Waist circumference as a predictor for severity of liver fibrosis in non-alcoholic fatty liver disease patients

Shalini Suri[1], Shraddha Singh[1], Sushma Swaraj Rapelly[1], Sumit Rungta[2], Ehsan Ahmad[1]

[1]Department of Physiology, King George Medical University Lucknow, Uttar Pradesh, India, [2]Department of Gastromedicine, King George Medical University Lucknow, Uttar Pradesh, India

Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) may in some cases progress to increasing grades of liver fibrosis and eventually cirrhosis. NAFLD patients often succumb to cardiovascular causes. Previous studies have linked visceral fat, a known cardiovascular risk factor, to NAFLD. Visceral fat is best quantified by measuring the waist circumference (WC). This study is aimed to determine the association of waist circumference with severity of liver fibrosis in NAFLD patients. **Methods:** In this cross-sectional study we recruited 82 NAFLD patients diagnosed via ultrasonography. They underwent anthropometric examination followed by transient elastography with Fibro Scan to assess of liver stiffness measure (LSM). A cutoff LSM value of 7kPa was used to indicate significant fibrosis. Among the participants, 40 patients had an LSM value of <7 kPa (insignificant/no fibrosis), while 42 were found to have >7 kPa (significant fibrosis). Biochemical parameters of Lipid profile and Liver enzymes were also analyzed. **Statistical Analysis Used:** SPSS software with Student *t*-test, Chi-square *t*-test, ANOVA, and Spearman correlation with 95% CI is used. P <0.05 is considered significant. **Results:** Patients with significant fibrosis had higher mean weight (P < 0.001), BMI (P = 0.009), WC (P = 0.002), and waist–hip ratio (WHR, P = 0.032) compared to those with no fibrosis. However, hip circumference (HC) was not significantly associated between the two groups. In correlation studies, BMI (P = 0.001), weight (P < 0.001), WC (P = 0.001), and HC (P = 0.008) positively correlated with severity of liver fibrosis in NAFLD patients. However, no significant correlation was found with WHR. **Conclusion:** Weight, BMI, and visceral fat indicators like WC and WHR are strongly associated with liver fibrosis severity in NAFLD patients. Notably, weight, BMI, WC, and HC positively correlate with fibrosis severity, while WHR does not. Early diagnosis of fatty liver is crucial to prevent progression to life-threatening conditions like NASH or NASH cirrhosis. Waist circumference could serve as a practical screening tool in primary health care centres for identifying NAFLD patients at risk of fibrosis progression.

Keywords: Analysis of variance, body mass index, hip circumference, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, waist circumference, waist hip ratio

Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by lipid deposition in >5% hepatocytes leading to liver dysfunction without any history of significant alcohol use.[1] NAFLD if unmanaged may progress and lead to non-alcoholic steatohepatitis (NASH) with the development of liver fibrosis and further to cirrhosis or hepatocellular carcinoma.[2,3] NAFLD is reported to have a prevalence of 20–30% worldwide.[3,4] Recently as per a meta-analysis prevalence of NASH was reported to be 5.5%.[5]

Earlier studies have reported that mortality from NASH is mainly due to increasing levels of severity of liver fibrosis.[6] Currently, the

Address for correspondence: Dr. Shalini Suri, 42/14 Peerpur Square, Saketpalli, Narahi, Lucknow, Uttar Pradesh - 226 001, India. E-mail: surishalini1970@gmail.com

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gold standard for detecting NASH and liver fibrosis in NAFLD is Liver biopsy. However as liver biopsy is expensive, invasive, has a risk of complications, and requires skilled manpower, it is not feasible in outpatient clinics.[7] Current guidelines promote the use of the Fatty Liver Index (FLI), NAFLD liver fibrosis score (NFS), Fibrosis-4 Index (FIB-4), and AST/ALT ratio to predict liver steatosis and fibrosis.[7-9] Cytokeratin-18 is a recognized serum marker for detecting NASH. In an earlier study, it was reported to correlate significantly with WC and liver fibrosis in NAFLD patients.[10] However, assessment of these indices could be difficult in primary care settings where quick, simple, easy, and non-invasive markers are required to stratify risk and prevent disease progression.

NAFLD and Metabolic Syndrome (MetS) are frequently found together.[11] Among the components of MetS, NAFLD is maximally associated with Obesity and Type II DM.[12] As per an earlier study, WC was the only MetS criteria associated with liver fibrosis and in comparison to general obesity, it was the driving factor giving rise to liver fibrosis in NAFLD patients.[13] An earlier study assessing the role of anthropometry in causing NAFLD concluded that an increase in WC was the only parameter which was associated with the development of NAFLD.[14] An earlier study from Brazil on NAFLD patients undergoing Bariatric surgery concluded that WC was significantly associated with hepatic steatosis and WHR with hepatic fibrosis.[15] Another study reported that WC and WHR were strongly associated with hepatic steatosis but not with hepatic fibrosis.[16] In an earlier large-scale cohort study association of WC has been found with the development of NAFLD.[17]

WC can be easily checked in an outpatient clinic. In earlier studies, WC is associated with hepatic steatosis but it has yet not been demonstrated whether WC is also associated with the severity of liver fibrosis in NAFLD. Therefore, the present study was planned to investigate the relationship between WC with the severity of liver fibrosis in NAFLD patients.

Material and Methods

This study was carried out in the Gastroenterology Department of King George Medical University (KGMU), Lucknow, from April 2023 to March 2024. The study followed all the standard guidelines required for good medical research. Ethical approval was obtained from the Institutional Ethics Committee of KGMU, Lucknow vide ref no XIV-PGTSC-IIA/P15. Only participants who volunteered were enrolled. The procedure, purpose, benefits, and risks of the study were explained to them, and they were enrolled after providing written consent. We aimed to determine the strength of the association between waist circumference (WC) and the degree of liver fibrosis in NAFLD patients. The sample size of the study was 80, based on the prevalence of NASH being 5.5%.[5]

Patients of NAFLD diagnosed by abdominal ultrasonography in the Gastroenterology outpatient clinic were recruited in the study. Age groups from 18 to 75 years and both genders were included. Patients with a history of significant alcohol consumption, seropositivity for Hepatitis B, C, and HIV, with endocrine disorders, chronic renal diseases, established cardiovascular diseases, diabetes mellitus or hypertension of >5 years, hereditary liver disorders, active malignant neoplasms, psychiatric disorders, pregnant and lactating mothers were excluded.

Study procedure

We recruited a total of 82 subjects (58 males and 24 females) with NAFLD for the present cross-sectional study. A Fibroscan of the liver was done with FIBROSCAN mini + 430 by ECHOSENS on all these subjects on empty stomachs with an M or XL probe as appropriate. The liver stiffness measure (LSM) values were recorded after taking 10 readings using the median value in kilo Pascals (kPa). The LSM values of all subjects were recorded. We took the cut-off value of 7 kPa for the presence of significant fibrosis.[9] In our study $n = 40$ subjects had NAFLD with insignificant/no fibrosis (<7 kPa) and $n = 42$ had NAFLD with significant fibrosis (≥7 kPa).

Anthropometric measurements

Subsequently, anthropometric measurements of all subjects were carried out. We measured the height of all subjects using a stadiometer, with each subject standing erect, without shoes, and looking straight ahead. Next, we recorded the weight using an electronic weighing scale, following standard precautions. We calculated the Body Mass Index (BMI) using the formula: weight (kg)/height^2 (m^2). After that, we measured the waist circumference (WC) in centimeters using a measuring tape. This measurement was taken while the subjects were standing, after expiration, at the midpoint between the lower margin of the lowest rib and the top of the iliac crest. Hip circumference (in cm) was measured at the level where the circumference of the buttocks was maximum. The waist-to-hip ratio (WHR) was also calculated.

Biochemical measurements

Biochemical measurements of Lipid profile and Liver enzymes were carried out.

Statistical tools

Statistical analysis was done. We analyzed the data using SPSS software version 23.0. A study of the association between the severity of Liver Fibrosis in NAFLD and anthropometric parameters was carried out. Chi-square tests were used for qualitative data. For non-parametric data we used

- Mann–Whitney U test and Unpaired *t*-test were used for comparing parametric data. Subsequently, to test the strength of the relationship between the two scale parameters, Spearman's rho correlation coefficient studies were carried out. Whenever a '*P* value' of <0.05 was found it was considered statistically significant.

Observation and Results

We found the average age of NAFLD subjects to be 41 years with approximately 68.8% of them between the ages of 31 and 50 years. However, age was not found to be associated with the severity of liver fibrosis. NAFLD was found to be more prevalent in males (70.7%) than in females (29.3%). Out of the total participants, 48.8% ($n = 40$) had NAFLD with insignificant or no fibrosis (F0-F1) and 51.2% ($n = 42$) had NAFLD with significant fibrosis (≥F2). Subsequently, a comparison was made between them.

Weight ($p <$ <0.001) and BMI ($P = 0.009$) of patients with fibrosis were significantly higher compared to those without fibrosis [Table 1; Diagram 1]. Patients with fibrosis had notably higher mean WC ($P = 0.002$) and WHR [$P = 0.032$; Table 1, Diagram 2] compared to those without fibrosis. However, hip circumference was not significantly different between the two groups.

Spearman's Correlation coefficient (r) was calculated to understand the relationship between various health parameters and LSM score [Table 2]. In anthropometry, a strong positive correlation was observed in weight [p = <0.001; Diagram 3] and degree of liver fibrosis indicated by kPa value. A similar strong positive correlation was observed with BMI [$P = 0.001$; Diagram 4] and waist circumference [$P = 0.001$; Diagram 5]. A positive correlation was found between hip circumference [$P = 0.008$; Diagram 6] and an increase in Liver Stiffness Measure score/degree of fibrosis in NAFLD patients. However, no significant correlation was observed between WHR or height and degree of liver fibrosis. No significant association or correlation was found when comparing with biochemical parameters [Table 3].

Table 1: Comparison of anthropometric parameters in NAFLD patients with and without liver fibrosis

	NAFLD patients with no fibrosis		NAFLD patients with fibrosis		P
	Mean	SD	Mean	SD	
Weight (kg)	72.02	8.88	80.71	10.20	<0.001
Height (m)	1.62	0.08	1.65	0.08	0.084
BMI	27.54	3.58	29.73	3.84	0.009
Waist Circumference	99.25	7.80	105.33	9.61	0.002
Hip Circumference	102.40	8.55	105.63	9.02	0.100
Waist Hip Ratio	0.97	0.05	1.00	0.05	0.032

Table 2: Correlation study with anthropometric parameters

	Spearman's rho Correlation coefficient (*r*)	P
LSM kPA value	1	-
Age	0.055	0.622
Weight	0.390**	<0.001
Height	0.09	0.422
BMI	0.359**	0.001
Waist Circumference	0.361**	0.001
Hip Circumference	0.293**	0.008
Waist Hip Ratio	0.165	0.139

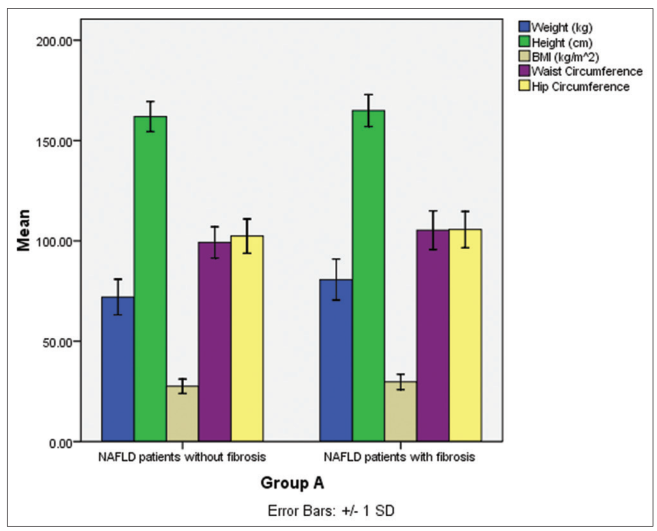

Diagram 1: Association between anthropometry in NAFLD with and without fibrosis

Discussion

NAFLD has now become a leading cause of chronic hepatic dysfunction worldwide. The likely contributors to an exponential rise in global NAFLD cases could be sedentary lifestyle, rising obesity levels, faulty diet, late eating, and late sleeping hours to name a few. The results of our study indicated that NAFLD was more commonly present in males (70.7%) than in females (29.3%) which corroborates findings in earlier studies.[18,19] This could be due to differential fat distribution in males and females. Lonardo *et al.*[19] observed that men and women store fat differently with men having more visceral adiposity and women having gluteo-femoral subcutaneous distribution of fat. Age was not found to be associated with the development of liver fibrosis.

In anthropometry, a significant association was seen in weight, BMI, WC, and WHR with the presence of fibrosis in NAFLD patients in comparison to those with no fibrosis. Out of these parameters, a strong positive correlation was also observed in weight, BMI, WC, and HC with an increase in LSM score (a measure of degree of fibrosis) in NAFLD patients. In an earlier study Unalp-Arida A *et al.*[20] observed that NAFLD liver stiffness was positively associated with BMI and liver steatosis grade. In an earlier study, Deepak Singh *et al.*[21] stated that WC, WHR, and BMI were significantly and independently associated with disease severity in patients of NASH. In another study Graupera I *et al.*[22] concluded that for the detection of advanced fibrosis cases, the parameter of WC was even better than the traditional non-invasive scores like FIB-4 and NAFLD Fibrosis Score. As per a recent study conducted in China, a strong association was found between Triglyceride Glucose index - Waist circumference and liver steatosis and fibrosis in NAFLD.[23] As per another

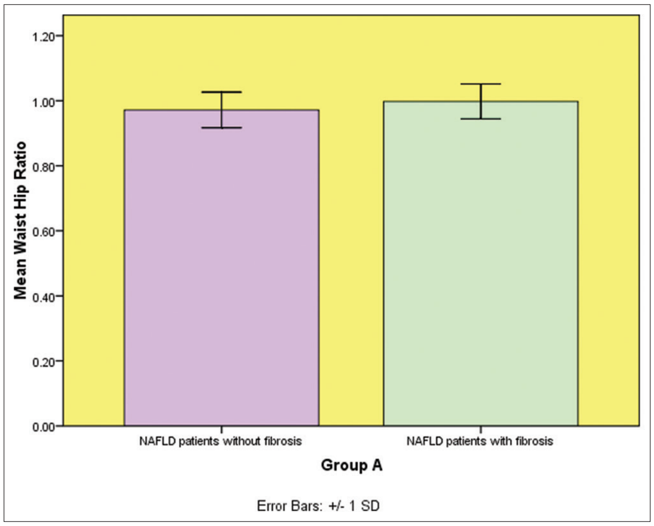

Diagram 2: Association between WHR in NAFLD patients with and without fibrosis

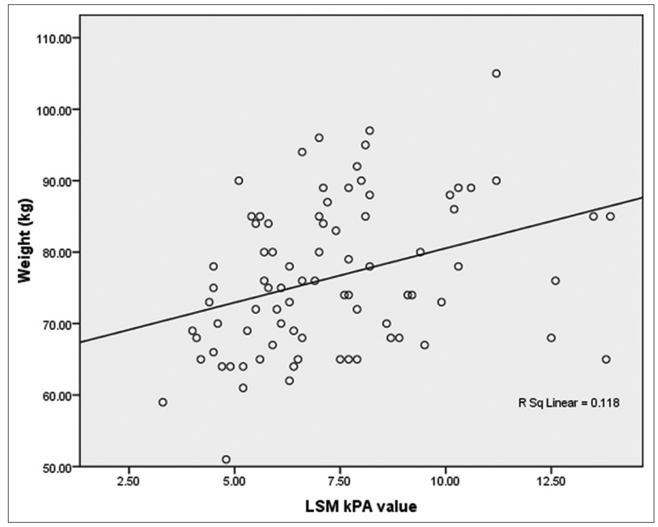

Diagram 3: Correlation between weight and LSM value

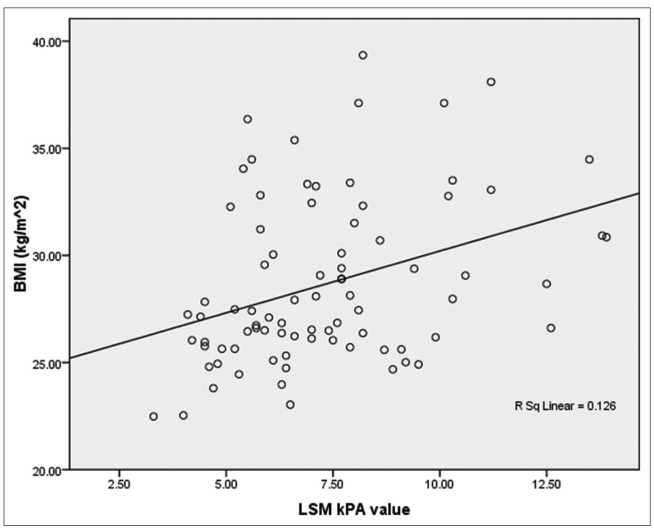

Diagram 4: Correlation between BMI and LSM value

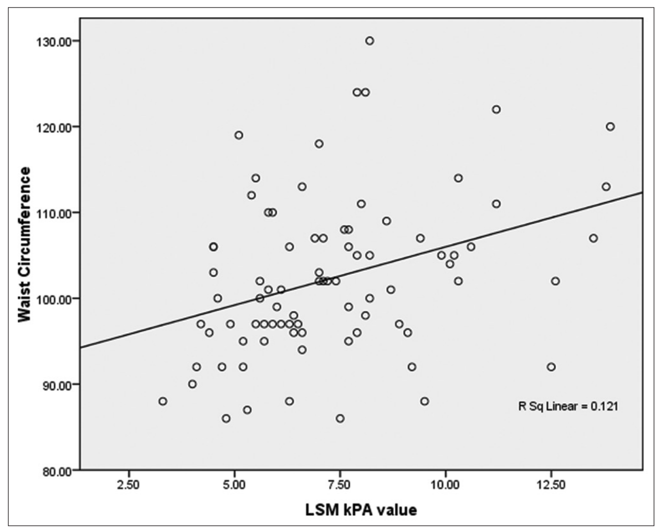

Diagram 5: Correlation between WC and LSM value

Table 3: Correlation coefficients with laboratory parameters

	Spearman's rho Correlation coefficient (*r*)	*P*
LSM kPA value	1	.
HBA1C	0.175	0.424
Serum Cholestrol	0.065	0.559
Serum Triglycerides	0.005	0.961
Serum HDL	-0.101	0.366
LDL	-0.076	0.499
VLDL	0.007	0.948
LDL/HDL ratio	0.01	0.928
SGOT	0.051	0.651
SGPT	0.026	0.817
Serum Alkaline Phosphatase	0.081	0.467

Chinese study published in 2024, different patterns of obesity were associated with the risk of NAFLD but an increase in WC in particular was associated with an increased risk of NAFLD.[24] In our study, WC was found to be strongly associated with the development of significant fibrosis and also strongly positively correlated with an increase in the severity of liver fibrosis.

This may be explained on the basis that an increase in abdominal (visceral) adiposity may lead to changes in carbohydrate and lipid metabolisms leading to the development of insulin resistance. An increase in visceral obesity generates excess free fatty acids which are directed towards the liver. This in turn could result in excessive lipid deposition in the liver. Excessive liver lipid deposition if unmanaged could lead to the development of lipotoxicity and mitochondrial dysfunction eventually leading to hepatocyte inflammation, and degeneration followed by fibrosis.

Currently, no FDA-approved drugs are available that can either prevent or treat NAFLD or NASH.[25,26] The development of

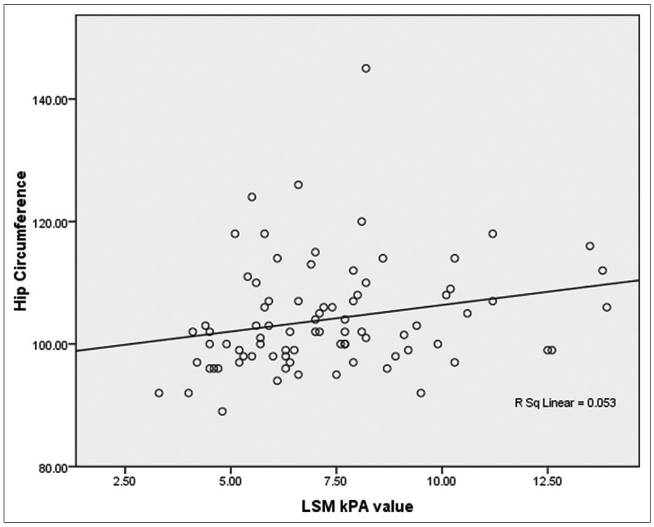

Diagram 6: Correlation between Hip Circumference and LSM value

fatty liver and its progression to significant fibrosis is usually by and large asymptomatic or has very few commonly occurring gastrointestinal symptoms. Also, it is not clear when and in whom a simple NAFL will progress to significant liver fibrosis. Estimation of liver fibrosis is either done by Liver biopsy which is invasive or by Transient Elastography which is expensive and requires skilled personnel. So, it is important to develop non-invasive, simple cost-effective screening tools that can be utilized in primary health care settings to detect NAFL patients with a risk of developing significant fibrosis. In our study higher WC was found to be correlated with higher LSM values, hence NAFLD patients at first visit with high WC would benefit from undergoing screening for liver fibrosis. Serial monitoring of waist circumference could be utilized in follow-up care of NAFLD patients. Cut-offs for the rise in WC could be developed and then used with other screening tools to predict the development of significant fibrosis. This would help in identifying patients in need of referral to higher centers for Transient Elastography.

Limitations of this study

Since we took cross-sectional data, the causal relationship could not be established. Additional studies with larger sample sizes should be undertaken to derive more meaningful results.

Conclusion

We concluded that in NAFLD patients, weight, BMI, and WC were found to be significantly associated and also positively correlated with the severity of liver fibrosis. WC is a reliable and already well-established method for quantifying visceral fat. Our study re-establishes the fact that increasing levels of visceral fat may be responsible for disease progression in NAFLD cases.

It is important to diagnose fatty liver in early stages so that the disease can be prevented from progressing to severe stages like NASH or NASH cirrhosis which are life-threatening. Waist circumference could be utilized in outpatient clinics as a follow-up screening tool along with other tools for identifying NAFLD patients at risk of developing liver fibrosis. We need to undertake further studies with a larger sample size to elucidate the role of visceral fat deposition, increased WC, and WHR in the genesis of NAFLD and its progression.

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Conflicts of interest

There are no conflicts of interest.

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