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Original Article

Non-alcoholic fatty liver disease and LV diastolic dysfunction in patients with type 2 diabetes mellitus

Maryam Faramarzpour (MD) [1]
Mohammadreza Mohammad Hosseiniazar (MD) [2]
Laya Hooshmand Gharabagh (MD) [3*]

1. Department of Cardiology, Imam Khomeini Hospital, Urmia University of Medical Sciences, Urmia, Iran
2. Department of Internal Medicine, School of Medicine, Taleghani Hospital, Imam Khomeini Hospital, Urmia University of Medical Sciences, Urmia, Iran
3. Department of Internal Medicine, School of Medicine, Imam Khomeini Hospital, Urmia University of Medical Sciences, Urmia, Iran

*** Correspondence:**
Laya Hooshmand Gharabagh, Assistant Professor of Endocrinology and Metabolism, Urmia University of Medical Sciences, Imam Khomeini Hospital, Urmia, Iran,

E-mail:
Laya.hooshmand58@gmail.com
Tel: +98 44 33457286

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Abstract

Background: To date, the clinical implications of the long-lasting non-alcoholic fatty liver disease (NAFLD) such as the left ventricular diastolic dysfunction (LVDD) in the course of type 2 diabetes mellitus (T2DM) are yet to be determined. The main aim of this study was to investigate the correlation between NAFLD and early LVDD progression along with demographic characteristics.

Methods: This cross-sectional study was performed on ninety consecutive diabetic outpatients referred to the endocrinology clinic. Demographic data were collected using a designed checklist. Ultrasound imaging was performed to assess the fatty liver condition. To assess LV diastolic function, echocardiography was performed, using a trans-thoracic tissue Doppler echocardiography.

Results: The results showed that the majority of participants were females (61.1%). The fasting blood glucose (FBG, mg/dl) level was 174.65 ±51.1. Also, the mean body mass index (BMI) was 28.92±4.19, which was significantly associated with NAFLD. It has been also estimated that 76.7% and 81.1% of diabetic patients had NAFLD and simultaneous LVDD, respectively. However, the statistical results did not show a significant association between non-progressive NAFLD and LVDD ($p<0.05$).

Conclusion: There was no correlation between NAFLD and LVDD progression. However, timely evaluation of LVDD in T2DM outpatients with NAFLD can strongly help to prevent possible cardiomyopathy in high-risk populations.

Keywords: Early diagnosis**,** Ventricular dysfunction, Fatty liver, Type 2 diabetes mellitus, Risk factors.

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Non-alcoholic fatty liver disease (NAFLD), a benign hepatic manifestation, and type 2 diabetes (T2DM) are co-existing conditions, remaining one of the concerning public health issues in the field of metabolic syndrome with increasing trend worldwide (1, 2). In this regard, epidemiological studies have also estimated that 40-70% of subjects with T2DM have underlying fatty liver disease (3). They are prone to up to a two-fold increase in favor of NAFLD development, followed by a more aggressive course of nonalcoholic steatohepatitis, as well as end-stage liver disease (4, 5). Besides, in a meta-analysis performed on patients with NAFLD, the rate of T2DM was 69%, considered the strongest leading cause for NAFLD when compared with other risk factors such as obesity, dyslipidemia, and hypertension (6). Notably, it has been thought that a close relationship between NAFLD and T2DM, as reciprocal risk factors, can jointly act to drive pertinent sequelae such as cardiovascular diseases (CVD) (7, 8).

Staging of NAFLD, from simple steatosis to severe non-alcoholic steatohepatitis, is based on demographic and paraclinical parameters such as age, gender, liver function biomarkers, platelet count, lipid profile, BMI, and noninvasive diagnostic assessment is employed through imaging modalities, including ultrasound imaging, transient elastography (TE), and magnetic resonance imaging (MRI) mass spectroscopy, which are emerging as imperative tools in the early diagnosis of NAFLD and predicting liver fibrosis (3). The existing gold standard of care involves tailoring, a therapeutic strategy to optimize the metabolic status improving liver phenotype (9).

Some metabolic disorders mainly participate in the pathophysiology of NAFLD, including insulin resistance, hepatic lipid accumulation, metabolic imbalance of visceral fat, and genetic factors. In this regard, recent literature has also indicated that NAFLD may lead to some negative impacts on the cardiac structure and function, likely due to impairment of both myocardial glucose uptake and fat infiltration, increased inflammatory response, and oxidative stress (10). However, more research is required to further perceive the underlying mechanisms driving NAFLD progression, proper anti-diabetic medications, and novel therapeutic targets (11). T2DM is also regarded as a predisposing condition for cardiomyopathy e.g., left ventricular (LV) diastolic dysfunction (LVDD), most likely due to simultaneous dyslipidemia which is defined as a major leading cause of death for diabetic patients (12, 13). Given the limited evidence-based reports, in the present study we aimed to determine any relationship between NAFLD and LVDD development in T2DM patients.

Methods

Study population: In this cross-sectional study with the code of ethics: IR.UMSU.REC.1400.032, diabetic outpatients with confirmed NAFLD were included, who attended the endocrinology clinic of a tertiary referral hospital from October 2020 to September 2021. All included patients filled up the designed checklist consisting of age, gender, fast blood glucose (FBG), and body mass index (BMI) at the first visit. The participants underwent liver ultrasound imaging, which was performed semi-quantitatively by a high-resolution ultrasound system, and transthoracic echocardiography was carried out to evaluate LV function at the cardiology department of the hospital.

NAFLD diagnosis and BMI definition: The NAFLD was diagnosed as hepatic steatosis without fibrosis during ultrasound examination and was defined as absent (0), mild (1), moderate (2), or severe (3) based on liver brightness, hepato-renal echo contrast, deep attenuation, and vascular blurring. To calculate BMI, height and body weight were measured. Briefly, each patient's weight was divided by the square of the height (kg/m2). Moreover, obesity was defined according to the Asia-Pacific region criteria (BMI ≥25 kg/m2) (14, 15). To assess lipid indices and glucose values, blood samples were taken.

Echocardiography: All diabetic patients also underwent a trans-thoracic tissue Doppler echocardiography, which is the most practical and reproducible tool for early LVDD diagnosis. All echocardiographic interrogations were performed via Siemens Acuson Sc2000 vendor, which was defined based on criteria issued by the American Society of Echocardiography/ The European Association of Cardiovascular Imaging (ASE/EACVI) 2016 update (16). In patients with normal LVEF and no echocardiographic findings indicating myocardial disease, relevant echocardiographic parameters, including E/e'>14 (a functional marker of LV), septal e' velocity< 7cm/s or lateral e' velocity <10cm/s, TR velocity = 2.8m/s, LA volume index (LAVI) >34ml/m2, and deceleration time (DT) were measured.

Diastolic function is considered normal if less than 50% of the measured values meet the mentioned criteria and interpreted as abnormal if > 50% of these criteria are met; moreover, the study is not reliable if 50 % of the parameters are normal. In patients with either LVDD or structural heart abnormalities, the E/A ratio and the E value were initially determined. When E/A and E were ≤ 0.8 and ≤ 50 cm/s, respectively, the left atrial pressure (LAP) was considered normal with grade I diastolic dysfunction. To define Grade II, the E/A ratio was > 0.8 to < 2, in which a high LAP is reported. The E/A ratio ≥ 2 was considered a high LAP and Grade III diastolic dysfunction. However, when the E/A ratio and E amounts were ≤ 0.8 and > 50 cm/s, respectively, or E/A ratio was calculated from > 0.8 to <2, three criteria were determined as follows:

1. Average E/e' >14, 2. TR velocity >2.8 m/s, and 3. LAVI >34 mL/m^2.

E= Trans-mitral peak early diastolic velocity, e' = Septal and lateral early mitral annular diastolic tissue velocities, A = Atrial peak filling velocity, TR= Tricuspid regurgitation.

If at least two criteria were negative, it was defined as normal LAP Grade I diastolic dysfunction, while two positive criteria and over was inferred as high LAP Grade III diastolic dysfunction. In addition, the diastolic function was considered unspecified when two measurable criteria were observed along with one positive criterion (16).

Inclusion/exclusion criteria: We included all patients with the age of thirty-five years old and over (35≤), a history of

T2DM for three years and more, and who were receiving anti-diabetic medications. Individuals with a history of ischemic heart disease, a history of acute/chronic hepatic diseases, excessive alcohol consumption, and fatty liver for other reasons were excluded. It is also worth noting that the patients with severe LV systolic dysfunction (LVSD), a low ejection fraction (EF), and severe valvular heart disease were excluded.

Statistical analysis: For data analysis, Statistical Package for the Social Sciences (SPSS) software Version 20.0 was used. The quantitative and qualitative data were also reported as mean ± standard deviation (SD) and frequency (percentage), respectively. In addition, for sub-group analysis, Pearson's chi-squared test (X^2) was performed. A p-value less than 0.05, was considered statistically significant.

Results

Demographic characteristics: In this cross-sectional and observational study, a total of ninety diabetic patients were included, of which fifty-five were females (61.1%). The mean age of participants was 52.74±8.77 years (min=36, max=72), the mean BMI (kg/m2) was calculated at 28.92±4.19, and the average diabetes duration was 6.32±4.53 years.

In table 1 and 2, baseline demographic data and lipid profile, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG), as well as ultrasound and echocardiography reports have been brought. As shown in table 1, significant differences were not observed regarding the baseline characteristics between female and male diabetic patients (p>0.05).

Table 1. Baseline demographic and metabolic characteristics among diabetic patients in different genders

Variables	Female (Total patients number = 90)	Male	
Gender	55 (61.1%)	35 (38.9%)	
Age (yr)	Mean ± SD 52.74±8.77		
Variables	**Gender**	**Mean ± SD**	**P value**
FBG (mg/dl)	Female	172.09±44.68	0.554
	Male	178.68±60.43	
HbA1C	Female	7.86±1.74	0.362
	Male	8.16±1.62	
2hpp Blood glucose	Female	268.67±79.25	0.493
	Male	206.34±88.44	
LDL (mmol/L)	Female	97.96±31.37	0.552
	Male	100.23±52.31	
TG (mmol/L)	Female	214.87±1.7.13	0.989
	Male	215.23±140.44	
HDL (mmol/L)	Female	47.72±11.12	0.557
	Male	46.05±15.62	
Diabetes Duration (yr)	Female	6.16±3.78	0.659
	Male	6.6±5.56	
BMI (Kg/m2)	Female	29.51±4.09	0.094
	Male	27.99±4.23	

2hpp blood glucose, 2-hour postprandial blood glucose, BMI, Body Mass Index; FBG, Fasting Blood Glucose; HBA1c, Hemoglobin A1C; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; TG, Triglyceride.

The impact of gender on NAFLD and LVDD severity: We also evaluated a possible association between gender and NAFLD progression by performing liver ultrasound imaging and determination of NAFLD severity. Our findings revealed no remarkable difference between the two genders in terms of NAFLD and LV dysfunction severity. Therefore, it can be concluded that gender is not a reliable determinant in this regard (table 2).

The impact of metabolic indicators on NAFLD and LVDD: Regarding the diabetic indicators, it has also been shown that serum levels of FBG but not glycosylated hemoglobin (HbA1C), and 2-hour postprandial blood glucose (2hpp) were significantly different, considering a predictive value for NAFLD development based on the ultrasonography examination and disease severity (table 3, $p<0.05$).

Table 2. Comparison of NAFLD prevalence and the LVDD severity in different genders of diabetic patients

Variable	Gender		Chi-square	P value	
NAFLD	Female	Positive n=41	0.356	0.37	
		Negative n=14			
	Male	Positive n=28			
		Negative n=7			
NAFLD Severity †	Grade	Female (N number)	Male (N number)		
	Normal	14	7		
	1	21	14	P value 0.366	0.833
	2	20	14		
	3	0	0		
LVDD Severity §	Grade	Female	Male		
	Normal	2	3		
	I	45	28	1.102	0.576
	II	8	4		
	III	0	0		

† measured by Ultrasound imaging. § measured by Echocardiography. LVDD, Left Ventricle Diastolic Dysfunction; NAFLD: Non-alcoholic Fatty Liver Disease.

However, the results of echocardiography revealed that the diabetes indicators would not be reliable values for the prediction of LV dysfunction (table 4, $p>0.05$). Notably, ultrasound findings exhibited a positive relationship between BMI ($p<0.05$) and TG ($p=0.003$) levels with fatty liver occurrence and related severity in diabetic patients (table 5). Besides, the levels of HDL but not LDL represented a negative association with NAFLD (table 5, $p<0.05$). Regarding the association between blood lipid indices and obesity value with LVDD progression, we did not observe a statistically significant association between lipid profile, and BMI with echocardiography grade (table 3). The results of the post hoc test about the BMI, FBS, and TG were also prepared in table 4.

The association between NAFLD and LVDD in T2DM patients: Additionally, our findings showed no significant correlation between the severity of NAFLD and LV dysfunction in diabetic patients (table 6, $p>0.05$). In this connection, LV dysfunction may occur independent of NAFLD development in a fraction of the patients.

Table 3. Association between NAFLD and diabetes indicators

Variable	NAFLD condition † (N number)	Mean	P value
FBG (mg/dl)	Positive n=69	182.58±52.03	0.007**
	Negative n=21	148.62±38.84	
HBA1C	Positive n=69	8.09±1.43	0.219
	Negative n=21	7.62±1.80	
HBS2hpp	Positive n=69	222.62±78.88	0.069
	Negative n=21	185.14±90.17	
FBG (mg/dl)	Normal n=21	148.62±38.84	0.017*
	1 n=35	177.03±50.6	
	2 n=33	188.3± 53.62	
	3 n=0	0	
HBA1C	Normal n=21	7.62±1.81	0.112
	1 n=35	7.78±1.39	
	2 n=33	8.4±1.42	
	3 n=0	0	
2hpp Blood glucose	Normal n=21	185.14±90.16	0.141
	1 n=35	230.28±97.46	
	2 n=33	214.73±53.92	
	3 n=0	0	

† measured by Ultrasound imaging, The Fisher LSD (Least Significant Difference) was used as a post hoc test. * p<0.05, ** p<0.01, *** p<0.001. 2hpp blood glucose, 2-hour postprandial blood glucose, FBG, Fasting Blood Glucose; HBA1c, Hemoglobin A1C; NAFLD, Non-Alcoholic Fatty Liver Disease.

Table 4. A possible association between LV function and diabetes indicators

Variable	Grade of LVDD § (N number)	Mean	P value
FBG (mg/dl)	Normal n=5	181.2±43.27	0.72
	I n=73	175.98±53.88	
	II n=12	163.83± 36.41	
	III n=0	0	
HBA1C	Normal n=5	7.62±1.81	0.112
	1 n=73	7.78±1.39	
	2 n=12	8.4±1.42	
	3 n=0	0	
2hpp Blood glucose	Normal n=5	169.8±34	0.141
	1 n=73	220.71±87.09	
	2 n=12	190.67±58.79	
	3 n=0	0	

§ measured by Echocardiography. 2hpp blood glucose, 2-hour postprandial blood glucose; HBA1c, Hemoglobin A1C; FBG, Fasting Blood Glucose; LVDD, Left Ventricle Diastolic Dysfunction.

Table 5. The Relationship between NAFLD with BMI and Lipid Profile

Variables	NAFLD (N number)	Mean ± SD	p-value
BMI	Positive n=69	29.41±4.14	0.044 *
	Negative n=21	27.31±4.02	
TG	Positive n=69	235.53±125.7	0.003*
	Negative n=21	147.57±67.55	
LDL	Positive n=69	99.39±31.69	0.795
	Negative n=21	102.05±62.59	

Variables	NAFLD (N number)	Mean ± SD	p-value
HDL	Positive n=69	45.47±10.91	0.033*
	Negative n=21	52.33±17.58	
BMI	Normal n=21	27.31±4.02	0.012*
	1 n=35	28.35±3.72	
	2 n=34	30.51±4.32	
	3 n=0	0	
TG	Normal n= 21	147.57±67.55	0.003**
	1 n=35	212.6±102.7	
	2 n=34	259.18±143.38	
	3 n=0	0	
LDL	Normal n= 21	102.047±62.59	0.966
	1 n=35	99.63±31.89	
	2 n=34	99.15±31.97	
	3 n=0	0	
HDL	Normal n= 21	52.33±17.58	0.093
	1 n=35	46.23±11.94	
	2 n=34	44.69±9.85	
	3 n=0	0	

† measured by Ultrasound imaging, The Fisher LSD (Least Significant Difference) was used as a post hoc test. * $p<0.05$, ** $p<0.01$, *** $p<0.001$. BMI, Body Mass Index; FBG, Fasting Blood Glucose; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; TG, Triglyceride; NAFLD: Non-alcoholic Fatty Liver Disease

Table 6. The Assessment of Relationship between NAFLD and LVDD in Diabetic Patients

Variable	LVDD Grade §				Pearson's chi-square	P value
	Normal	I	II	III		
Confirmed NAFLD†	5	54	10	0	2.116	0.347
	0	19	2	0		
Grade of NAFLD †	**LVDD Grade §**				**Pearson's chi-square**	**P value**
	Normal	**I**	**II**	**III**		
Normal	0	19	2	0	5.56	0.234
1	1	30	4	0		
2	4	24	6	0		
3	0	0	0	0		

† measured by Ultrasound imaging, § measured by Echocardiography. The Fisher LSD (Least Significant Difference) was used as a post hoc test. * p<0.05, ** p<0.01, *** p<0.001. Abbreviation: LV, Left Ventricular Diastolic Dysfunction; NAFLD: Non-alcoholic Fatty Liver Disease.

Discussion

In the present study, our data showed that the majority of diabetic patients with NAFLD status were females and a significant difference could be found between the two genders. We also showed that BMI can be considered a reliable prognostic value for NAFLD and T2DM co-morbidities. Regarding the lipid profile, HDL levels, but not LDL, have a negative correlation with NAFLD development in these patients. Noteworthy, serum levels of TG had a positive association with both ultrasound-confirmed and the grade of NAFLD (p-value <0.05). In addition, the results elegantly showed that there is a statistically significant link between the FBG index and the ultrasound-confirmed NAFLD, as well as hepatic steatosis grade (p-value <0.05). Meanwhile, the FBG can be considered an indicator of simultaneous diabetes and NAFLD. Finally, to determine NAFLD role on LVDD, our data demonstrated that in those with T2DM, although the prevalence of NAFLD is positively associated with BMI and FBG levels, a significant correlation with LVDD was not observed.

In line with our finding, a study conducted in Italy similarly revealed a higher prevalence in females even amongst the larger population (n=222, 36.1% vs. 14.7%, p<0.01) (17). Also, we examined diabetic patients of a wide range of age (≥ 35 years), while Moise et al. merely included the young diabetic population (15-45 years old), and reported that nonalcoholic steatosis is directly linked to the echocardiographic features of early diastolic dysfunction. To date, the co-existence of T2DM and fatty liver disease is considered a common epiphenomenon under metabolic syndromes (18, 19). Moreover, it has been well-documented that such metabolic disorders can contribute to developing structural and functional myocardial abnormalities (20), originating from the expanded and inflamed adipose tissue (lipotoxicity) (21), as well as exuberant secretion of pro-inflammatory adipokines, leading to insulin resistance (IR) (17). As a mechanistic view of the diastolic dysfunction under metabolic syndromes, the buildup of advanced glycation end-products, fibrosis, dysregulated hepatokine secretion, and even increased myocyte resting tension may result in LV diastolic stiffness (22, 23), which can subsequently derive the accumulation of free fatty acid (FFA) and lipid metabolites in the cardiomyocytes (24).

We also focused on simple steatosis due to its higher prevalence compared to severe forms. In this regard, accumulating evidence highlighted that any clinical modification can profoundly affect the cardiac parameters following non-alcoholic steatohepatitis (NASH), and advanced fibrosis to a lesser extent in simple NAFLD. Therefore, it can be inferred that liver fibrosis has the potential to modify epicardial fat thickness, structural (cardiac geometry), and functional (EF) alternation in LV, resulting in further lipotoxicity (25, 26).

However, it is yet to be determined whether NAFLD can be considered a strong independent risk factor for developing cardiomyopathy in diabetic patients or not. Under the diabetic condition, the liver may exhibit two distinct functions, including (i) a target organ for adipose tissue dysfunction, and (ii) the main source involved in cardiometabolic abnormalities. According to our results, there is no correlation between ultrasound-confirmed

hepatic steatosis and its severity with echocardiography features in patients suffering from diabetes. However, NAFLD and impaired cardiac function are considered metabolic-related pathologies, in which the hepatic steatosis in advanced levels is independently associated with subclinical myocardial remodeling or dysfunction such as EF preserved LV dysfunction, following either three-dimensional speckle-tracking echocardiography (3D-STE) or Doppler echocardiography (17, 18, 27, 28).

Sheba et al. emphasized that regardless of ventricular systolic function, NAFLD is associated with preserved EF LVDD, which can be regarded as an independent risk factor for early modification in LV diastolic function in T2DM patients (29). In this line, a recent meta-analysis elegantly revealed that in comparison with non-NAFLD patients, T2DM patients with NAFLD had a remarkably lower E/A ratio (weighted mean difference [WMD]: −0.05 (95% CI −0.08 to −0.02); p<0.01), lower e' velocity (WMD: −1.37 (95% CI −1.82 to −0.91); p<0.01), higher E/e' ratio (WMD: 2.10 (95% CI 1.72 to 2.49); p<0.01), and higher peak A velocity (WMD: 2.12 (95% CI 0.11 to 4.14); p<0.05). The conclusive result clarified that the risk of incident LVDD significantly increased in T2DM patients with NAFLD compared with patients without NAFLD (30), while we did not observe a significant association between simple steatosis and LVDD progression in this setting. After adjusting for visceral adiposity in non-cirrhotic subjects, in line with our findings, Lee et al. also claimed that LVDD was not associated with simple steatosis (31).

In the current study, the sample size was rather small because of the COVID-19 pandemic, when the rate of admission for other conditions robustly declined, particularly in the tertiary referral hospitals. Although the diagnosis of fatty liver disease was based on ultrasound imaging, the gold standard modality for diagnosis is the biopsy, which should be considered in future research direction. Given that LVDD Grade III, is most likely observed in patients with a long history of diabetes (ten years and over), therefore, the duration of diabetes should be also considered due to the potential clinical impact on LVDD severity. In addition, the results were not compared with healthy counterparts (non-diabetic group), and even diabetic patients without NAFLD, therefore, it is better to design a case-control study in further research. Finally, it is highly recommended to design a multi-center and large-scale study to achieve more reliable results.

Although our findings highlighted that diabetes can be considered a leading cause of the risk of NAFLD and LVDD, it was determined that there is an intricate association between NAFLD and LVDD progression in diabetic outpatients. The results of the current study designated that there is no correlation between NAFLD (simple steatosis defined based on nonalcoholic fatty liver disease fibrosis score, NFS) and early LVDD in T2DM patients. Nevertheless, the early diagnosis of LVDD in diabetic outpatients with NAFLD can greatly help to prevent cardiomyopathy progression in the population at risk.

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Conflict of Interests: The authors declared that they have no competing interest regarding this study.

Authors' contribution: Maryam Faramarzpour: Conceptualization, Investigation, Methodology, Formal analysis, Writing – original draft, Writing – Review & Editing. Mohammadreza Mohammad Hosseiniazar: Conceptualization, Investigation, Visualization, Validation, Methodology, Data curation, Supervision, Project administration, Writing – Original draft, Writing – Review & Editing. Laya Hooshmand Gharabagh: Conceptualization, Investigation, Methodology. Formal analysis.,Supervision, Writing – Review & Editing

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