ASSESSING THE RISK OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN NON-OBESE AND OBESE NON-ALCOHOLIC FATTY LIVER DISEASE

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ABSTRACT

OBJECTIVE: To determine the risk of left ventricular diastolic dysfunction in obese and non-obese Non-Alcoholic Fatty Liver disease

MATERIALS AND METHODS: This cross-sectional study was done in Khyber Teaching Hospital and Maqsood Medical Complex Peshawar. Sample size was 384. Mandatory approval synopsis was sought from graduate committee and ASRB of Khyber Medical University Peshawar. For diagnosis Ultrasound Abdomen of both the groups (BMI<23 and >28) was done for diagnosing fatty liver. Statistical analysis was done using SPSS 23 software package. Mean and SD were applied to quantitative data. Frequency % was be applied for categorical data. Chi Square test was applied to see the association of left ventricular diastolic dysfunction in obese and non-obese NAFLD and odds ratio will be calculated by multinomial logistic regression to see the risk of LVD among both the groups with a p value less than 0.05 as significant.

RESULTS: Mean age of patients in obese and non-obese group was 46.34±12.52 and 45.43±11.83 years. In obese group minimum and maximum age of patients was 22 and 74 while in non-obese group it was 19 and 73 years. In obese group 109(56.8%) patients were males and 83(43.2%) were females while in non-obese group 101(52.6%) patients were males and 91(47.4%) were females. Mean body mass index of patients in obese and non-obese patients was 34.25±5.42 and 20.38±1.45 respectively. Severity of LVDD show significant difference between groups. The Grade-I LVDD was significantly higher in obese patients as compared to non-obese group respectively. i.e. p-value=0.036. Among non-obese patients age and gender were significant predictors of LVDD. As for gender it was OR:0.459. Among non-obese patients for gender the risk of LVDD was 0.459 times higher for female patients as compared to male patients

CONCLUSION: The left ventricular diastolic dysfunction is a common finding in NAFLD patients and routine echocardiography should be performed on time.

KEYWORDS: NAFLD, Obese, Non-Obese, Fatty Liver, Gender

INTRODUCTION

Non-Alcoholic Fatty Liver Disease is the build of fat in the liver that in the long run cause chronic liver disease.[1] It has been the prime focus of hepatologists across the world and there has been greater emphasis on screening of these patients with noninvasive modalities such as ultrasound abdomen and fibro scan, the later not readily available in our country and so not preferred.[2] It is one of the most common hepatic diseases in the west affecting 25% of the total adult population. [3]

It is the documented fact that nonalcoholic fatty liver disease is a part of metabolic syndrome along with type 2 diabetes and hypertriglyceremia, being essential risk factors for developing ischemic heart disease. [4]There has been considerable increase in cardiovascular mortality with metabolic syndrome keeping in mind the unhealthy dietary habits and life style of people who are mostly sedentary. Whether NALFD alone is a cardiovascular risk factor for patients is still controversial and under continuous debate. [5]

There is an increased risk of cardiovascular abnormality in NAFLD patients and many of them are generally ignored in our setup as far as their appropriate management is concerned. So, assessing the risk of left ventricular diastolic dysfunction will be an essential step for screening them and starting them on timely

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treatment. [6] It is linked with an enhancing chance of having cardiovascular disease having adverse effects. Studies have shown that there is dangerously enhancing risk for LVD according to the grades of disease in NAFLD patients. The management of NAFLD is rapidly changing.[7]

Traditionally drugs like metformin and statins are still being used for the treatment of NAFLD. Metformin has been used quite successfully in the treatment of NAFLD especially in diabetics as it has additional benefit of optimizing the blood sugar level with no risk of hypoglycemia. Still there needs to be extensive surveillance of renal function as there is an element of renal dysfunction in patients using metformin.[8]

Weight loss remains the cardinal step for treatment of NAFLD and according to the guidelines losing 10% of weight or more is highly recommended for the treatment [9].The drastic loss of weight has its own side effects and should be avoided .There is a consensus about the use of cholesterol lowering drugs as that can control hypercholesterolemia and reduce the risk of ischemic heart disease .In addition the risk of developing cirrhosis in such patients is quite high and that should be monitored as a priority .Nonalcoholic steatohepatitis leading to cirrhosis is of the most vital indications for liver transplant in the west where alcohol still remains of the essential culprits for end stage liver disease.[10]

The prevalence of NAFLD is increasing slowly and gradually. While obesity remains one of the most essential factors for causing the disease apart from high cholesterol levels. Interestingly thin lean individuals have NALFD during routine scans as a part of routine health checkup. There have been numerous studies about the risk of LVDD in such patients, lesser attention has been given to patients who have a low body mass index.[11]There are less researches about the impact of NAFLD on heart function in non-obese patients. That is the rationale for this research as this will be extremely useful for clinicians and patients will remind them to be vigilant and give attention to structure and function of the heart even in non-obese individuals and early intervention in this regard will be helpful to prevent myocardial dysfunction.

MATERIALS AND METHODS

This cross-sectional study was done in Khyber Teaching Hospital and Maqsood Medical Complex Peshawar. Sample size of 384 patients was calculated with 95% confidence level,5% margin of error and by taking the expected percentage of LV dysfunction in NAFLD as 54.7% in non-obese and 49.2% in obese. The sampling technique was non-probability convenient sampling. The inclusion criteria were obese and non-obese NAFLD patients on the basis of BMI. Obesity was defined as BMI ≥ 28 kg/m^2 and non-obesity was defined as BMI < 23 kg/m^2. The exclusion criteria were those who did not give consent for the study, patients of liver cirrhosis, alcoholic liver disease, autoimmune hepatitis, detected positive serum markers of hepatitis B and C and drug induced liver injury. The synopsis was presented to the graduate committee and ASRB of Khyber Medical University Peshawar followed by ethical approvals from the concerned hospitals. The rationale was explained to the participants. Obtaining an informed consent was mandatory. All the patients did have baseline liver function tests, viral serology, autoimmune screen to make sure secondary causes of deranged liver function are excluded. For diagnosis fatty liver, ultrasound abdomen of both the groups (BMI<23 and >28) was done being an essential tool for grading of the fatty liver as well. The procedure was performed by experienced radiologist by applying a probe after gel application and all antiseptic measures and getting the images. Echocardiography was performed by a nurse or a technician, which in turn was reviewed by expert cardiologists before formally giving the report to the patients which contained their detailed demographic profile in addition to comments on different essential parameters of heart. The required information and demographic variables like age, weight, gender were provided in reports of Ultrasound.

Statistical analysis was conducted using SPSS 23 software package. Mean and SD were applied to quantitative data. Frequency % was applied for categorical data. Chi Square test was used to see the association of LVD in obese and non-obese NAFLD and odds ratio was calculated to see the risk of LVD among both the groups with a p value less than 0.05 as significant

RESULTS

Table-1: Age of Patients

	Obese	Non-Obese
N	**192**	**192**
Mean	46.34	45.43
SD	12.52	11.83
Minimum	22	19
Maximum	74	73

Mean age of patients in obese and non-obese group was 46.34±12.52 and 45.43±11.83 years. In obese group minimum and maximum age of patients was 22 and 74 years while in non-obese group it was 19 and 73 years respectively. In obese group 109(56.8%) patients were males and 83(43.2%) were females while in non-obese group 101(52.6%) patients were male and 91(47.4%) were females. In obese group and non-obese group mean height of patients was 1.65±0.12 and 1.70±0.14 respectively. In obese group and non-obese group mean weight of patients was 94.31±17.51 and 58.19±7.04 Kg respectively. In obese group minimum and maximum weight of patients was 65 and 145 while in non-obese group it was 41 and 76 kg respectively.

Mean body mass index of patients in obese and non-obese patients was 34.25±5.42 and 20.38±1.45 respectively. Among obese patients minimum and maximum BMI was 28 and 57 while among non-obese it was 16.20 and 22.90 respectively. Among obese patients 61(31.8%) patients had grade-I, 84(43.8%) had grade-II and 47(24.5%) patients had grade-III fatty liver while among non-obese patients 49(25.5%) patients had grade-I, 75(39.1%) patients had grade-II and 68(35.4%) patients had grade-III fatty liver disease.

Table-2: Ventricular function among patients

	Obese	Non-Obese	Total
LVDD	130(67.7%)	129(67.2%)	**259**
Grade-I	86(44.8%)	65(33.9%)	**151**
Grade-II	35(18.2%)	43(22.4%)	**78**
Grade-III	9(4.7%)	21(10.9%)	**30**
Normal Ventricular Function	62(32.3%)	63(32.8%)	**125**
Total	**192**	**192**	**384**
Chi Square test		**8.54**	
p-value		**0.036**	

Among obese patients 130(67.7%) patients and among non-obese patients 129(67.2%) patients had LVDD. Severity of LVDD showed significant difference between groups. As it can be seen in above table that Grade-I LVDD was significantly higher in obese patients as compared to non-obese group while on other hand grade -II and grade -III were significantly higher in non-obese group as compared to obese group i.e. p-value=0.036

Table- 3: Univariate analysis of the risk of left Ventricular diastolic dysfunction among Obese & Non-Obese NAFLD patients

Among non-obese patients age and gender were significant predictors of LVDD. As for age OR: 1.062 and for gender it was OR:0.459. Among non-obese patients with 1 unit increase in age risk of LVDD

	B	SE	Wald	OR	95% CI		p-value
					Lower	Upper	
Non-Obese Patients							
Age	**0.060**	**0.015**	**16.301**	**1.062**	**1.032**	**1.094**	**<0.001**
Gender	**-0.779**	**0.314**	**6.173**	**0.459**	**0.248**	**0.848**	**0.013**
Fatty Liver							
Grade-1	**-.315**	**.404**	**.608**	**0.730**	**.331**	**1.611**	**0.436**
Grade -2	**-.372**	**.362**	**1.057**	**0.689**	**.339**	**1.401**	**0.304**
Grade -3[(ref)]	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Obese Patients							
Age	**.068**	**.015**	**21.688**	**1.071**	**1.040**	**1.102**	**<0.001**
Gender	**-.697**	**.313**	**4.960**	**0.498**	**0.270**	**0.920**	**0.026**
Fatty Liver							
Grade-1	**-1.539**	**.451**	**11.655**	**0.215**	**.089**	**.519**	**0.001**
Grade -2	**-.342**	**.448**	**.581**	**0.711**	**.295**	**1.710**	**0.446**
Grade -3[(ref)]	**-**	**-**	**-**	**-**	**-**	**-**	**-**

Increase by 1.062 times and for gender the risk of LVDD was 0.459 times higher for female patients as compared to male patients. However, among obese patients age, gender and grade-I fatty liver disease was significant predictors. Among obese patients with 1-unit increase in age the risk of LVDD increase by 1.071 times. For gender as the higher code was given for female so the risk of LVDD was 0.498 times higher as compared to male patients. Patients with grade-I fatty liver had 0.215 times more chances for LVDD.

Table-4: Prediction of Left Ventricular Diastolic Dysfunction in presence of Independent factors

Grades		B	Wald	p-value	OR	95% CI	
						Lower Bound	Upper Bound
Grade-1	**Intercept**	**-2.551**	**21.980**	**0.000**	**-**	**-**	**-**
	Age	**.054**	**22.678**	**0.000**	**1.056**	**1.033**	**1.080**
	[Obesity=0]	**-.217**	**.714**	**0.398**	**.805**	**.486**	**1.332**

	[Obesity=1]	**0**	**-**	**-**	**-**	**-**	**-**
	[Gender=1]	**.810**	**9.762**	**0.002**	**2.248**	**1.352**	**3.736**
	[Gender=2]	**0**	**-**	**-**	**-**	**-**	**-**
Grade-2	**Intercept**	**-4.038**	**35.229**	**0.000**	**-**	**-**	**-**
	Age	**.075**	**31.063**	**0.000**	**1.078**	**1.050**	**1.107**
	[Obesity=0]	**.251**	**.676**	**0.411**	**1.286**	**.706**	**2.341**
	[Obesity=1]	**0**	**-**	**-**	**-**	**-**	**-**
	[Gender=1]	**.094**	**.096**	**0.757**	**1.099**	**.605**	**1.998**
	[Gender=2]	**0**	**-**	**-**	**-**	**-**	**-**
Grade-3	**Intercept**	**-5.396**	**27.590**	**0.000**	**-**	**-**	**-**
	Age	**.063**	**11.072**	**0.001**	**1.065**	**1.026**	**1.105**
	[Obesity=0]	**.924**	**4.223**	**0.040**	**2.518**	**1.044**	**6.077**
	[Obesity=1]	**0**	**-**	**-**	**-**	**-**	**-**
	[Gender=1]	**1.075**	**5.777**	**0.016**	**2.930**	**1.219**	**7.040**
	[Gender=2]	**0**	**-**	**-**	**-**	**-**	**-**

For grade-1 LVDD Age (OR:1.056, CI: 1.03-1.08), p-value<0.001), and gender (OR:2.24, CI: 1.35-3.73), p-value=0.002) is the only significant predictor while for grade-II LVDD age (OR:1.078, CI: 1.05-1.10), p-value<0.001) was the only significant predictor and for grade-III LVDD age (OR:1.065, CI: 1.02-1.10), p-value=0.001), obesity (OR:2.518, CI: 1.04-6.07), p-value=0.004) and gender (OR:2.930, CI: 1.21-7.04), p-value=0.016) was the significant predictor.

DISCUSSIONS

The results of our study did prove a strong association between NAFLD and LVDD in obese and non-obese individuals. The presence of LVDD in non-obese patients is an eye opener for clinicians to focus more on screening such individuals with care and vigilance. This is reflected by the results seen above that grade -II and grade -III were significantly higher in non-obese group as compared to obese group i.e. p-value=0. 036.This is very important and similar to the findings by Ziyin Zhang who came to a conclusion that patients with T2DM, non-obese or lean NAFLD had no better cardio-metabolic risk profile than obese NAFLD.[12]

Wei-Chib Hung did investigate the association of NAFLD with prolonged QT interval and left ventricular hypertrophy by examining a data of 2998 workers in the steel factory .A baseline abdominal ultrasound was done to assess the severity of NAFLD followed by an Echocardiography .QT interval more than 451ms was considered prolonged and less than 431ms was taken as normal .[11]The results showed that both QT interval and left ventricular hypertrophy were significantly correlated with the corresponding grades of fibrosis with p value <0.05.The multivariate analysis that those workers had NAFLD ,the odds ratio of having prolonged QT and LVH were 2.54 with 95% CI:1.22-5.39 and a highly significant p value 0.013 . These results were very significant and stressed for regular echocardiography of NAFLD patients to evaluate the risk of cardiac arrhythmias.

NV Gohil and colleagues found a significant correlation between and cardiac abnormalities mainly LVDD on echocardiography by doing a systematic review of 13 articles which contained 9 cross sectional studies, three narrative reviews and one large meta- analysis. [13] These studies did include 13,341 patients.

The data was extracted followed by qualitative synthesis to determine the association between NAFLD and left ventricular diastolic dysfunction. As there was a significant relationship between two of them. It was recommended that NAFLD patients should be treated on time to avoid complications since they are very likely to develop cardiac dysfunction in long run. [14]

In another narrative review done by Mantovani et al which included 15 articles and 1499 patients with NAFLD, a very strong association was found between it and left ventricular diastolic dysfunction including the potential risk of developing ventricular arrhythmias. [15]In another cross-sectional study conducted by Van Wagner in which 271 patients were diagnosed by computed tomography, NAFLD was to be associated with diastolic dysfunction as shown by echocardiography findings of lower E/A ratio, ejection fraction. The limitation of this study the use of CT scan as diagnostic modality for grading the fatty liver disease keeping in mind it is less sensitive. [16]

Farouk did perform a cross sectional study on 35 patients with non-alcoholic fatty liver disease and assessed the risk of LVDD by doing an echocardiography. Significant association was seen between the disease and left ventricular diastolic dysfunction as reflected by p value of less than 0.05. The major limitation of this study was a small sample size limiting the generalizability of results. [17]

Lee et al conducted a study on 606 adults with type 2 diabetes mellitus .Out of them.355 were found to have NALFD.The NAFLD patients were further divided into subgroups, with simple steatosis and second one with advanced hepatic fibrosis on the basis of NAFLD fibrosis score .The patients with advanced fibrosis had a greater diastolic dysfunction as compared to ones with simple steatosis and liver fibrosis was independently linked with diastolic dysfunction according to multivariate logistic regression analysis. So, the above study showed that NALFD in type 2 diabetics is significant associated with left ventricular diastolic dysfunction and the association becomes more significant with increasing degree of fibrosis. [18]

Dong et al studied 97 diabetic patients and classified them into three groups. Group A didn't have any NALFD as shown by ultrasound, while group 2 and 3 had mild and severe steatosis respectively. A compared to group A and B, C had suboptimal cardiac parameters as shown by echocardiography. The major flaws of the study were a sample size and that fact there wasn't any adjustment done for confounding variables. [19]

STRENGTHS OF THE STUDY

1- Our study is first of its rare kind to have enrolled patients with NALFD having a low body weight. Many lean patients were taken for granted and this is a bitter reality even they develop ischemic heart disease as reflected by these results showing a high percentage of LVVD.[20]

2- The research is extremely useful for clinicians and patients as it will remind them to be vigilant and give attention to structure and function of the heart even in non-obese individuals and early intervention in this regard will be helpful to prevent myocardial dysfunction.

3- The thesis has a well-defined objective, which is to determine the risk of left ventricular dysfunction (LVD) in obese and non-obese Non-Alcoholic Fatty Liver Disease (NAFLD) patients.

4- Data collection procedures are thorough, including baseline assessments, diagnostic tests, and demographic profiling, ensuring the exclusion of confounding factors.

5- The use of statistical tests such as chi-square and t-test demonstrates a rigorous approach to data analysis, enhancing the validity of the study findings.

LIMITATIONS OF THE STUDY:

1- The study has many limitations. First of all, it is a cross sectional study and was therefore difficult to explore the causal relationship between NAFLD and dysfunction of the left ventricle.

2- Secondly the diagnostic investigation was ultrasound abdomen which is not a gold standard for staging of fatty liver. Tests such as fibro scan are available nowadays and can be used.

3- We did excluded patients with known ischemic heart disease with history only and further research should focus on performing coronary angiography as a gold standard diagnostic modality to rule out coronary artery disease.

4- The study involved patients from hospitals of Peshawar only and therefore the results will be difficult to be generalized.

5- Convenience sampling may introduce selection bias and limit the generalizability of the findings to the broader population.

6- While necessary for ethical reasons, exclusion criteria based on consent and willingness to participate may introduce potential bias if these factors are associated with the outcome.

7- The focus on NAFLD patients may limit the applicability of findings to other populations or liver diseases.

8- While our cross-sectional study utilizes odds ratios to assess the association between obesity and LVDD in NAFLD patients, it is important to note that these findings indicate association rather than causation. Further longitudinal studies are recommended to establish temporal relationships and to better quantify the risk.

CONCLUSION

This study found strong association of NAFLD with left ventricular diastolic dysfunction both in obese and non-obese patients. The risk for LV dysfunction does increase according to grades of fibrosis and surprising patients with decreased BMI had a high prevalence of LV dysfunction. All clinicians and general practitioner should screen the patients for left ventricular diastolic dysfunction by advising echocardiography in patients with NAFLD. More research is need to establish the risk of LVDD in non-obese NAFLD. Further studies should be done in multicenter across the country to persuade the cardiologists and physicians to screen such patents on time to reduce cardiovascular mortality and morbidity.[20] The significance of early detection of LVDD by performing echocardiography and timely treatment by cardiologist is the need of the day. Conducting longitudinal studies would enable the exploration of causal relationships and the identification of risk factors over time. Future research could employ more diverse sampling methods to ensure representation across different demographics and geographic regions. Evaluating the effectiveness of interventions targeting obesity and NAFLD in reducing the risk of LVD could inform clinical practice and public health strategies.

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