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Assessment of Left Ventricular Diastolic Function in Nonalcoholic Fatty Liver Disease

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ABSTRACT

Background: nonalcoholic fatty liver disease (NAFLD) is a spectrum of fat-associated liver conditions that can result in end stage liver disease**.** NAFLD patients when compared to control subjects have a higher prevalence of atherosclerosis which is independent of obesity and other established risk factors. Recent studies have identified NAFLD as a risk factor for early subclinical abnormalities in myocardial metabolism as well as in cardiac structure and function. In particular, it has been shown that NAFLD is associated with left ventricular hypertrophy and impaired diastolic function.

The Objective: the aim of this study is to assess left ventricular diastolic function in NAFLD patients.

Patients and Methods: the study included thirty Egyptian NAFLD patients their age between 20 and 45 years old, and twenty healthy control subjects who were age and sex matched. Full medical history, complete physical examination and laboratory tests were done in form of ALT, AST, total cholesterol, LDL, HDL, triglyceride, hemoglobin A1C, creatinine, urea and CBC. Abdominal ultrasonography and transthoracic echocardiography also were done.

Results: NAFLD patients had higher diastolic blood pressures, increased body mass indices, ALT, AST and glycated hemoglobin A1C more than controls. Also in our study the mean of E, E/A ratio, DT, lateral E/e` and septal E/e` is significant higher in NAFLD patients than control group. The mean of lateral e` and septal e` is lower in NAFLD patients than control group.

Conclusion: patients with NAFLD had significant impairment on diastolic function in the non-diabetic and normotensive NAFLD patients compared to the controls as measured by two-dimensional echocardiography Doppler imaging in addition to tissue Doppler imaging.

Keywords: Left ventricular diastolic function, nonalcoholic fatty liver disease, echocardiography, tissue Doppler.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of fat associated liver conditions that can result in end stage liver disease and the need for liver transplantation. Simple steatosis or fatty liver occurs early in NAFLD and may progress to nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis with increased risk of hepatocellular carcinoma[1].

NAFLD patients when compared to control subjects who do not have hepatic steatosis, patients with NAFLD have a higher prevalence of atherosclerosis which are independent of obesity and other established risk factors[2].

Studies have reported that the increased age related mortality observed in patients with NAFLD is attributable to cardiovascular as well as liver related deaths[3].

More recent work has identified NAFLD as a risk factor for early subclinical abnormalities in myocardial metabolism as well as in cardiac structure and function[4].

In particular, it has been shown that NAFLD is associated with left ventricular hypertrophy and impaired diastolic function[5].

PATIENTS AND METHODS

The study included thirty Egyptian NAFLD patients diagnosed by evidence of hepatic steatosis by abdominal ultrasound and their age between 20 and 45 years old, and twenty healthy

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control group had age and sex matched the study group and had completely normal ultrasonography findings of the liver.

All patients were recruited from outpatient clinic and wards of Al-Azhar University Hospitals.

Inclusion criteria:

Nonalcoholic fatty liver disease patients diagnosed by evidence of hepatic steatosis by ultrasound their age between 20 and 45 years old.

Exclusion criteria:

Patients with hypertension, diabetes, obesity (BMI more than 30), dyslipidemic, heart failure, valvular heart disease and coronary artery disease were excluded from the study. In addition, patients with a history of alcohol intake, medications that might affect liver function tests or viral hepatitis were excluded from the study.

The nature of the study was explained to all participants & verbal consent was obtained from all participants. All our patients were subjected to full medical history & complete physical examination were done. Laboratory investigation in form of Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), lipid profile (Total cholesterol – HDL – LDL – Triglycerides), hemoglobin A1C, serum creatinine, urea and complete blood count.

Radiological investigation in form o f abdominal ultrasonography was used. Also, we used scoring system based on hepatorenal echo contrast, liver brightness and deep attenuation and vascular blurring criteria for evaluation of NAFLD. Patient with a score ≥ 2 were labeled as NAFLD and those with a score of zero were included in the control group.

In addition to transthoracic echocardiography to evaluate left ventricular diastolic function based on measuring from the apical four chamber view, pulse wave doppler recordings of the mitral inflow were obtained with the sample volume placed at the tips of the mitral valve leaflets. The following parameters were measured by pulse wave doppler: peak velocity of early (E), late (A) diastolic filling and deceleration time (DT). The ratio of early diastolic to late diastolic mitral inflow velocities was calculated (E/A).

The tissue doppler echocardiography program was set to pulse wave doppler mode. The diastolic velocities were obtained from the apical four chamber view. A 1.5 mm sample volume was placed at the lateral and septal corner of the mitral annulus and measure lateral E` and septal E`. In addition E/E' was calculated as another indicator of diastolic function.

Left atrial size measuring from the parasternal long axis view using M-Mode at end ventricular systole to measure anterior-posterior diameter. From apical four chamber view at end ventricular systole using 2D mode to measure transverse diameter and longitudinal diameter.

Statistical analysis:

All data were entered and analyzed using SBSS version 17 and Microsoft excel. Data were expressed as mean ± standard deviation (SD). Comparison between the two different groups was performed by unpaired student t-test. Comparison between categorized data was performed using logistic regression analysis, odd ratio were calculated with 95% confident interval. Probability less than 0.05 was considered significant.

RESULTS

Demographic data of the study population:

The patients included in our study were thirty Egyptian NAFLD patients [23 females (76%) and 7 males (24%)] with mean age 34.8 years ± 1.14 SD. In addition to twenty healthy matched control group [14 females (70%) and 6 males (30%)] with mean age 32.5 years ± 0.9 SD.

Clinical data of the study population:

The mean BMI in our NAFLD patients is 28.3 kg/m^2 ± 0.12 SD. While among our controls ia 25.8 kg/m^2 ± 0.19 SD.

Also in our NAFLD patient, the mean systolic blood pressure is 120.8 mmHg ± 1.5 SD and the diastolic blood pressure is 81.3 mmHg ± 1.2 SD. While among our controls, the systolic blood pressure is 120 mmHg ± 1.7 SD and the diastolic blood pressure is 73 mmHg ± 1.3 SD **(Table 1)**.

Our analysis revealed a highly statistical significant difference in the BMI and diastolic blood pressure between cases and controls with higher levels in cases than controls (P value <

0.001, < 0.001), respectively **(Table 4 and Figure 1)**.

Laboratory investigation data:

In our NAFLD patients, the mean ALT is 30.4 U/L ± 3.4 SD and the AST is 27.4 U/L ± 2.6 SD. While among the controls, the ALT is 19.5 U/L ± 1.2 SD and the AST is 18.7 U/L ± 0.8 SD. With highly statistical significant difference in ALT and AST levels between cases and controls with higher levels in cases than controls (P value 0.005, 0.004), respectively **(Figure 2).**

The mean glycated hemoglobin A1C of our NAFLD patients is 5.56 ± 0.1 SD. While among the controls is 4.8 ± 0.11 SD. With highly statistical significance difference with higher levels in cases than controls (P value < 0.001) **(Figure 3)**.

In our NAFLD patients, the mean total cholesterol is 169.9 mg/dl ± 2.5 SD, the HDL is 60.9 mg/dl ± 0.17 SD, the LDL is 77.7 mg/dl ± 3.1 SD and the triglyceride is 123.53 mg/dl ± 3.8 SD. While among the controls, the total cholesterol is 162.8 mg/dl ± 3.1 SD, the HDL is 61 mg/dl ± 0.2 SD, the LDL is 60.9 mg/dl ± 4.7 SD and the triglyceride is 98.4 mg/dl ± 4.6 SD. We also found a highly statistical significance difference between cases and controls regarding triglycerides and LDL with higher levels in cases than controls (P value < 0.001, 0.006), respectively. **(Table 5 and Figure 4)**.

Echocardiography data:

In our NAFLD patients, the mean peak velocities of early diastolic filling (E) is 81.23 cm/s ± 2.8 SD, the peak velocities of late diastolic filling (A) is 62.53 cm/s ± 2.5 SD and the E/A ratio is 1.33 ± 0.05 SD. While among our controls, the peak velocities of early diastolic filling (E) is 96.8 cm/s ± 2.4 SD, the peak velocities of late diastolic filling (A) is 62.23 cm/s ± 2.1 SD and the E/A ratio is 1.53 ± 0.04 SD. Also in our NAFLD patients, the mean deceleration time (DT) is 187.7 ms ± 8.1 SD, the lateral e` on tissue doppler imaging (TDI) is 13.7 cm/s ± 0.55 SD, lateral E/e` is 6.05 ± 0.27 SD, the septal e` on TDI is10.4 cm/s ± 0.45 SD and the septal E/e` is 8.12 ± 0.4 SD. While among our controls, the mean DT is 158.7 ms ± 3.5 SD, the lateral e` on TDI is 19.1 cm/s ± 0.29 SD, the lateral E/e` is 5.03 ± 0.13 SD, the septal e` on TDI is 14.4 cm/s ± 0.4 SD and the septal E/e` is 6.76 ± 0.24 SD.

There was a highly statistical significance difference between cases and controls in the peak velocities of early diastolic filling (E), the E/A ratio and DT with higher levels in cases than controls (P value < 0.001, 0.005, 0.002), respectively. Also we found a highly statistical significance difference in lateral e` and septal e` between cases and controls with lower levels in cases than controls (P value < 0.001, < 0.001), respectively. On the contrary, there was no a statistical significance difference regarding the peak velocities of late diastolic filling (A).

Also there was a statistical significance difference between patients and controls regarding lateral E/e` and septal E/e` with higher levels in cases than controls (P value = 0.01, 0.02), respectively. There was no a statistical significance difference between patients and controls regarding left atrium antro-posterior, longitudinal and transverse diameters **(Table 6 and Figure 5, 6, 7)**.

Also in our NAFLD patients, there was a statistical significant association between age and E/A ratio (P value = 0.04, r = 0.37), BMI had a statistical significant association with the peak velocities of early diastolic filling (E) and the peak velocities of late diastolic filling (A) (P value = 0.04, 0.03, r = 0.36, 0.38) respectively. Also diastolic blood pressure had a statistical significant association with the left atrium antro-posterior diameter (P value = 0.04, r = 0.36), ALT had a statistical significant association with E/A ratio, Lateral E/e` and left atrium transverse diameter (P value = 0.04, 0.01, 0.04, r = 0.36, 0.42, 0.36) respectively **(Table 7)**.

We found a statistical significant association between total cholesterol with DT, septal E/e`, left atrium antro-posterior diameter and left atrium transverse diameter (P value = 0.007, 0.04, 0.04, 0.01, r = 0.48, 0.36, 0.36, 0.45) respectively. Also there was statistical significant association between LDL with DT, left atrium antro-posterior diameter and left atrium transverse diameter (P value = 0.02, 0.04, 0.04, r = 0.39, 0.36, 0.36) respectively **(Table 7)**.

TABLES AND FIGURES

Table (1): Demographic and clinical data of our NAFLD patients

	Minimum	Maximum	Mean	SD
Age (yrs)	21	44	34.8	1.14
BMI (KG/m^2)	27	29	28.3	0.12
SBP (mmHg)	100	135	120.8	1.5
DBP (mmHg)	60	90	81.3	1.2

Table (2): Laboratory data of our NAFLD patients

	Minimum	Maximum	Mean	SD
ALT (U/L)	11	104	30.4	3.4
AST (U/L)	10	77	27.4	2.6
Hb A1c	4.3	6.3	5.5	0.1
T. Cholesterol (mg/dl)	134	186	169.9	2.5
HDL (mg/dl)	60	63	60.9	0.17
LDL (mg/dl)	45	99	77.7	3.1
TGs (mg/dl)	78	148	123.5	3.8
HB (gm/dl)	8.1	16	12.9	0.32
Platelets (x10^9/L)	135	418	259.9	13.2
TLC (x10^9/L)	4.3	9.6	6.6	0.28
Creatinine (mg/dl)	0.3	1.2	0.69	0.03
Urea (mg/dl)	12.8	36.4	24.7	1.03

Table (3): Echocardiographic data of our NAFLD patients

	Minimum	Maximum	Mean	SD
E (cm/s)	50	122	81.23	2.8
A (cm/s)	44	94.3	62.53	2.5
E/A	0.8	1.9	1.33	0.05
DT (ms)	125	280	187.7	8.1
Lateral è (cm/s)	8.4	20	13.7	0.55
Lateral E/è	3.6	11.4	6.05	0.27
Septal è (cm/s)	6	15.2	10.4	0.45
Septal E/è	5.3	14.3	8.12	0.4
LA APD (cm)	3.2	3.8	3.5	0.04
LA LD (cm)	4.1	5.9	4.8	0.08
LA TD (cm)	2.6	4.8	3.6	0.08

Table (4): Comparison between our NAFLD patients and controls regarding demographic and clinical data

	Patient (n=30)	Control (n=20)	P value
Age (Years)	34.8 ± 1.14	32.5 ± 0.9	0.54
Sex (M/F)	7 / 23 (24% / 76%)	6 / 14 (30% / 70%)	0.43
BMI (kg/m^2)	28.3 ± 0.12	25.8 ± 0.19	< 0.001
SBP (mmHg)	120.8 ± 1.5	120 ± 1.7	0.7
DBP (mmHg)	81.3 ± 1.2	73 ± 1.3	< 0.001

Table (5): Comparison between our NAFLD patients and controls regarding laboratory data

	Patient (n=30)	Control (n=20)	P value
ALT (IU/L)	30.4 ± 3.4	19.5 ± 1.2	0.005
AST (IU/L)	27.4 ± 2.6	18.7 ± 0.8	0.004
HbA1c	5.56 ± 0.1	4.8 ± 0.11	< 0.001
T. Cholesterol (mg/dl)	169.9 ± 2.5	162.8 ± 3.1	0.08
TGs (mg/d)	123.53 ± 3.8	98.4 ± 4.6	< 0.001
HDL (mg/dl)	60.9 ± 0.17	61 ± 0.2	0.9
LDL (mg/dl)	77.7 ± 3.1	60.9 ± 4.7	0.006
Hb (gm/dl)	12.8 ± 0.32	12.9 ± 0.27	0.7
Platelets ($x10^9$/L)	259.9 ± 13.2	280 ± 11.5	0.23
TLC ($x10^9$/L)	6.6 ± 0.28	6.5 ± 0.3	0.73
Creatinine (mg/dl)	0.69 ± 0.03	0.71 ± 0.04	0.74
Urea (mg/dl)	24.7 ± 1.03	24.6 ± 0.85	0.9

Table (6): Comparison between our NAFLD patients and controls regarding echocardiographic data

	Patient (n=30)	Control (n=20)	P value
E (cm/s)	81.23 ± 2.8	96.8 ± 2.4	< 0.001
A (cm/s)	62.53 ± 2.5	62.23 ± 2.1	0.9
E/A	1.33 ± 0.05	1.53 ± 0.04	0.005
DT (ms)	187.7 ± 8.1	158.7 ± 3.5	0.002
Septal e` (cm/s)	10.4 ± 0.45	14.4 ± 0.4	< 0.001
Lateral e` (cm/s)	13.7 ± 0.55	19.1 ± 0.29	< 0.001
Septal E/e`	8.12 ± 0.4	6.76 ± 0.24	0.01
Lateral E/e`	6.05 ± 0.27	5.03 ± 0.13	0.022
LA APD (cm)	3.5 ± 0.04	3.4 ± 0.06	0.1
LA LD (cm)	4.8 ± 0.08	4.7 ± 0.09	0.5
LA TD (cm)	3.6 ± 0.08	3.5 ± 0.06	0.19

Table (7): The correlation analysis

		E	A	E/A	DT	Septal E/e	Lateral E/e	LA APD	LA TD
Age	**r**	0.07	0.29	0.37	0.18	0.07	-0.017	0.24	-0.19
	p	0.68	0.11	0.04	0.32	0.71	0.9	0.19	0.29
BMI	**r**	0.36	0.38	-0.08	-0.18	0.24	0.2	-0.02	-0.05
	p	0.04	0.03	0.67	0.32	0.2	0.28	0.89	0.7
DBP	**r**	0.21	0.04	0.16	0.07	0.04	0.13	0.36	0.21
	p	0.29	0.8	0.38	0.6	0.82	0.49	0.04	0.25
ALT	**r**	0.017	-0.32	0.36	0.08	0.27	0.42	0.29	0.36
	p	0.9	0.08	0.04	0.67	0.14	0.01	0.11	0.04
T.Chol	**r**	0.18	0.001	-0.06	0.48	0.36	0.01	0.36	0.45
	p	0.9	0.9	0.7	0.007	0.04	0.92	0.04	0.01
LDL	**r**	0.008	-0.27	-0.032	0.39	0.19	-0.02	0.36	0.36
	p	0.98	0.8	0.8	0.02	0.31	0.9	0.04	0.04

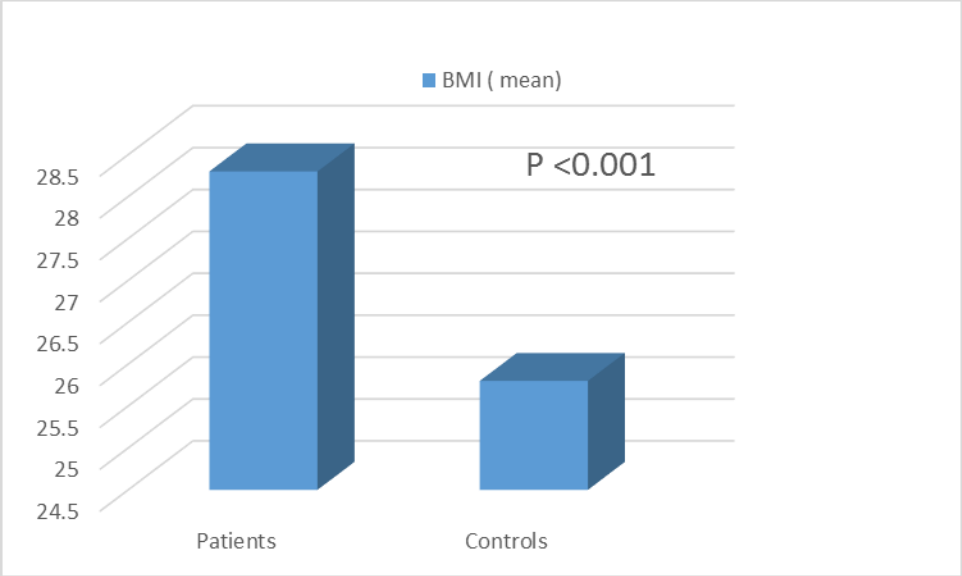

Figure (1): Comparison between NAFLD patients and controls as regard the BMI

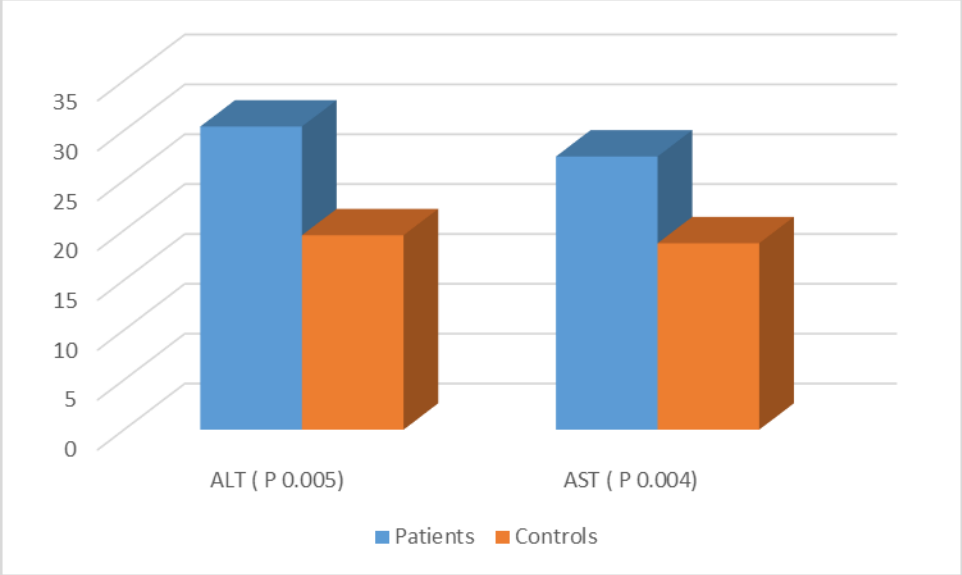

Figure (2): Comparison between NAFLD patients and controls as regard the Liver Enzymes (ALT and AST)

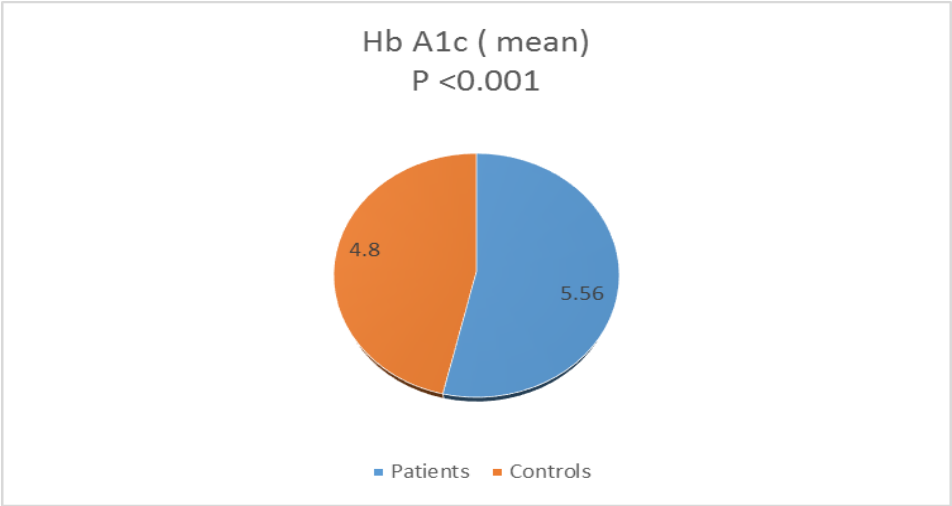

Figure (3): Comparison between NAFLD patients and controls as regard the glycated hemoglobin A1c

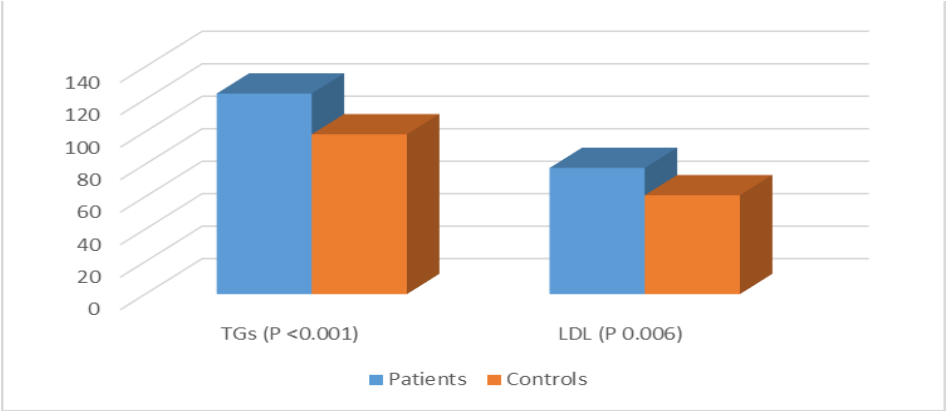

Figure (4): Comparison between NAFLD patients and controls as regard the Lipid Profile (Triglycerides and LDL)

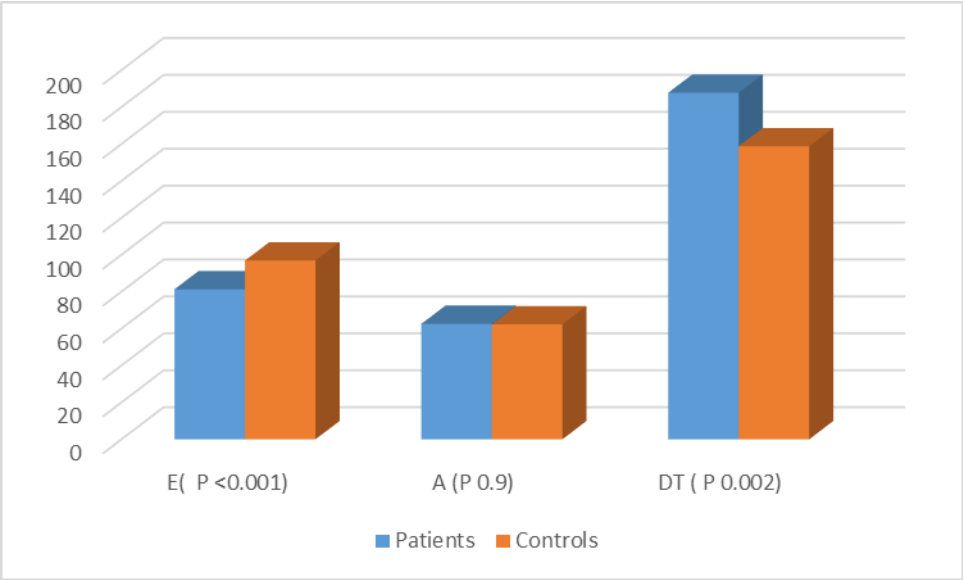

Figure (5): Comparison between NAFLD patients and controls as regard the echocardiographic data (E, A and DT)

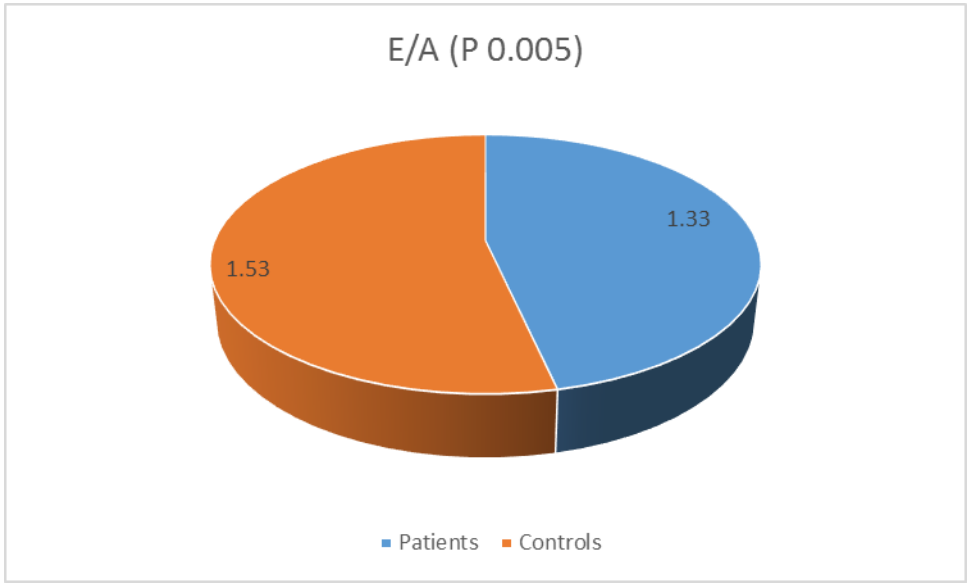

Figure (6): Comparison between NAFLD patients and controls as regard the echocardiographic data (E/A ratio)

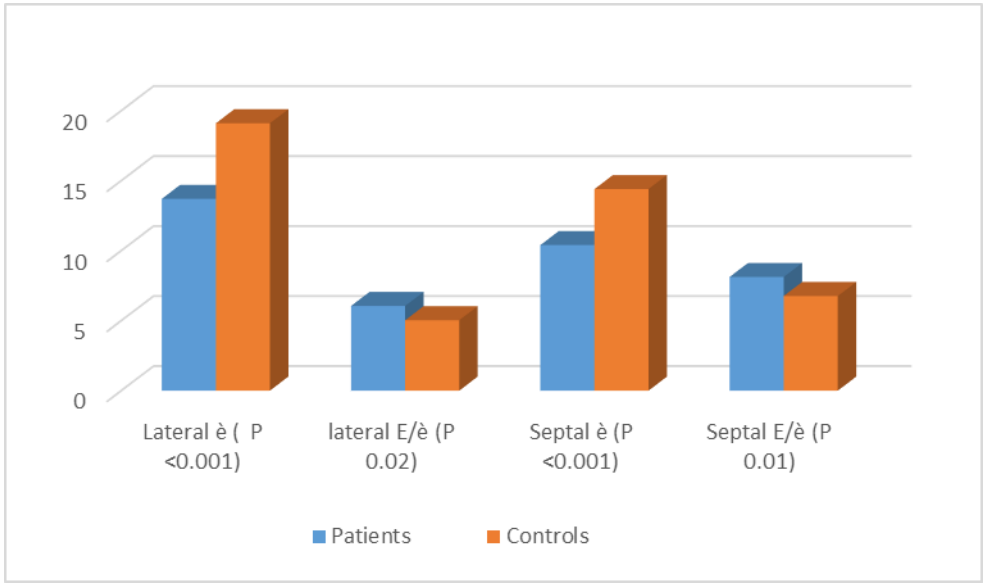

Figure (7): Comparison between NAFLD patients and controls as regard the echocardiographic data by Tissue Doppler

DISCUSSION

In the last 20 years, NAFLD has become the leading cause of chronic liver disease worldwide, primarily as a result of the epidemic of obesity [6].

NAFLD is a spectrum of fat-associated liver conditions that can result in end-stage liver disease and the need for liver transplantation[7].

Simple steatosis, or fatty liver, occurs early in NAFLD and may progress to NASH, fibrosis, and cirrhosis with increased risk of hepatocellular carcinoma [1].

NAFLD is strongly associated with obesity, insulin resistance, hypertension, and dyslipidemia and is now regarded as the liver manifestation of the metabolic syndrome, a highly atherogenic condition even at a very early age [8].

When compared to control subjects who do not have hepatic steatosis, patients with NAFLD have a higher prevalence of atherosclerosis, as shown by increased carotid wall intimal thickness, increased numbers of atherosclerotic plaques, and increased plasma markers of endothelial dysfunction, which are independent of obesity and other established risk factors.

Consistent with these observations, natural history studies have reported that the increased age-related mortality observed in patients with NAFLD is attributable to cardiovascular as well as liver-related deaths [3].

More recent work has identified NAFLD as a risk factor also for early subclinical abnormalities in myocardial metabolism as well as in cardiac structure and function [4].

In particular, it has been shown that NAFLD is associated with myocardial insulin resistance, altered cardiac energy metabolism, left ventricular hypertrophy, and impaired diastolic function [5].

Our study was done to assess left ventricular diastolic function in NAFLD patients. The study included thirty patients with NAFLD diagnosed by evidence of hepatic steatosis by abdominal ultrasound and their age between 20 to 45 years old, in addition to age and sex matched twenty healthy control subjects.

In the present study out of 30 NAFLD patients 7 were males and 23 were females which had BMI and diastolic blood pressure significant higher than control group. Which was in agreement with **Ratnasari et al., 2012** who studied Nonalcoholic Fatty Liver Disease Related to Metabolic Syndrome [9].

Raised serum activity of liver enzymes independently predicted the future development of metabolic syndrome and DM as well as cardiovascular events and/or total cardiovascular mortality. Importantly, these associations can be partly attributed to NAFLD and insulin resistance, there may be additional underlying mechanisms that contribute to the increased cardiovascular risk (e.g., inflammation and oxidative stress) [10].

In our study the mean of ALT and AST in NAFLD patients were significant higher than control group. Which is in agreement with **Pacifico *et al*.** who studied Left Ventricular Dysfunction in Obese Children and Adolescents with Nonalcoholic Fatty Liver Disease [5].

NAFLD is associated with atherogenic dyslipidaemia (an increase in LDL, TG, apolipoprotein B, and decrease in HDL) this associated with an increase in risk of CVD [10].

In our study the mean of glycated hemoglobin, triglyceride and LDL in NAFLD patients were significant higher than control group. Which is in agreement with **Azharuddin et al., 2016** who studied Nonalcoholic Fatty Liver Disease, Hyperuricemia and Carotid Intima-Medial Thickness [11].

Assessment of diastolic function begins with the transmitral flow velocity profile. Decreases in the ratio of early to late diastolic filling (E/A), increases in the deceleration time. However, in the presence of impaired relaxation, increases in filling pressure progressively modify the transmitral gradient and mitral inflow pattern [12].

In our study the mean of the peak velocities of early diastolic filling (E), E/A ratio and DT in NAFLD patients were significant higher than control group . Which is in agreement with **Fotbolcu et al., 2010** who studied Impairment of the Left Ventricular Systolic and Diastolic Function in Patients with Nonalcoholic Fatty Liver Disease [13].

The transmitral flow pattern alone cannot be used to assess relaxation in patients with HF. Measurement of the velocity of mitral annular during early diastole (e′) with tissue Doppler imaging provides a relatively preload-independent measure of LV relaxation.

Also we found a highly statistical significance difference in lateral e` and septal e` which is lower in NAFLD patients than control group. Also there was a statistical significance difference between patients and controls regarding lateral E/e` and septal E/e` which is higher in NAFLD patients than control group.. Which is in agreement with **Fotbolcu et al., 2010** who studied Impairment of the Left Ventricular

Systolic and Diastolic Function in Patients with Nonalcoholic Fatty Liver Disease [13].

On the light of the presented result of this work, we can conclude that: there was significant impairment on diastolic function in the non-diabetic and normotensive NAFLD patients compared to the controls as measured by two-dimensional echocardiography Doppler imaging in addition to tissue Doppler imaging which is more accurate and sensitive than conventional echocardiography for detecting early alterations in LV diastolic function.

We suggest that patients with NAFLD require aggressive cardiac risk factor modification and closer follow-up for the prevention of diastolic heart failure.

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