestingly, previous studies examining oxidized LDL in liver disease are limited, and some reports—particularly in primary biliary cirrhosis—have suggested lower oxidized LDL levels, possibly related to the antioxidant effects of bilirubin (31). In contrast, our study demonstrated markedly higher oxidized LDL levels in patients with cirrhosis compared with healthy controls (588.3 ng/mL vs. 127.9 ng/mL, $p < 0.001$). This finding suggests that despite reduced circulating lipid levels, increased oxidative stress in cirrhosis may contribute to enhanced LDL oxidation, which may represent an alternative pathway influencing vascular alterations in these patients.

Glucose intolerance and diabetes are common metabolic abnormalities in cirrhosis, and hyperinsulinemia and insulin resistance have been reported in up to 80% of affected patients (32). This metabolic disturbance, often referred to as hepatogenous diabetes, differs pathophysiologically from classical type 2 diabetes mellitus and is thought to result from reduced insulin sensitivity in the liver, muscle, and adipose tissue, impaired hepatic insulin degradation, increased pancreatic beta-cell responsiveness to glucose, and the presence of portosystemic shunting (32). Although diabetes may worsen the prognosis of cirrhosis by contributing to hepatic decompensation, it does not appear to increase ischemic cardiovascular events to the same extent observed in the general diabetic population (33). Kim and Choi reported significantly higher fasting insulin and HOMA-IR values in patients with hepatogenous diabetes than in those with type 2 diabetes (34). In line with these reports, our study

demonstrated significantly higher fasting blood glucose, fasting insulin, and HOMA-IR levels in the cirrhosis group compared with controls, indicating increased insulin resistance despite the absence of a parallel increase in CIMT. This finding suggests that, in cirrhosis, insulin resistance may coexist with other metabolic or vascular factors that attenuate the structural expression of subclinical atherosclerosis.

Hemodynamic alterations may also contribute to the distinctive vascular profile of cirrhotic patients. Cirrhosis is characterized by a hyperdynamic circulatory state associated with increased cardiac output, peripheral vasodilation, reduced systemic vascular resistance, and relative arterial hypotension, largely mediated by increased nitric oxide production (3,35). In addition, commonly used medications in cirrhosis, such as diuretics and beta-blockers, may further lower systemic blood pressure. In our cohort, systolic and diastolic blood pressure values did not differ significantly between the cirrhosis and control groups.

Beyond lipid abnormalities and insulin resistance, several inflammatory, hemostatic, and oxidative stress-related markers may influence vascular risk in cirrhosis. Elevated homocysteine, fibrinogen, hsCRP, and Lp(a) have all been recognized as independent risk factors for atherosclerotic vascular disease (36). Studies have reported higher homocysteine levels in cirrhosis (37,38). In our study, however, homocysteine levels were slightly lower in cirrhotic patients and did not differ significantly from controls. In contrast, hsCRP levels were significantly higher in the cirrhosis group, consistent with previous studies showing that low-grade inflammation persists in cirrhosis and may theoretically promote atherogenesis (39,40). Nevertheless, this pro-inflammatory signal was accompanied by markedly lower platelet counts and fibrinogen levels in the cirrhosis group. Elevated fibrinogen has been associated with increased coronary and cerebrovascular risk and with greater CIMT and coronary calcium burden (41,42). In our study, both fibrinogen and platelet counts were significantly lower in cirrhotic patients, supporting the hypothesis that a reduced prothrombotic milieu may counterbalance some of the metabolic and inflammatory drivers of atherosclerosis.

A similar paradox emerged in relation to oxidative stress and bilirubin metabolism. Oxidized LDL is a major mediator of endothelial dysfunction and vascular inflammation and has been linked to increased coronary lesion burden and cardiovascular risk (43). In our study, oxidized LDL levels were markedly higher in cirrhotic patients than in controls, which would ordinarily be expected to favor atherosclerotic progression. However, bilirubin levels—both total and direct—were also significantly higher in the cirrhosis group. Bilirubin has potent antioxidant properties through the biliverdin–bilirubin redox cycle and has been inversely associated with coronary artery disease and myocardial infarction in previous studies (44,45). Thus, our findings suggest that cirrhosis is characterized by the coexistence of both pro-atherogenic and potentially protective influences: increased oxidized LDL, insulin resistance, and hsCRP on the one hand, and decreased total cholesterol, LDL-cholesterol, triglycerides, Lp(a), platelet count, and fibrinogen together with increased bilirubin on the other. Taken together, these data support the interpretation that, in cirrhosis, anti-atherogenic and anti-thrombotic factors may predominate over pro-atherogenic stimuli, which may explain why CIMT was lower in our cirrhotic patients despite the presence of several unfavorable metabolic markers.

This study has several limitations that should be considered when interpreting the findings. First, the sample size was relatively small, which may limit the generalizability of the results and reduce the statistical power for detecting differences in some parameters. Second, the cross-sectional design of the study does not allow causal relationships between cirrhosis-related metabolic alterations and atherosclerosis to be established. Third, although CIMT is a

well-validated surrogate marker of subclinical atherosclerosis, it does not fully reflect the complexity of vascular disease. Additional methods such as coronary artery calcium scoring or arterial stiffness measurements could provide complementary information.

Despite these limitations, the present study provides clinically relevant insights into the vascular profile of patients with cirrhosis. Our findings suggest that cirrhosis is associated with a unique metabolic and hemostatic milieu, characterized by reduced levels of atherogenic lipids, Lp(a), fibrinogen, and platelet counts, together with increased bilirubin levels. These factors may exert protective vascular effects, potentially counterbalancing the pro-atherogenic influences of insulin resistance, inflammation, and elevated oxidized LDL levels. Understanding this complex balance may help clinicians better interpret cardiovascular risk in patients with advanced liver disease.

Conclusion

In conclusion, using carotid intima–media thickness as a marker of subclinical atherosclerosis, our study demonstrated that patients with liver cirrhosis have lower CIMT values compared with healthy controls, despite the presence of several metabolic alterations traditionally associated with cardiovascular risk. The coexistence of both pro- and anti-atherogenic factors in cirrhosis suggests that protective mechanisms related to altered lipid metabolism, thrombocytopenia, hypofibrinogenemia, and increased bilirubin levels may outweigh pro-atherogenic influences, resulting in a relatively attenuated atherosclerotic burden in this population. Further large-scale prospective studies are needed to better clarify the complex relationship between cirrhosis and cardiovascular disease.

Ethical approval

Ethical approval was obtained from the Local Ethics Committee of Trakya University (approval date: April 6, 2011). The study was supported by the Trakya University Scientific Research Projects Unit (TÜBAP; project number: 2011-170).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: MT, HCÜ; data collection: MT, HCÜ; analysis and interpretation of results: MT, HCÜ; draft manuscript preparation: MT, HCÜ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Jagdish RK, Roy A, Kumar K, et al. Pathophysiology and management of liver cirrhosis: from portal hypertension to acute-on-chronic liver failure. Front Med (Lausanne). 2023;10:1060073. [Crossref]
2. World Health Organization (WHO). Liver cirrhosis, age-standardized death rates (15+), per 100,000 population. Global Health Observatory Data Repository. Geneva: WHO; 2019. Available at: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/liver-cirrhosis-age-standardized-death-rates-(15-)-per-100-000-population
3. Møller S, Henriksen JH, Bendtsen F. Extrahepatic complications to cirrhosis and portal hypertension: haemodynamic and homeostatic aspects. World J Gastroenterol. 2014;20(42):15499-517. [Crossref]
4. Del Giudice E, Dilillo A, Tromba L, et al. Aortic, carotid intima-media thickness and flow- mediated dilation as markers of early atherosclerosis in a cohort of pediatric patients with rheumatic diseases. Clin Rheumatol. 2018;37(6):1675-1682. [Crossref]

5. Głowińska-Olszewska B, Tołwińska J, Urban M. Relationship between endothelial dysfunction, carotid artery intima media thickness and circulating markers of vascular inflammation in obese hypertensive children and adolescents. J Pediatr Endocrinol Metab. 2007;20(10):1125-36.

6. Azarpazhooh MR, Andalibi MSS, Hackam DG, Spence JD. Interaction of smoking, hyperhomocysteinemia, and metabolic syndrome with carotid atherosclerosis: a cross-sectional study in 972 non-diabetic patients. Nutrition. 2020;79-80:110874. [Crossref]

7. Lechner K, von Schacky C, McKenzie AL, et al. Lifestyle factors and high-risk atherosclerosis: pathways and mechanisms beyond traditional risk factors. Eur J Prev Cardiol. 2020;27(4):394-406. [Crossref]

8. Flore R, Ponziani FR, Tinelli G, et al. New modalities of ultrasound-based intima-media thickness, arterial stiffness and non-coronary vascular calcifications detection to assess cardiovascular risk. Eur Rev Med Pharmacol Sci. 2015;19(8):1430-41.

9. Zhang L, She ZG, Li H, Zhang XJ. Non-alcoholic fatty liver disease: a metabolic burden promoting atherosclerosis. Clin Sci (Lond). 2020;134(13):1775-1799. [Crossref]

10. Kazankov K, Munk K, Øvrehus KA, et al. High burden of coronary atherosclerosis in patients with cirrhosis. Eur J Clin Invest. 2017;47(8):565-573. [Crossref]

11. Zhang C, Wang J, Ding S, et al. Relationship between lifestyle and metabolic factors and carotid atherosclerosis: a survey of 47,063 fatty and non-fatty liver patients in China. Front Cardiovasc Med. 2022;9:935185. [Crossref]

12. Andreassi MG. Metabolic syndrome, diabetes and atherosclerosis: influence of gene-environment interaction. Mutat Res. 2009;667(1-2):35-43. [Crossref]

13. Aboonabi A, Meyer RR, Singh I. The association between metabolic syndrome components and the development of atherosclerosis. J Hum Hypertens. 2019;33(12):844-855. [Crossref]

14. Assmann G, Gotto AM. HDL cholesterol and protective factors in atherosclerosis. Circulation. 2004;109(23 Suppl 1):III8-14. [Crossref]

15. Stocker R, Keaney JF. Role of oxidative modifications in atherosclerosis. Physiol Rev. 2004;84(4):1381-478. [Crossref]

16. Wilkins JT, Ning H, Stone NJ, et al. Coronary heart disease risks associated with high levels of HDL cholesterol. J Am Heart Assoc. 2014;3(2):e000519. [Crossref]

17. Sharrett AR, Ballantyne CM, Coady SA, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2001;104(10):1108-13. [Crossref]

18. Xu L, Yang Q, Zhou J. Mechanisms of abnormal lipid metabolism in the pathogenesis of disease. Int J Mol Sci. 2024;25(15):8465. [Crossref]

19. Pei K, Gui T, Kan D, et al. An Overview of lipid metabolism and nonalcoholic fatty liver disease. Biomed Res Int. 2020;2020:4020249. [Crossref]

20. Drüeke TB, Massy ZA. Atherosclerosis in CKD: differences from the general population. Nat Rev Nephrol. 2010;6(12):723-35. [Crossref]

21. Fracanzani AL, Tiraboschi S, Pisano G, et al. Progression of carotid vascular damage and cardiovascular events in non-alcoholic fatty liver disease patients compared to the general population during 10 years of follow-up. Atherosclerosis. 2016;246:208-13. [Crossref]

22. Siddiqui MS, Fuchs M, Idowu MO, et al. Severity of nonalcoholic fatty liver disease and progression to cirrhosis are associated with atherogenic lipoprotein profile. Clin Gastroenterol Hepatol. 2015;13(5):1000-8.e3. [Crossref]

23. Ghadir MR, Riahin AA, Havaspour A, Nooranipour M, Habibinejad AA. The relationship between lipid profile and severity of liver damage in cirrhotic patients. Hepat Mon. 2010;10(4):285-8.

24. Kawakami M, Koda M, Murawaki Y. The prevalence of atherosclerosis in cirrhotic patients: assessment of two aspects of atherosis and sclerosis. Hepatol Res. 2007;37(2):152-7. [Crossref]

25. Boffa MB, Koschinsky ML. Lipoprotein (a): truly a direct prothrombotic factor in cardiovascular disease? J Lipid Res. 2016;57(5):745-57. [Crossref]

26. Colantonio LD, Goonewardena SN, Wang Z, et al. Incident CHD and ischemic stroke associated with lipoprotein(a) by levels of Factor VIII and inflammation. J Clin Lipidol. 2023;17(4):529-537. [Crossref]

27. Chrostek L, Supronowicz L, Panasiuk A, Cylwik B, Gruszewska E, Flisiak R. The effect of the severity of liver cirrhosis on the level of lipids and lipoproteins. Clin Exp Med. 2014;14(4):417-21. [Crossref]

28. Yadav R, Satyawali VN, Joshi SC, Kumar Y. Lipid profile alterations in chronic liver disease: association with Child-Pugh score. International Journal of Medicine and Public Health. 2025;15(4):325-30.

29. Jaiswal P, Choubey PP. Lipid profile versus severity of cirrhosis: a child-pugh score based study. People's Journal of Scientific Research. 2018;11(1):28-32.

30. Ghosh J, Mishra TK, Rao YN, Aggarwal SK. Oxidised LDL, HDL cholesterol, LDL cholesterol levels in patients of coronary artery disease. Indian J Clin Biochem. 2006;21(1):181-4. [Crossref]

31. Dudnik LB, Azyzova OA, Solovyova NP, Savchenkova AP, Pokrovskaya MA. Primary biliary cirrhosis and coronary atherosclerosis: protective antioxidant effect of bilirubin. Bull Exp Biol Med. 2008;145(1):18-22. [Crossref]

32. Garcia-Compean D, Jaquez-Quintana JO, Gonzalez-Gonzalez JA, Maldonado-Garza H. Liver cirrhosis and diabetes: risk factors, pathophysiology, clinical implications and management. World J Gastroenterol. 2009;15(3):280-8. [Crossref]

33. Liu TL, Trogdon J, Weinberger M, Fried B, Barritt AS. Diabetes is associated with clinical decompensation events in patients with cirrhosis. Dig Dis Sci. 2016;61(11):3335-3345. [Crossref]

34. Kim MG, Choi WC. Differential diagnosis of diabetes mellitus caused by liver cirrhosis and other type 2 diabetes mellitus. Korean J Hepatol. 2006;12(4):524-9.

35. Møller S, Bendtsen F. The pathophysiology of arterial vasodilatation and hyperdynamic circulation in cirrhosis. Liver Int. 2018;38(4):570-580. [Crossref]

36. Wang H, Wu P, Jiang D, et al. Relationship between serum homocysteine, fibrinogen, lipoprotein-a level, and peripheral arterial disease: a dose-response meta-analysis. Eur J Med Res. 2022;27(1):261. [Crossref]

37. Bosy-Westphal A, Petersen S, Hinrichsen H, Czech N, J Müller M. Increased plasma homocysteine in liver cirrhosis. Hepatol Res. 2001;20(1):28-38. [Crossref]

38. Culafić DM, Marković ML, Obrenović RZ, Mijac DD. Plasma homocysteine levels in patients with liver cirrhosis. Vojnosanit Pregl. 2013;70(1):57-60. [Crossref]

39. León-Pedroza JI, González-Tapia LA, del Olmo-Gil E, Castellanos-Rodríguez D, Escobedo G, González-Chávez A. Low-grade systemic inflammation and the development of metabolic diseases: from the molecular evidence to the clinical practice. Cir Cir. 2015;83(6):543-51. [Crossref]

40. Ho CM, Ho SL, Jeng YM, et al. Accumulation of free cholesterol and oxidized low-density lipoprotein is associated with portal inflammation and fibrosis in nonalcoholic fatty liver disease. J Inflamm (Lond). 2019;16:7. [Crossref]

41. Green D, Foiles N, Chan C, Schreiner PJ, Liu K. Elevated fibrinogen levels and subsequent subclinical atherosclerosis: the CARDIA Study. Atherosclerosis. 2009;202(2):623-31. [Crossref]

42. Kersche G, Liblik D, Hétu MF, et al. The association of carotid plaque burden and composition and the coronary artery calcium score in intermediate cardiovascular risk patients. Int J Cardiovasc Imaging. 2024;40(8):1683-1692. [Crossref]

43. Jiang H, Zhou Y, Nabavi SM, et al. Mechanisms of oxidized LDL-mediated endothelial dysfunction and its consequences for the development of atherosclerosis. Front Cardiovasc Med. 2022;9:925923. [Crossref]

44. Jain V, Ghosh RK, Bandyopadhyay D, et al. Serum bilirubin and coronary artery disease: intricate relationship, pathophysiology, and recent evidence. Curr Probl Cardiol. 2021;46(3):100431. [Crossref]

45. Punzo A, Silla A, Fogacci F, Perillo M, Cicero AFG, Caliceti C. Bile acids and bilirubin role in oxidative stress and inflammation in cardiovascular diseases. Diseases. 2024;12(5):103. [Crossref]