Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1628609
J Health Sci Med. 2025;8(3):371-374

Flow-mediated dilatation deficiency of the brachial artery and increased carotid intimal thickness in non-alcoholic fatty liver disease

Umut Özdamarlar[1], Yaşar Çolak[2]

[1]Department of Radiology, Pendik Medicalpark Hospital, İstanbul, Turkiye
[2]Department of Gastroenterology, İstanbul Medeniyet University, Göztepe Training and Research Hospital, İstanbul, Turkiye

Cite this article as: Özdamarlar U, Çolak Y. Flow-mediated dilatation deficiency of the brachial artery and increased carotid intimal thickness in non-alcoholic fatty liver disease. *J Health Sci Med.* 2025;8(3):371-374.

Received: 04.02.2025 ◆ **Accepted**: 24.03.2025 ◆ **Published**: 30.05.2025

ABSTRACT

Aims: This study aimed to evaluate endothelial dysfunction and vascular changes in non-alcoholic fatty liver disease (NAFLD) patients by measuring carotid intima-media thickness (C-IMT) and flow-mediated dilation (FMD).

Methods: This prospective observational cohort study included 51 biopsy-proven NAFLD patients and 21 healthy controls. Endothelial function was assessed using high-resolution ultrasonography to measure brachial artery FMD and C-IMT. Patients with hepatotoxic drug use, significant alcohol consumption, or other liver diseases were excluded. Demographic data, body-mass index (BMI), and waist circumference were recorded. Statistical analyses were conducted using SPSS, with significance set at $p<0.05$.

Results: NAFLD patients showed significantly higher BMI, waist circumference, and diastolic blood pressure compared to controls. The mean C-IMT was elevated in NAFLD patients (0.67±0.09 mm) compared to controls (0.52±0.11 mm; $p<0.001$), and FMD was significantly reduced in NAFLD patients (7.3±4.8%) compared to controls (16.5±7.1%; $p<0.001$). FMD and C-IMT values were lower in NASH cases than in simple steatosis. A significant negative correlation was observed between FMD and BMI, waist circumference, and C-IMT values.

Conclusion: NAFLD patients, particularly those with NASH, exhibit significant endothelial dysfunction characterized by reduced FMD and increased C-IMT, indicating early atherosclerosis. These findings suggest that endothelial dysfunction increases with progression of NAFLD. Early recognition of vascular changes in NAFLD patients could facilitate timely interventions to reduce cardiovascular risk and disease progression.

Keywords: Non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, vascular, carotid intima, liver disease

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is recognized as the most common chronic liver disease in the general population.[1-3] Due to the asymptomatic nature of most cases, the true prevalence of NAFLD remains unknown. Population-based screening studies in adults estimate the prevalence of NAFLD to be 17-33%, with rates reaching 75% in the presence of obesity. The prevalence of non-alcoholic steatohepatitis (NASH) is approximately 3%.[1-3] While the disease is more common in Western societies, its incidence is increasing significantly worldwide due to changes in dietary habits and the transition to urban lifestyles.[1] A portion of cases with simple steatosis progress to NASH. Approximately 20% of NASH cases result in progressive fibrosis and cirrhosis, and 30-40% of cirrhotic patients succumb to liver-related complications.[4,5] Furthermore, though the frequency remains unclear, subacute liver failure, hepatocellular carcinoma, and post-transplant disease recurrence are among other complications.[2,4,5] NAFLD encompasses a broad spectrum ranging from simple steatosis to NASH, fibrosis, cirrhosis, and hepatocellular carcinoma.[1]

In the etiology of NAFLD, metabolic factors such as diabetes mellitus, obesity, and hyperlipidemia play a leading role, while congenital causes, environmental factors, and certain medications may also contribute to this condition.[1-4] Insulin resistance and the factors leading to it are considered the most significant etiological contributors. Genetic predisposition, increased caloric intake, obesity (particularly central obesity), and a sedentary lifestyle are the primary risk factors for insulin resistance.[4,5]

Although some evidence has been obtained regarding the pathogenesis of hepatic steatosis, it has not yet been fully elucidated.[1,2] Why NAFLD does not develop in all obese individuals or why some individuals with simple steatosis

Corresponding Author: Umut Özdamarlar, drumutozdamarlar@outlook.com

develop necroinflammatory processes remains unclear.[1-3] The "two-hit" hypothesis is currently the prevailing theory in the pathogenesis of NAFLD.[3] According to this hypothesis, the first hit leads to steatosis, while the second hit initiates necroinflammatory processes, eventually resulting in NASH.[1-4]

Due to the close association between metabolic syndrome and NAFLD, diabetes and hyperlipidemia are frequently observed in affected individuals. However, it should not be overlooked that NAFLD may also occur in individuals with normal weight, without comorbidities, and even in children.[5]

The most commonly used radiological diagnostic method for NAFLD is ultrasonography (USG). USG findings include increased liver echogenicity (compared to spleen and kidney echogenicity), posterior acoustic attenuation, blurring of the margins of intrahepatic lacunar structures, and loss of clear demarcation of the right hepatic lobe and diaphragm. Similarly, computed tomography (CT) and magnetic resonance imaging (MRI) can also be effectively utilized for diagnosis.[6-8]

In our study, we aimed to evaluate differences in endothelial function in the brachial and carotid arteries of patients with NAFLD using vascular ultrasonography by measuring brachial artery flow-mediated dilation (FMD) and carotid intima-media thickness (C-IMT) levels.

METHODS

Ethics

This prospective observational cohort study was conducted with a total of 51 patients who were histopathologically diagnosed with non-alcoholic fatty liver disease (NAFLD) and admitted to the Gastroenterology and Radiology outpatient clinics of İstanbul Medeniyet University, Göztepe Training and Research Hospital between July 2010 and July 2011. The follow-up period for all patients was 24 months. The study was prepared as a specialty thesis. Ethical committee approval was not obtained. Institutional approwal was obtaned. Written informed consent was obtained from all participants. All procedures were conducted in accordance with ethical guidelines and the principles of the Declaration of Helsinki.

Exclusion Criteria

The following were used as exclusion criteria: use of hepatotoxic drugs, herbal medicines, or hormone replacement therapy; history of alcohol consumption exceeding 20 grams per day; viral hepatitis, autoimmune hepatitis, biliary diseases, malignancies, alpha-1 antitrypsin deficiency, Wilson's disease, hemochromatosis; being under the age of 18; and pregnancy.

Patients with a biopsy-proven diagnosis of NAFLD were included in the study. The healthy control group consisted of individuals with normal liver findings on sonographic evaluation and no exclusion criteria.

Clinical And Laboratory Assessment

All patients were evaluated by the gastroenterology department. Height, weight, and waist circumference (cm) were measured, and the BMI (kg/m^2) was calculated.

Carotid ultrasound (US) evaluation was performed using a 7.5 MHz transducer (Aplio, Toshiba, Tokyo, Japan). The patients were assessed in a supine position. Measurements were taken at the common carotid artery (CCA) bifurcation and the internal carotid artery. C-IMT (carotid intima-media thickness) was measured on the far wall of the CCA at a point 1 cm proximal to the bifurcation. The distance between the lumen-intima interface and the media-adventitia interface was measured. Measurements were taken from plaque-free regions. Each measurement was repeated three times for both CCAs, and the mean values were calculated. The average of the mean values from both CCAs was considered the C-IMT.

The anterior, posterior, and lateral walls of both carotid arterial systems were scanned longitudinally and transversely for the presence of plaques. Plaque dimensions, numbers, and locations were recorded.

Vascular endothelial functions were evaluated by measuring flow-mediated dilation (FMD) of the brachial artery (99). The examination was performed using a 10 MHz high-resolution linear probe (Aplio, Toshiba, Tokyo, Japan). The right brachial artery was assessed in the longitudinal axis, approximately 2 cm proximal to the antecubital fossa, with the patients in a supine position. First, baseline diameter and spectral Doppler parameters, including peak systolic velocity (PSV) and end-diastolic velocity (EDV), were measured at this location, which was marked.

A cuff was then placed on the right forearm and inflated to 250 mmHg to induce ischemia in the right brachial artery. The cuff pressure was maintained at this level for 5 minutes. Following cuff release, PSV and EDV measurements were repeated at the previously marked site 15 seconds later using spectral Doppler. One minute after cuff deflation, the brachial artery diameter was measured in the longitudinal axis for FMD assessment. FMD was calculated as the percentage change between the baseline diameter and the maximum post-ischemic diameter.

Statistical Analysis

The data were analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The student's T test (for parametric data) or the Mann-Whitney U test (for non-parametric data) was used for statistical comparison between two independent groups. For comparisons between more than two groups, one-way ANOVA was used for parametric data, and the Kruskal-Wallis test was used for non-parametric data. Correlations between variables were assessed using Spearman's correlation analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

The study group consisted of 25 male and 26 female patients, with an average age of 42.8±9.8 years. A total of 21 individuals (average age: 40.5±9.7 years; 11 males and 10 females) were included in the control group. The age and gender distribution were similar between the NAFLD group and the control group. The demographic characteristics of the patients are shown in **Table 1**.

Table 1. Demographic data and arterial measurement differences in NAFLD and control groups

Parameter	NAFLD group (n=51)	Control group (n=21)	p-value
Gender (male/female)	25/26	11/10	0.440
Age (years)	42.8±9.8	40.5±9.7	0.070
BMI (kg/m²)	31.6±5.5	24.4±2.1	<0.001
Waist circumference (cm)	102.2±9.2	85.2±7.2	<0.001
Systolic BP (mmHg)	122±16.8	115.6±16.7	0.080
Diastolic BP (mmHg)	82±10.3	73.7±11.8	0.002
C-IMT (mm)	0.67±0.09	0.52±0.11	0.002
FMD (%)	7.3±4.8	16.5±7.1	<0.001

NAFLD: Non-alcoholic fatty liver disease, BMI: Body-mass index, BP: Blood pressure, C-IMT: Carotid intima media thickness, FMD: Foot and mouth disease

BMI, waist circumference, and diastolic blood pressure were significantly higher in patients with NAFLD compared to the control group. In the NAFLD group, the mean carotid intima-media thickness (C-IMT) was measured as 0.67±0.09 mm, compared to 0.52±0.11 mm in the control group, indicating a statistically significant increase (p<0.001) (Table 1).

In the NAFLD group, as shown in Table 2, eight patients (15.6%) were diagnosed with simple steatosis, 25 patients (49%) with borderline NASH, and 18 patients (35.3%) with definitive NASH.

The mean C-IMT values were 0.52±0.11 mm in the control group, 0.63±0.07 mm in patients with simple steatosis, and 0.68±0.1 mm in NAFLD cases diagnosed with either borderline or definitive NASH. The differences between these groups were statistically significant (p<0.001) and are summarized in Table 2.

No significant difference in C-IMT measurements was observed between cases with borderline NASH and those with definitive NASH (0.68±0.64 mm vs. 0.68±1.22 mm, respectively).

Atherosclerotic plaques were not detected in any individuals within the control group. However, six patients in the NAFLD group were found to have atherosclerotic plaque formation. The mean C-IMT values in patients with plaques were significantly higher compared to those without plaques (0.76±0.09 mm vs. 0.66±0.09 mm, p<0.001).

In the measurements of basal brachial artery diameter among NAFLD cases and the control group, no statistically significant differences were observed between the groups. The basal brachial artery diameters were 3.961±0.7 mm in the NASH group, 3.63±0.83 mm in the simple steatosis group, and 3.66±0.59 mm in the control group (p=0.276).

Brachial artery FMD measurements were significantly lower in NAFLD cases (7.3±4.8%) compared to the control group (16.5±7.1%) (p<0.001).

The FMD measurements of the brachial artery were recorded as 16.5±7.1% in the control group, 9.64±6.63% in the simple steatosis group, and 7.03±4.57% in NAFLD cases with NASH. The differences between the groups were considered statistically significant.

No significant differences in FMD responses were observed between patients with borderline and definitive NASH (7.9±5.8% and 6.1±2.5%, respectively).

Correlation analysis revealed a significant negative correlation between FMD measurements and BMI, waist circumference, and C-IMT measurements.

DISCUSSION

In our study, endothelial functions were evaluated in 51 biopsy-proven NAFLD patients and 21 healthy individuals in the control group using C-IMT and FMD measurements. Significant endothelial dysfunction was observed in NAFLD patients compared to the control group.

Endothelial dysfunction was more pronounced in NAFLD cases with NASH. NAFLD contributes to endothelial dysfunction, induces early atherosclerosis,[6-10] and increases the risk of cardiovascular diseases.[10] Carotid atherosclerosis, assessed by C-IMT thickness and plaque presence or frequency, was found to be increased in NAFLD patients.[6-8] Similarly, in this study, C-IMT measurements and carotid atherosclerosis were significantly increased in NAFLD patients (p<0.001).

When comparing patients with simple steatosis and those with NASH correlated with histopathological parameters, a significant increase in C-IMT measurements was detected in NASH patients.

Furthermore, FMD measurements were found to be associated with increased C-IMT values, which are another indicator of endothelial dysfunction. Previous studies have also demonstrated a significant reduction in brachial artery FMD measurements in NAFLD cases compared to those without NAFLD, and this reduction was associated with the histological progression of the disease.[9-11] Similarly, in our study, we observed that FMD measurements were significantly lower in NAFLD patients, regardless of whether metabolic syndrome was present, compared to the healthy control group (p<0.001). Additionally, the reduction in FMD measurements was more pronounced in NASH cases and in progressive NAFLD compared to simple steatosis. These findings suggest that the deterioration in endothelial function worsens with disease progression.[8,11]

Table 2. Comparison of arterial characteristics between simple steatosis, borderline NASH, and control patients

Parameter	Simple steatosis (mean±SD)	Borderline NASH (mean±SD)	NASH (mean±SD)	Control (mean±SD)	p-value*
BAD (mm)	3.63±0.83	4.1±0.9	4.09±0.72	3.66±0.6	0.060
FMD (%)	9.6±6.6	7.9±5.8	6.1±2	16.5±7.1	0.001
C-IMT (mm)	0.63±0.07	0.68±0.64	0.68±1.22	0.52±0.11	<0.001

*One-way ANOVA test results, ANOVA: Analysis of variance, NASH: Non-alcoholic steatohepatitis, SD: Standard deviation, BAD: Brachial artery diameter, FMD: Flow-mediated dilation, C-IMT: Carotid intima-media thickness

The biochemical and metabolic components underlying the relationship between NAFLD and atherosclerosis remain unclear. However, several hypotheses have been proposed. Hepatic and peripheral insulin resistance is prevalent in NAFLD patients. An impaired lipid profile may also contribute to the increased atherosclerosis risk.[7-11] Another potential mechanism is the role of increased oxidative stress, which may drive a chronic inflammatory process.[7-9]

Limitations

This study has certain limitations. The small sample size is the most significant limitation. Additionally, while endothelial-dependent vasodilation was assessed using the FMD method, endothelial-independent vasodilation was not evaluated.

CONCLUSION

In NAFLD patients, compared to healthy individuals, a reduction in flow-mediated dilation of the brachial artery and an increase in carotid intimal thickness were observed, indicating impaired endothelial function as a marker of early atherosclerosis. Moreover, endothelial dysfunction was more pronounced in patients with definitive NASH.

ETHICAL DECLARATIONS

Ethics Committee Approval

This prospective observational cohort study was prepared as a specialty thesis between July 2010 and July 2011. Ethics committee approval was not obtained at that time. Institutional approval was obtained.

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Oni ET, Agatston AS, Blaha MJ, et al. A systematic review: burden and severity of subclinical cardiovascular disease among those with nonalcoholic fatty liver; should we care? *Atherosclerosis*. 2013;230(2):258-267. doi:10.1016/j.atherosclerosis.2013.07.052
2. Pastori D, Loffredo L, Perri L, et al. Relation of nonalcoholic fatty liver disease and Framingham Risk Score to flow-mediated dilation in patients with cardiometabolic risk factors. *Am J Cardiol*. 2015;115(10):1402-1406. doi:10.1016/j.amjcard.2015.02.032
3. Cattazzo F, Lombardi R, Mantovani A, et al. Subclinical and clinical atherosclerosis in non-alcoholic fatty liver disease is associated with the presence of hypertension. *Nutr Metab Cardiovasc Dis*. 2022;32(12):2839-2847. doi:10.1016/j.numecd.2022.08.005
4. Chen Y, Xu M, Wang T, et al. Advanced fibrosis associates with atherosclerosis in subjects with nonalcoholic fatty liver disease. *Atherosclerosis*. 2015;241(1):145-150. doi:10.1016/j.atherosclerosis.2015.05.002
5. Velarde-Ruiz Velasco JA, García-Jiménez ES, García-Zermeño KR, et al. Extrahepatic complications of non-alcoholic disease fatty liver R. *Rev Gastroenterol Mex (Engl Ed)*. 2019;84(4):472-481. doi:10.1016/j.rgmx.2019.05.004
6. Li N, Zhang GW, Zhang JR, et al. Non-alcoholic fatty liver disease is associated with progression of arterial stiffness. *Nutr Metab Cardiovasc Dis*. 2015;25(2):218-223. doi:10.1016/j.numecd.2014.10.002
7. Oni E, Budoff MJ, Zeb I, et al. Nonalcoholic fatty liver disease is associated with arterial distensibility and carotid intima-media thickness: (from the multi-ethnic study of atherosclerosis). *Am J Cardiol*. 2019;124(4):534-538. doi:10.1016/j.amjcard.2019.05.028
8. Zhu W, Deng CJ, Xuan LP, et al. Peripheral artery disease and risk of fibrosis deterioration in nonalcoholic fatty liver disease: a prospective investigation. *Biomed Environ Sci*. 2020;33(4):217-226. doi:10.3967/bes2020.031
9. Taharboucht S, Guermaz R, Brouri M, Chibane A. Subclinical atherosclerosis and arterial stiffness in nonalcoholic fatty liver disease: a case-control study in Algerian population. *J Med Vasc*. 2021;46(3):129-138. doi:10.1016/j.jdmv.2021.03.008
10. Liu S, Wang J, Wu S, et al. The progression and regression of metabolic dysfunction-associated fatty liver disease are associated with the development of subclinical atherosclerosis: a prospective analysis. *Metabolism*. 2021;120:154779. doi:10.1016/j.metabol.2021.154779
11. Cicero AFG, Gitto S, Fogacci F, et al. Fatty liver index is associated to pulse wave velocity in healthy subjects: data from the Brisighella heart study. *Eur J Intern Med*. 2018;53:29-33. doi:10.1016/j.ejim.2018.03.010