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Early cardiac electrical and structural changes in patients with non-obese non-alcoholic fatty liver disease

Background — Obese non-alcoholic fatty liver disease (NAFLD) was found to increase the risk of developing atrial fibrillation (AF) regardless of the metabolic syndrome subgroups that may accompany it. In this study, the effect of NAFLD on the structural and electrical functions of the heart was investigated using tissue Doppler echocardiography (TDE) in non-obese NAFLD patients without any known risk factors for AF.

Material and methods — The study included 43 female patients (31.3±3.8 years), who had stage 2–3 hepatosteatosis detected by liver ultrasonography and diagnosed as non-obese NAFLD (patient group), and 31 healthy women (control group, 32.5±3.6 years). In addition to standard echocardiographic parameters, inter- and intra-atrial electromechanical delay (EMD) were evaluated by TDE.

Results — Interatrial EMD (PA lateral – PA tricuspid) and intraatrial EMD (PA septum – PA tricuspid) were significantly longer in patient group (16.1±3.4 vs. 12.5±2.3 ms, p<0.001, and 8.4±1.6 vs. 6.6±1.6 ms, p<0.001, respectively). At the subclinical level. atrial size, left ventricular diastolic function, and left ventricular wall thickness measurements were greater in the patient group.

Conclusion — Inter-atrial and intra-atrial EMD were detected in young women with non-obese NAFLD. In addition, at the subclinical level, structural and functional impairment was detected However, large-volume prospective studies are required to cobfirm these findings regarding the development of AF in non-obese NAFLD patients.

Keywords — Atrial electromechanical delay; nonalcoholic fatty liver disease; tissue doppler echocardiography; atrial fibrillation

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Nonalcoholic fatty liver disease (NAFLD) is defined as having fat accumulation of at least 5% of the liver weight without significant alcohol consumption (>30 g/day in men, >20 g/day in women) [1]. Although NAFLD is frequently seen with obesity, it occurs in non-obese patients. Non-obese NAFLD, which has been the center of attention in recent years, has a prevalence rate between 5% and 26% in the general population and between 20% and 50% among individuals with NAFLD [2]. Non-obese NAFLD is associated with higher plasma glucose levels, insulin resistance, total cholesterol levels, systolic and diastolic blood pressure, and waist circumference than seen in healthy subjects [3]. NAFLD is an independent risk factor for cardiovascular disease [4]. Similar to obese NAFLD, cardiovascular disease causes a significant portion of mortality in patients with non-obese NAFLD [5, 6]. Arrhythmic disorders are one of the main causes of high cardiovascular mortality. In a recent meta-analysis with large participation, NAFLD was found to increase the risk of developing atrial fibrillation (AF), regardless of the metabolic syndrome subgroups that may accompany it [7]. Atrial fibrillation (AF) is an arrhythmia that can cause increased mortality and morbidity. As far as we know, the effect of non-obese NAFLD on cardiac structure and electrical function has not been reported.

Tissue Doppler imaging (TDI), a non-invasive test that is sensitive and safe, is used to evaluate atrial electromechanical properties [8]. Atrial electromechanical delay (EMD), which can be measured by TDI, is a useful non-invasive electrophysiological marker for identifing atria prone to fibrillation [9]. However, the use of EMD in determining the risk of AF is still not included in AF guidelines. However, it has been shown to predict silent AF attacks in patients with high risk of AF [10–12]. In addition, EMD has been successfully used to detect arrhythmia-prone atria in the early stages of some diseases that increase the risk of AF [13–15]. Detecting early cardiac electrical and structural effects in non-obese NAFLD patients may be important in reducing mortality and morbidity. These

early effects may also be useful in evaluating the isolated cardiac effects of NAFLD. The purpose of this study was to investigate, by using standard echocardiography and TDI methods, the independent effect of NAFLD in the early period when steatohepatitis has not affected cardiac structure and electrical function.

Material and methods

Patient selection

This study was designed as a cross-sectional, cohort study. A group of 43 patients under 40 yrs of age were studied. They had been admitted to the gastroenterology outpatient clinic of our hospital and had no additional pathology other than grade ≥2 hepatosteatosis by liver ultrasonography (USG). The control group was formed of 31 healthy volunteers, who had normal USG and laboratory values (AST, ALT, GGT, ALP, bilirubin and albumin, etc.), and who had applied to the gastroenterology outpatient clinic, and who had similar age, height, and weight as the patient group. Subjects under 18 or over 40 yrs of age, or with any of the following conditions were not included in the study: male sex, coronary artery disease, diabetes mellitus, hypertension, heart failure, renal failure (glomerular filtration rate <60 ml/min/1.73 m^2), a history of atrial fibrillation, collagen tissue disease, obesity (body mass index >30 kg/m^2), metabolic syndrome, bronchial asthma, chronic obstructive pulmonary disease, thyroid disorder, obstructive sleep apnea, polycystic ovarian disease, smoking, alcohol use, chronic hepatitis B and C, cardiac valvular disease, electrolyte disorders, cardiac rhythm disorder, drug use that affects cardiac rhythm (such as antiarrhythmic, antihistamine, and antipsychotic drugs), and drug use that can cause hepatosteatosis (such as tamoxifen, oral contraceptives, methotrexate, and amiodarone). Body mass index (BMI) was calculated that weight in kilograms divided by the square of the height in meters.

Laboratory analyses

Venous blood samples were taken after a 12-hr fast. Blood was placed in tubes containing EDTA, and a complete blood count was performed. Leukocyte, neutrophil, hemoglobin, hematocrit, and platelet count were recorded. Fasting blood glucose (FBG), transaminases, and lipid profile levels were measured in the serum obtained after centrifuging 5 ml of blood which had been collected in biochemistry tubes.

Electrocardiography

Standard, 12-lead standard electrocardiograms (ECG, 10 mm/mV and 25 mm/s) were recorded from all subjects at rest and lying on their backs.

Transthoracic Echocardiography

USG examinations were performed from the left lateral decubitus position with a Vivid 7 (General Electric, Horten, Norway, 2-4 MHz phased array transducer) echocardiography machine. USG measurements were taken together with simultaneous ECG recordings by an experienced cardiologist who was blinded to the groups. Data from three cardiac cycles were averaged. Left ventricular (LV), left atrium (LA), and aortic root measurements were made using the M-mode method from the parasternal long-axis window. The LV ejection fraction (LVEF) was measured using the Teichholz formula. Right ventricular (RV) diameter, right atrial (RA) diameter, tricuspid annular plane systolic excursion (TAPSE), and the RA and LA areas were obtained from the apical four-chamber view. LA volume was assessed by the biplane area-length method from apical 4- and 2-chamber views. The LA volume index (LAVI) was calculated by dividing the LA volume by the estimated body surface area [16]. The normal value of the LA volume index has been reported to be 20±6 ml/m^2 [17]. All measurements were made according to the guidelines of the American Society of Echocardiography [18].

LV end-diastolic and end-systolic volumes (LVEDV, LVESV) were determined using the Teichholz equations: LVEDV (ml) = [7/(2.4 + LVEDD)] × LVEDD3 and LVESV (ml) = [7/(2.4 + LVESD)] × LVESD3. Using the Devereux formula [19], left ventricular masses (LVM) were calculated: LVM = 0.8 (1.04 (IVSd + LVDD + PWd)) 3 – (LVDD) 3) + 0.6. Left ventricular mass indexes (LVMI) were obtained by dividing LVM by body surface area. In a study where all participants were women, LVMI values greater than 99 g/m^2 were considered as evidence of LV hypertrophy [20]. Mitral early diastolic (E), and late diastolic (A) velocities were measured with PW Doppler during diastole by placing sample volume at the tips of mitral leaflets, and the ratio of the early (E) to late (A) ventricular filling velocities (E/A) was calculated.

A pulsed Doppler sample volume of 5 mm at transducer frequencies of 3.5–4.0 MHz was used for TDI. Spectral Doppler signal filters were set to obtain a Nyquist limit of 15 to 20 cm/s with minimal optimal gain settings. The sweep speed was 50 to 100 mm/s. A single-lead ECG was recorded simultaneously. In the apical four-chamber view, the sample volume was subsequently placed at the levels of the LV lateral mitral annulus, septal mitral annulus, and RV tricuspid annulus. The sampling window was positioned as parallel as possible to the myocardial segment of interest to obtain the optimal angle of imaging. Peak systolic (Sm), early diastolic (Em), late diastolic (Am) myocardial velocities were obtained from the mitral and tricuspid annulus. The diastolic myocardial velocity ratio (Em/Am) ratio for both ventricle and the ratio of the early transmitral flow velocity to the early

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Figure 1. Measurement of myocardial conduction velocity and atrial conduction time on tissue Doppler image

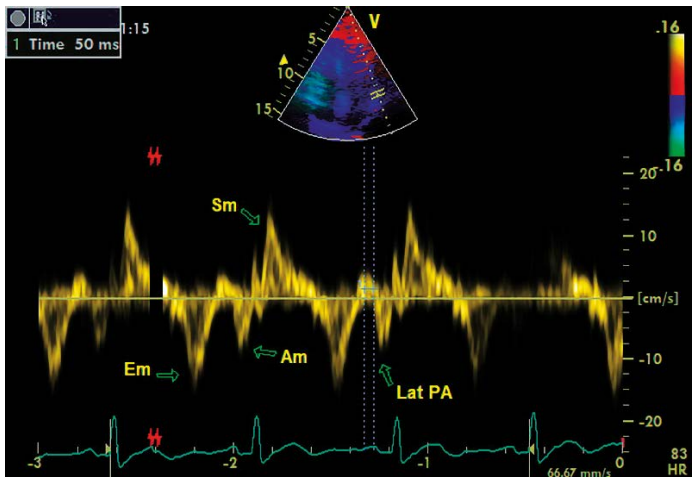
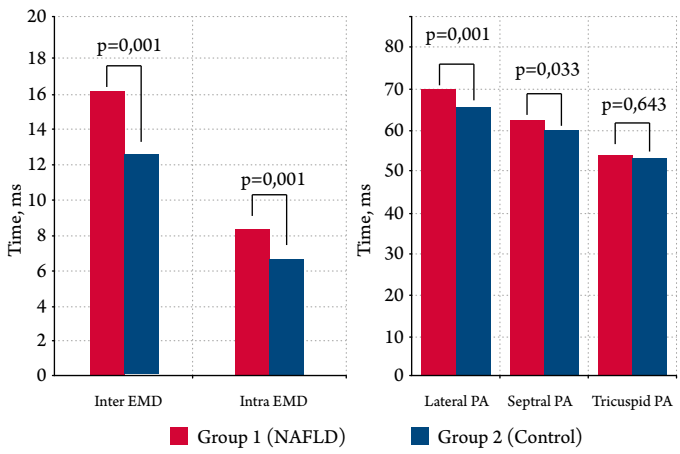


Figure 2. Comparisons of electrical conduction function of the groups



diastolic tissue velocity (E/Em) for the left ventricle were calculated. Grade I diastolic dysfunction was defined as a mitral E/A ratio <0.8, isovolumic relaxation time ≥100 ms, septal and lateral mitral annular E wave (Em) <8 cm/s, and mean E/Em ≤8 by TDI [21]. Time intervals from the onset of the P wave on the surface ECG to the beginning of the A wave (PA), representing atrial conduction, were obtained from the lateral mitral annulus, septal mitral annulus, and tricuspid annulus and named PA lateral, PA septum, and PA tricuspid, respectively. The difference between PA lateral and PA tricuspid (PA lateral – PA tricuspid) was defined as inter-atrial EMD. The difference between PA septum and PA tricuspid (PA septum – PA tricuspid) was defined as intra-atrial EMD (Figure 1).

Hepatic Ultrasonography

An experienced gastroenterologist performed hepatic USG on all patients using a 3.5MHz convex probe with the GE LOGIQ P5 USG device. NAFLD was evaluated based on the presence of hepatic brightness, hepatorenal echo contrast, deep attenuation, and vascular turbidity in the USG [22]. According to these criteria, hepatosteatosis was classified as grade 1, 2, or 3. Grade 1 (mild hepatosteatosis): minimal diffuse increase in hepatic echogenicity; the edges of the intrahepatic vessels and diaphragm can be seen as normal. Grade 2 (moderate hepatosteatosis): moderate increase in hepatic echogenicity; the edges of intrahepatic vessels and diaphragm are not seen very well. Grade 3 (severe hepatosteatosis): significant increase in echogenicity, lack of ultrasonic wave penetration into the posterior segment of the right liver lobe, and pure or no visualization of the hepatic vessels, and diaphragm. Those patients with grade 2–3 hepatosteatosis were included in the NAFLD group, and those with grade 0 hepatosteatosis were included in the control group. Those with Grade 1 hepatosteatosis were excluded.

Ethics Statement

The protocol of the present study was reviewed and approved by the institutional review board before onset (approval date: November 27, 2019; number 5). The research was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

The Shapiro-Wilk test was used to determine the normality of distributions. Normally distributed, continuous variables are expressed as mean ± standard deviation (SD), and non-normally distributed variables are expressed as median (interquantile range, 25-75th percentiles (Q1-Q3)) Categorical variables are expressed as percentages. For categorical variables, the differences between the groups were compared with the Chi-square test. According to the normality of the distributions, the differences between the groups were compared with the Student t-test or the Mann-Whitney U test. The correlation between the laboratory and echocardiographic findings and inter- and intraatrial-EMD was analyzed with Spearman's test. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, USA).

Results

45 female patients (group 1) diagnosed as NAFLD formed the study group, and 31 healthy women (group 2) comprised the control group. The demographic data and laboratory findings of the groups were similar (Table 1). Standard echocardiographic measurements are listed in Table 2.

The data obtained from TDI are shown in Table 3. Also, comparisons of electrical conduction functions between groups are shown in Figure 2. Lateral PA (70.1±5.2 ms and 66.0±4.4 ms, respectively; p=0.001), septal PA (62.4±4.4 ms and 60.1±4.3 ms, respectively; p=0.033), inter EMD (16.1±3.4

Table 1. Demographic and laboratory values of the groups

Parameters	Group 1 (NAFLD), n=45	Group 2 (Control), n=31	p
Age (yrs)	31.3±3.8	32.5±3.6	0.190
BMI (kg/m²)	25.7±2.6	24.8±2.7	0.154
Systolic BP (mmHg)	125.7±9.2	126.5±7.1	0.689
DiastolicBP (mmHg)	76.2±7.8	76.0±7.1	0.885
Heart rate (beats/min)	80.8±10.6	78.3±11.0	0.321
FBG (mg/dl)	86.7±8.6	85.1±7.7	0.391
Total Cholesterol(mg/dl)	180.9±29.6	171.8±27.8	0.181
Triglyceride (mg/dl)	194.00 (155.50-213.50)	123.00 (80.00-160.00)	<0.001†
HDL Cholesterol(mg/dl)	38.00 (34.00-43.00)	48.00 (40.00-55.00)	<0.001†
LDL Cholesterol (mg/dl)	113.00 (96.50-133.00)	103.00 (84.00-115.00)	0.005†
AST (IU/l)	19.00 (15.00-25.00)	17.00 (15.00-18.00)	0.034†
ALT (IU/l)	26.00 (20.00-30.00)	14.00 (12.00-18.00)	<0.001†
Hemoglobin (g/dl)	12.7±1.5	12.7±1.0	0.887
Leukocytes (#/μl)	8.4±2.2	7.3±2.3	0.054
Platelets (#/μl)	290,000 (245,000-332,500)	287,000 (245,000-332,000)	0.933†

Data are mean ± SD or median (interquantrile range, Q1-Q3). †Mann–Whitney U test. BMI, body mass index; BP, blood pressure; FBG, fasting blood glucose; HDL, high density lipoprotein; LDL, low density lipoprotein; AST, aspartate transaminase; ALT, alanine transaminase.

Table 2. Comparisons of standard echocardiographic measurements of the groups

Parameters	Group 1 (NAFLD), n=45	Group 2 (Control), n=31	p
LVDD (mm)	43.7±2.8	41.7±2.6	0.002
LVSD (mm)	30.2±3.0	28.8±3.6	0.056
IVSd (mm)	10.3±1.3	9.0±1.2	<0.001
PWd (mm)	9.4±1.21	8.2±1.2	<0.001
LVEF (%)	64.5±4.1	67.2±1.7	0.001
LA (mm)	31.1±3.4	29.1±2.7	0.007
RA (mm)	30.4±5.4	29.7±4.6	0.571
RV (mm)	28.6±3.0	27.1±2.5	0.026
LA volume (ml)	28.9±2.5	31.3±2.3	0.026
LAVI (ml/ m²)	19.1±1.6	17.2±1.2	<0.001
RA area (mm²)	13.2±1.2	11.8±0.9	<0.001
TAPSE (mm)	29.5±2.6	29.1±2.9	0.601
LVEDV (ml)	127.3±17.2	115.4±14.8	0.003
LVESV (mlL)	59.9±12.3	54.4±13.6	0.067
LVM (g)	144.4±30.2	109.6±20.9	<0.001
LVMI (g/m²)	80.6±17.5	65.2±12.1	<0.000
E velocity (cm/sec)	72.0±11.7	80.8±10.1	<0.001
A velocity (cm/sec)	60.9±13.7	61.7±9.6	0.744
E/A ratio	1.2±0.3	1.3±0.3	0.115
E/A<1	9 (20.0)	2 (6.5)	0.099

Data are mean ± SD or n (%).
LVDD, left ventricular diastolic diameter; LVSD, left ventricular sistolic diameter; IVS, inter ventricular septum thickness; PW, posterior wall thickness; LVEF, left ventricular ejection fraction; LA; left atrium; RA, right atrium; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; LVEDV (ml), left ventricular end diastolic volume; LVESV. left ventricular end diastolic volume; LVM, left ventricular mass; LVMI, left ventricular mass index; E, early diastolic velocity; A, late diastolic velocity.

Table 3. Tissue doppler echocardiographic findings of the groups

Parameters	Group 1 (NAFLD), n=45)	Group 2 (Control), n=31)	p
Lateral Sm (cm/s)	9.3±2.7	10.0±2.6	0.250
Lateral Em (cm/s)	13.5±3.9	15.6±3.5	0.020
Lateral Am (cm/s)	12.4±2.4	9.3±2.6	<0.001
Septal Sm (cm/s)	8.5±2.2	9.6±1.9	0.029
Septal Em (cm/s)	9.8±2.4	13.1±2.8	<0.001
Septal Am (cm/s)	10.3±2.3	9.1±1.6	0.015
Tricuspid Sm (cm/s)	14.2±2.2	14.1±2.4	0.829
Tricuspid Em (cm/s)	14.0±4.0	15.6±3.9	0.110
Tricuspid Am (cm/s)	16.7±4.6	13.8±4.4	0.009
Lateral E/Em	5.8±1.9	5.5±2.0	0.611
Septal E/Em	7.8±2.2	6.5±2.0	0.013
Lateral Em/Am	1.1±0.3	1.8±0.6	<0.001
Septal Em/Am	1.0±0.4	1.5±0.5	<0.001
Tricuspid Em/Am	0.9±0.3	1.3±0.5	<0.001

Data are mean±SD. Sm, systolic myocardial wave; Em, diastolic early myocardial wave; Am, diastolic late myocardial wave; E, diastolic mitral flow early wave velocity; A, diastolic mitral flow late wave velocity; Inter EMD, electromechanical delay between the atria; Intra EMD, electromechanical delay in the right atrium.

ms and 12.5±2.3 ms, respectively; p<0.001), and intra EMD (8.4±1.6 ms and 6.6±1.6 ms, respectively; p<0.001), which are the parameters showing atrial EMD, were significantly higher in the NAFLD group than the control group. Tricuspid PA was similar between groups. (14.2±2.2 ms and 14.1±2.4 ms, respectively; p=0.829) (Figure 2).

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Table 4. Correlation coefficients between inter- and intra-atrial electromechanical delay and laboratory and echocardiographic findings

	Inter-atrial EMD		Intra-atrial EMD	
	r	p	r	p
Inter-atrial EMD	1.000	-	0.743	<0.001
Intra-atrial EMD	0.743	<0.001	1.000	–
ALT (IU/l)	0,331	0.003	0.348	0.002
IVSd (mm)	0.496	<0.001	0.458	<0.001
PWd (mm)	0.411	<0.001	0.342	0.003
LVEF (%)	–0.256	0.025	–0.363	0.001
LA volume (ml)	0.326	0.004	0.439	0.001
LAVI	0.355	0.002	0.460	<0.001
RA area (mm^2)	0.334	0.003	0.304	0.008
LVMI (g/m^2)	0.335	0.003	0.298	0.009
Lateral PA	0.520	<0.001	0.296	0.010
Septal PA	0.261	0.023	0.335	0.003
Lateral E/Em	–0.331	0.003	–0.309	0.007
LateralAm (cm/s)	0.309	0.007	0.339	0.003
Septal Em (cm/s)	–0.238	0.038	–0.211	0.067

EMD, electromechanical delay; ALT, alanine transaminase; IVS, inter ventricular septum thickness; PW, posterior wall thickness, LVEF, left ventricular ejection fraction; LA, left atrium; LAVI, left atrium volume index; RA, right atrium; LVMI, left ventricular mass index; Em, diastolic early myocardial wave; Am, diastolic late myocardial wave; E, diastolic mitral flow early wave velocity.

Table 5. Comparisons of structural and electrical functions between patients with and without left ventricular hypertophy in the NASH group

Variable	non-LVH, n=30	LVH, n=15	p
LA volume (ml)	19.1±1.7	19.1±1.3	1.00
TAPSE (mm)	29.3±2.4	29.8±31	0.590
Mitral E/A	1.3±0.3	1.1±0.3	0.174
Lateral E/Em	5.9±1.8	5.5±2.0	0.535
Septal E/Em	7.6±1.6	8.1±3.0	0.505
Lateral Em/Am	1.1±0.2	1.1±0.3	0.866
Septal Em/Am	1.0±0.3	0.9±0.3	0.161
İnteratriyl EMD	16.5±4.5	19.9±5.5	0.049
İntraatriyal EMD	10.0±4.2	12.5±4.7	0.096
LVM (g)	132.9±23.1	171.9±23.6	<0.001
LVMI (g/m^2)	75,1±15.5	95.1±12.5	<0.001

Data are mean±SD. LA, left atrium; TAPSE, tricuspid annular plane systolic excursion; E, early diastolic velocity; A, late diastolic velocity; Inter EMD, electromechanical delay between the atria; Intra EMD, electromechanical delay in the right atrium; LVM, left ventricular mass; LVMI, left ventricular mass index.

Correlations of inter-atrial EMD and intraatrial-EMD with laboratory and echocardiographic findings are presented in Table 4.

The NAFLD group was divided into two groups: those with left ventricular hypertrophy (>99 gr/m^2) and those without left ventricular hypertrophy (<99 gr/m^2) according to the LMCI value. Structural and electrical function markers are compared between the two groups in Table 5.

Discussion

This study showed that non-obese NAFLD was significantly associated with interatrial, and intraatrial EMD. These findings may be related to structural changes such as IVSDd, PWd, LA volume, LAVI, RA area, LVMI, and alterations in LV diastolic function parameters.

NAFLD is observed in 25% of the world population and is the most important cause of liver failure [23]. The most important cause of mortality due to NAFLD is cardiovascular disease. While the prevalence of NAFLD is 15% in those with normal weight and without metabolic risk factors, it can reach 90% in the presence of diabetes mellitus, hyperlipidemia, and obesity [24]. Thus, NAFLD is an important public health problem due to its high incidence and its close relationship with cardiovascular disease [23, 25]. In the etiology of non-obese NAFLD, besides genetic diseases such as palatine-like phospholipase domain-containing 3 (PNPLA3), hypertension, dyslipidemia, and an increase in food consumption with a high content of fructose and cholesterol, and sedentary life are also blamed [26, 27].

NAFLD is generally asymptomatic and diagnosed incidentally in laboratory tests performed for other reasons. Although the most common laboratory finding is several-fold increased transaminases (AST, ALT), transaminases may be within normal limits in many patients [28]. Although it does not have clinical significance, steatosis is generally graded between grades 1–3. Therefore, liver USG is important and widely used in the diagnosis of moderate and severe hepatosteatosis due to its easy access, high sensitivity, and specificity. In this study, hepatosteatosis was diagnosed with USG, consistent with the literature [29].

Arrhythmias are one of the main cardiovascular diseases in which NAFLD causes an increased risk. Clinical studies have found that NAFLD is associated with increased frequency of supraventricular and ventricular arrhythmias [30, 31]. AF is the most common arrhythmia in these patients with increased risk of NAFLD [32, 33]. Subcomponents of metabolic syndromes such as diabetes mellitus, hypertension and hypertriglyceridemia, which frequently accompany NAFLD, have also been shown to be associated with increased risk of AF [7]. Advanced age and male gender are other clinical conditions associated with increased risk of AF [34]. To prevent the confounding role of these factors, this study included only participants who did not have additional risk factors for AF. The low incidence and prevalence of AF, together with the low cardiovascular risk status of the female gender in the pre-menopausal period, was the main reason we choose women as participants.

The pathogenesis of obese and non-obese NAFLD is still unclear. Some clinical studies of obese NAFLD patients

observed that adiponectin levels decreased, and leptin and proinflammatory cytokine levels increased [35]. It has been claimed that the increased risk of AF in obese NAFLD may be associated with subclinical inflammation, insulin resistance, autonomic dysfunction, and myocardial remodeling due to activation of the renin-angiotensin system [30, 36, 37]. It has also been claimed that insulin resistance may play a key role in non-obese NAFLD [38]. In the non-obese group, proinflammatory cytokine levels were similar to those in the healthy group [38]. However, results of studies on leptin and adiponectin levels in non-obese patients are contradictory [39, 40]. It was reported that activation of phagocytic Kupffer cells played a main role in the development of irreversible liver fibrosis in mouse experiments in which non-obese modeling occurred with a methionine/choline deficient diet [41]. The development of liver fibrosis is the main factor affecting the extent of cardiac involvement [42]. The pathogenesis of cardiac involvement in non-obese NAFLD remains unclear. In this study, only cardiac structural and functional status was investigated in non-obese NAFLD.

Standard and TDI echocardiography methods were used to detect possible structural cardiac changes in NAFLD. LV septum (IVSDd) and posterior wall thickness (PWd), LVM, LVMI, LVEDV, and area values of both atria were significantly increased in the non-obese NAFLD group. LV hypertrophy can cause diastolic dysfunction and enlargement of the left atrium, which causes fibrosis and electrical remodeling in the atria [43]. To reveal the relationship between left ventricular hypertrophy and diastolic function and the function of the electrical conduction system of the atrium, the NAFLD group was divided into two subgroups according to the presence of left ventricular hypertrophy, as defined by the LVMI value. These two groups were found to be similar in terms of structural properties, diastolic function and electrical function.

Many studies have shown that NAFLD may be associated with the development of LV diastolic dysfunction [44, 45]. A close relationship of increased liver fibrosis with diastolic dysfunction has been demonstrated in non-obese NAFLD [42]. Insulin resistance, which plays a major role in the pathogenesis of non-obese NAFLD, is one of the main mechanisms related to diastolic function [38, 46, 47]. In this study, TDI parameters were used to evaluate diastolic function. The Em/Am ratios obtained from the tricuspid, septal and lateral annulus were significantly lower in the NAFLD group than the control group, and the septal E/Em was significantly higher. Although these findings are not sufficient to make a diagnosis of diastolic function, they may be important because they reveal the development of diastolic dysfunction.

These structural and functional changes at the subclinical level may be preliminary signs of atrial remodeling. Atrial EMD has been defined as a transient delay between the onset of electrical activity and mechanical activation of the atrial myocardium. Atrial EMD can be measured by invasive and non-invasive methods [9]. TDI, a non-invasive test, is a sensitive and safe test used to evaluate atrial electromechanical properties [8]. It has been reported that EMD may be an independent predictor of AF development [10–12]. In this study, it was also observed that inter- and intra-EMD decreased significantly in the NAFLD patients in comparison to the control group. On the other hand, this amount of delay was less than the predictive levels reported in the literature [10–12].

The correlation of structural and electrical function markers shown to affect subclinical level of inter- and intra-atrial EMD in non-obese NAFLD patients was examined. In this study, a positive correlation was observed between inter-atrial EMD and intra-atrial EMD and serum alanine transaminase (ALT), PWd, LA volume, LAVI, RA area, LVMI, lateral PA, septal PA, IVSDd, and lateral Am. In addition, a negative correlation was observed between inter-atrial EMD and intra-atrial EMD and LVEF, lateral E/Em and septal Em. This study showed that, even in the case where the subcomponents of metabolic syndrome were not present, there was a subclinical-level deterioration in the cardiac structure and the electrical system in the early period of NAFLD. Considering also the comorbidity of increased metabolic syndrome subcomponents in non-obese NAFLD, the fact that metabolic syndrome subcomponents that would make cardiac influence more noticeable were used as exclusion criteria in this study and, thus, may explain the subclinical level of affectedness. While liver fibrosis was not investigated here, another reason for the subclinical level of influence may be the low probability of liver fibrosis indicated by that the participants did not have clinical signs of steatohepatitis.

It appears that the only study showing EMD in NAFLD was reported by Ozveren et al. [48]). However, in that study, patients with NAFLD were obese. Obesity causes an independent increase in risk for development of AF [49]. In addition, obesity is a disease that can cause inter- and intra-atrial EMD [13].

To the best of our knowledge, the current study is the first to show atrial EMD in non-obese NAFLD patients. The current findings also showed that, even if patients appear healthy, NAFLD is not actually an innocent disease, so early diagnosis and treatment may be important to prevent long-term cardiovascular complications. Additionally, due to the design of this study, the results may be useful by showing an independent effect of NAFLD on the risk of AF development in the long term.

Limitations

The small number of patients and the cross-sectional study design are limitations. Moreover, since larger prospective studies are needed to confirm the relationship of these preliminary results with the development of AF, the significance

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of the results in clinical practice is not yet known. In this study, the TDI technique, which is a sensitive technique, was used. A even more sensitive technique such as the myocardial deformation imaging technique would have made the findings more definite. Also, hepatosteatosis was diagnosed with hepatic USG. Since the patients were not biopsied, their diagnosis of hepatosteatosis was not confirmed pathologically and the possibility that steatohepatitis might have been confused with NAFLD can not be excluded. In addition, the present findings may not include patients with mild hepatosteatosis, since patients in the NAFLD group consisted of grade 2–3 patients. Also, semi-quantitative ultrasonographic indices [50] were not used. This study was conducted with a relatively small number of participants since NAFLD was frequently associated with metabolic disorders such as obesity, hypertension, diabetes mellitus, and its incidence in women is lower than in men [51]. The applicability of the results to men and women over the age of 40 is controversial.

Conclusion

This study showed significant delays and subclinical-level structural and functional deterioration in the inter-atrial and intra-atrial EMD of the young women with non-obese NAFLD in comparison to healthy volunteers. The results of this study may be encouraging for large-volume and prospective studies that aim to show the predictive value of atrial EMD in AF development in NAFLD and include non-obese NAFLD patients with silent atrial fibrillation in one of their groups.

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REFERENCE

1. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328–57. DOI: 10.1002/hep.29367
2. Wang AY, Dhaliwal J, Mouzaki M. Lean non-alcoholic fatty liver disease. Clinical Nutrition. 2019;38(3):975–81. DOI: 10.1016/j.clnu.2018.08.008
3. Sookoian S, Pirola CJ. Systematic review with meta-analysis: risk factors for non-alcoholic fatty liver disease suggest a shared altered metabolic and cardiovascular profile between lean and obese patients. Alimentary Pharmacology and Therapeutics. 2017;46(2):85–95. DOI: 10.1111/apt.14112
4. Xin Z, Zhu Y, Wang S, Liu S, Xu M, Wang T et al. Associations of subclinical atherosclerosis with nonalcoholic fatty liver disease and fibrosis assessed by non-invasive score. Liver International. 2020;40(4):806–14. DOI: 10.1111/liv.14322
5. Stepanova M, Rafiq N, Makhlouf H, Agrawal R, Kaur I, Younoszai Z et al. Predictors of All-Cause Mortality and Liver-Related Mortality in Patients with Non-Alcoholic Fatty Liver Disease (NAFLD). Digestive Diseases and Sciences. 2013;58(10):3017–23. DOI: 10.1007/s10620-013-2743-5
6. Yousef MH, Juboori AA, Albarrak AA, Ibdah JA, Tahan V. Fatty liver without a large "belly": Magnified review of non-alcoholic fatty liver disease in non-obese patients. World Journal of Gastrointestinal Pathophysiology. 2017;8(3):100–7. DOI: 10.4291/wjgp.v8.i3.100
7. Cai X, Zheng S, Liu Y, Zhang Y, Lu J, Huang Y. Nonalcoholic fatty liver disease is associated with increased risk of atrial fibrillation. Liver International. 2020;40(7):1594–600. DOI: 10.1111/liv.14461
8. Deniz A, Sahiner L, Aytemir K, Kaya B, Kabakci G, Tokgozoglu L et al. Tissue Doppler echocardiography can be a useful technique to evaluate atrial conduction time. Cardiology Journal. 2012;19(5):487–93. DOI: 10.5603/cj.2012.0089
9. Daubert J-C, Pavin D, Jauvert G, Mabo P. Intra- and Interatrial Conduction Delay:. Implications for Cardiac Pacing. Pacing and Clinical Electrophysiology. 2004;27(4):507–25. DOI: 10.1111/j.1540-8159.2004.00473.x
10. Akamatsu K, Ito T, Miyamura M, Kanzaki Y, Sohmiya K, Hoshiga M. Usefulness of tissue Doppler-derived atrial electromechanical delay for identifying patients with paroxysmal atrial fibrillation. Cardiovascular Ultrasound. 2020;18(1):22. DOI: 10.1186/s12947-020-00205-2
11. Gunes H, Sokmen A, Kaya H, Gungor O, Kerkutluoglu M, Guzel FB et al. Evaluation of Atrial Electromechanical Delay to Predict Atrial Fibrillation in Hemodialysis Patients. Medicina. 2018;54(4):58. DOI: 10.3390/medicina54040058
12. Russo V, Rago A, Ciardiello C, Russo MG, Calabrò P, Politano L et al. The Role of the Atrial Electromechanical Delay in Predicting Atrial Fibrillation in Myotonic Dystrophy Type 1 Patients: Myotonic Dystrophy and Atrial Fibrillation. Journal of Cardiovascular Electrophysiology. 2016;27(1):65–72. DOI: 10.1111/jce.12821
13. Hizal Erdem F, Ozturk S, Baltaci D, Donmez I, Alçelik A, Ayhan S et al. Detection of atrial electromechanical dysfunction in obesity. Acta Cardiologica. 2015;70(6):678–84. DOI: 10.1080/AC.70.6.3120180
14. Demir K, Avci A, Kaya Z, Marakoglu K, Ceylan E, Yilmaz A et al. Assessment of atrial electromechanical delay and P-wave dispersion in patients with type 2 diabetes mellitus. Journal of Cardiology. 2016;67(4):378–83. DOI: 10.1016/j.jjcc.2015.06.003
15. Avci BK, Gulmez O, Donmez G, Pehlivanoglu S. Early Changes in Atrial Electromechanical Coupling in Patients with Hypertension: Assessment by Tissue Doppler Imaging. Chinese Medical Journal. 2016;129(11):1311–5. DOI: 10.4103/0366-6999.182846
16. Basnight MA, Gonzalez MS, Kershenovich SC, Appleton CP. Pulmonary Venous Flow Velocity: Relation to Hemodynamics, Mitral Flow Velocity and Left Atrial Volume, and Ejection Fraction. Journal of the American Society of Echocardiography. 1991;4(6):547–58. DOI: 10.1016/S0894-7317(14)80213-7
17. Wang Y, Gutman JM, Heilbron D, Wahr D, Schiller NB. Atrial Volume in a Normal Adult Population by Two-dimensional Echocardiography. Chest. 1984;86(4):595–601. DOI: 10.1378/chest.86.4.595
18. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA et al. Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, Developed in Conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. Journal of the American Society of Echocardiography. 2005;18(12):1440–63. DOI: 10.1016/j.echo.2005.10.005
19. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I et al. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. The American Journal of Cardiology. 1986;57(6):450–8. DOI: 10.1016/0002-9149(86)90771-X
20. Harkness A, Ring L, Augustine DX, Oxborough D, Robinson S, Sharma V. Normal reference intervals for cardiac dimensions and function for use in echocardiographic practice: a guideline from the British Society of Echocardiography. Echo Research and Practice. 2020;7(1):G1–18. DOI: 10.1530/ERP-19-0050

21. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Journal of the American Society of Echocardiography. 2009;22(2):107–33. DOI: 10.1016/j.echo.2008.11.023
22. Mehta SR, Thomas EL, Bell JD, Johnston DG, Taylor-Robinson SD. Non-invasive means of measuring hepatic fat content. World Journal of Gastroenterology. 2008;14(22):3476–83. DOI: 10.3748/wjg.14.3476
23. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73–84. DOI: 10.1002/hep.28431
24. Gaggini M, Morelli M, Buzzigoli E, DeFronzo R, Bugianesi E, Gastaldelli A. Non-Alcoholic Fatty Liver Disease (NAFLD) and Its Connection with Insulin Resistance, Dyslipidemia, Atherosclerosis and Coronary Heart Disease. Nutrients. 2013;5(5):1544–60. DOI: 10.3390/nu5051544
25. Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. Journal of Hepatology. 2016;65(3):589–600. DOI: 10.1016/j.jhep.2016.05.013
26. Kim D, Kim WR. Nonobese Fatty Liver Disease. Clinical Gastroenterology and Hepatology. 2017;15(4):474–85. DOI: 10.1016/j.cgh.2016.08.028
27. Nishioji K, Mochizuki N, Kobayashi M, Kamaguchi M, Sumida Y, Nishimura T et al. The Impact of PNPLA3 rs738409 Genetic Polymorphism and Weight Gain ≥10 kg after Age 20 on Non-Alcoholic Fatty Liver Disease in Non-Obese Japanese Individuals. PLOS ONE. 2015;10(10):e0140427. DOI: 10.1371/journal.pone.0140427
28. Riley TR, Bhatti AM. Preventive strategies in chronic liver disease: part I. Alcohol, vaccines, toxic medications and supplements, diet and exercise. American Family Physician. 2001;64(9):1555–60. PMID: 11730310
29. Ballestri S, Nascimbeni F, Lugari S, Lonardo A, Francica G. A critical appraisal of the use of ultrasound in hepatic steatosis. Expert Review of Gastroenterology and Hepatology. 2019;13(7):667–81. DOI: 10.1080/17474124.2019.1621164
30. Anstee QM, Mantovani A, Tilg H, Targher G. Risk of cardiomyopathy and cardiac arrhythmias in patients with nonalcoholic fatty liver disease. Nature Reviews Gastroenterology and Hepatology. 2018;15(7):425–39. DOI: 10.1038/s41575-018-0010-0
31. Mangi MA, Rehman H, Minhas AM, Rafique M, Bansal V, Constantin J. Non-Alcoholic Fatty Liver Disease Association with Cardiac Arrhythmias. Cureus. 2017;9(4):e1165. DOI: 10.7759/cureus.1165
32. Roh J, Lee J, Lee H, Yoon Y, Kim M, Kim Y et al. Association between non-alcoholic fatty liver disease and risk of new-onset atrial fibrillation in healthy adults. Liver International. 2020;40(2):338–46. DOI: 10.1111/liv.14236
33. Markus MRP, Meffert PJ, Baumeister SE, Lieb W, Siewert U, Schipf S et al. Association between hepatic steatosis and serum liver enzyme levels with atrial fibrillation in the general population. Atherosclerosis. 2016;245:123–31. DOI: 10.1016/j.atherosclerosis.2015.12.023
34. Lankarani KB, Mahmoodi M, Lotfi M, Zamiri N, Heydari ST, Ghaffarpasand F et al. Common Carotid Intima-media Thickness in Patients with Non-alcoholic Fatty Liver Disease: A Population-based Case-control Study. The Korean Journal of Gastroenterology. 2013;62(6):344–51. DOI: 10.4166/kjg.2013.62.6.344
35. Stojsavljević S, Gomerčić Palčić M, Virović Jukić L, Smirčić Duvnjak L, Duvnjak M. Adipokines and proinflammatory cytokines, the key mediators in the pathogenesis of nonalcoholic fatty liver disease. World Journal of Gastroenterology. 2014;20(48):18070–91. DOI: 10.3748/wjg.v20.i48.18070
36. Sun W, Zhang D, Sun J, Xu B, Sun K, Wang T et al. Association between non-alcoholic fatty liver disease and autonomic dysfunction in a Chinese population. QJM. 2015;108(8):617–24. DOI: 10.1093/qjmed/hcv006
37. Paschos P, Tziomalos K. Nonalcoholic fatty liver disease and the renin-angiotensin system: Implications for treatment. World Journal of Hepatology. 2012;4(12):327–31. DOI: 10.4254/wjh.v4.i12.327
38. Sinn DH, Gwak G-Y, Park HN, Kim JE, Min YW, Kim KM et al. Ultrasonographically Detected Non-Alcoholic Fatty Liver Disease Is an Independent Predictor for Identifying Patients With Insulin Resistance in Non-Obese, Non-Diabetic Middle-Aged Asian Adults. American Journal of Gastroenterology. 2012;107(4):561–7. DOI: 10.1038/ajg.2011.400
39. Feldman A, Eder SK, Felder TK, Kedenko L, Paulweber B, Stadlmayr A et al. Clinical and Metabolic Characterization of Lean Caucasian Subjects with Non-alcoholic Fatty Liver. American Journal of Gastroenterology. 2017;112(1):102–10. DOI: 10.1038/ajg.2016.318
40. Kumar R, Prakash S, Chhabra S, Singla V, Madan K, Gupta SD et al. Association of pro-inflammatory cytokines, adipokines & oxidative stress with insulin resistance & non-alcoholic fatty liver disease. The Indian Journal of Medical Research. 2012;136(2):229–36. PMID: 22960889
41. Itagaki H, Shimizu K, Morikawa S, Ogawa K, Ezaki T. Morphological and functional characterization of non-alcoholic fatty liver disease induced by a methionine-choline-deficient diet in C57BL/6 mice. International Journal of Clinical and Experimental Pathology. 2013;6(12):2683–96. PMID: 24294355
42. Chung GE, Lee J-H, Lee H, Kim MK, Yim JY, Choi S-Y et al. Nonalcoholic fatty liver disease and advanced fibrosis are associated with left ventricular diastolic dysfunction. Atherosclerosis. 2018;272:137–44. DOI: 10.1016/j.atherosclerosis.2018.03.027
43. Rosenberg MA, Gottdiener JS, Heckbert SR, Mukamal KJ. Echocardiographic diastolic parameters and risk of atrial fibrillation: the Cardiovascular Health Study. European Heart Journal. 2012;33(7):904–12. DOI: 10.1093/eurheartj/ehr378
44. VanWagner LB, Wilcox JE, Ning H, Lewis CE, Carr JJ, Rinella ME et al. Longitudinal Association of Non-Alcoholic Fatty Liver Disease With Changes in Myocardial Structure and Function: The CARDIA Study. Journal of the American Heart Association. 2020;9(4):e014279. DOI: 10.1161/JAHA.119.014279
45. VanWagner LB, Wilcox JE, Colangelo LA, Lloyd-Jones DM, Carr JJ, Lima JA et al. Association of nonalcoholic fatty liver disease with subclinical myocardial remodeling and dysfunction: A population-based study. Hepatology. 2015;62(3):773–83. DOI: 10.1002/hep.27869
46. Park SH, Kim BI, Yun JW, Kim JW, Park DI, Cho YK et al. Insulin resistance and C-reactive protein as independent risk factors for non-alcoholic fatty liver disease in non-obese Asian men. Journal of Gastroenterology and Hepatology. 2004;19(6):694–8. DOI: 10.1111/j.1440-1746.2004.03362.x
47. Novo G, Manno G, Russo R, Buccheri D, Dell'Oglio S, Morreale P et al. Impact of insulin resistance on cardiac and vascular function. International Journal of Cardiology. 2016;221:1095–9. DOI: 10.1016/j.ijcard.2016.07.087
48. Ozveren O, Izgi C, Eroglu E, Simsek MA, Turer A, Kucukdurmaz Z et al. Doppler Tissue Evaluation of Atrial Conduction Properties in Patients With Non-alcoholic Fatty-liver Disease. Ultrasonic Imaging. 2016;38(3):225–35. DOI: 10.1177/0161734615595015
49. Wang TJ, Parise H, Levy D, D'Agostino RB, Wolf PA, Vasan RS et al. Obesity and the Risk of New-Onset Atrial Fibrillation. JAMA. 2004;292(20):2471–7. DOI: 10.1001/jama.292.20.2471
50. Ferraioli G, Monteiro LBS. Ultrasound-based techniques for the diagnosis of liver steatosis. World Journal of Gastroenterology. 2019;25(40):6053–62. DOI: 10.3748/wjg.v25.i40.6053
51. Ballestri S, Nascimbeni F, Baldelli E, Marrazzo A, Romagnoli D, Lonardo A. NAFLD as a Sexual Dimorphic Disease: Role of Gender and Reproductive Status in the Development and Progression of Nonalcoholic Fatty Liver Disease and Inherent Cardiovascular Risk. Advances in Therapy. 2017;34(6):1291–326. DOI: 10.1007/s12325-017-0556-1

ISSN 0022-9040. Кардиология. 2021;61(5). DOI: 10.18087/cardio.2021.5.n1416