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Original Article

Radiology Section

Association of Severity of Non Alcoholic Fatty Liver Disease and Cardiometabolic Risk: A Cross-sectional Study

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ABSTRACT

Introduction: Diagnosis of Nonalcoholic Fatty Liver Disease (NAFLD) and identifying its association with Metabolic Syndrome (MS) and other Cardiovascular (CV) risk factors will aid in early intervention and prompt treatment.

Aim: To determine the association of the severity of NAFLD defined by ultrasonography with the cardiometabolic profile of patients.

Materials and Methods: A cross-sectional study was conducted in the Department of Radiology, Sri Venkateshwaraa Medical College Hospital and Research Centre, Puducherry, India. The study was conducted in six months from January to June 2021. All the 100 patients diagnosed in the hospital with NAFLD, during the study period based on history and ultrasound imaging were included. Demographic data, co-morbidities, and data on metabolic profiles were collected. Grayscale B-mode transabdominal ultrasound imaging was used. The severity of NAFLD was assessed and graded by a blinded examiner. One-way ANOVA test was used to compare the severity of NAFLD and metabolic profile. The p-value <0.05 was considered statistically significant. Data were analysed by using co-Guide software V.1.03.

Results: The mean age of the patients were 46.87 years. Majority (65%) were males. There was a statistically significant difference in Triglycerides (TG) (mg/dL) (p-value <0.001), Total Cholesterol (TC) (mg/dL) (p-value <0.001), HbA1c (p-value <0.05) and Alanine Transaminase (ALT) (p-value <0.034) among the patients across the groups graded according to severity of NAFLD.

Conclusion: An increase in metabolic parameters like TG, TC, HbA1c, and ALT were observed with the increase in the severity of NAFLD. The grading according to the severity of NAFLD will help in identifying the patients who are at increased CV risk.

Keywords: Diabetes mellitus, Metabolic syndrome, Triglycerides, Ultrasonography

INTRODUCTION

The NAFLD represents a broad spectrum of hepatic steatosis with or without inflammation and occurs in those who do not consume alcohol in amounts generally considered to be harmful to the liver and is the most common liver disease [1]. The prevalence of NAFLD appears to be around 20-30% in Western adults and 15% in Asians. NAFLD has been recognised as a common cause of abnormal liver function within the Indian population [2-4]. Studies in severely obese patients Body Mass Index (BMI >35 kg/m^2) undergoing bariatric surgery have reported prevalence's of NAFLD and Non Alcoholic Steatohepatitis (NASH) of 91% and 37%, respectively, while a postmortem study reported NASH to be present in 3% of non obese, 19% of obese and 50% of morbidly obese individuals [5,6].

The NAFLD is strongly correlated with insulin resistant states such as obesity, MS, and Type 2 Diabetes Mellitus (T2DM). One large population based study in the United States has reported that people with NAFLD were more than twice as likely to have T2DM, and NAFLD was independently associated with the presence of T2DM [7]. The long-term hepatic prognosis of patients with NAFLD depends on the histological stage of the disease at presentation. Among patients with simple steatosis 12-40% will develop NASH with early fibrosis after 8-13 years. About 7% of subjects with compensated cirrhosis associated with NAFLD will develop Hepatocellular Carcinoma (HCC) within 10 years, while 50% will require a transplant or die from a liver-related cause [8,9]. The diagnosis is based on establishing the presence of fatty liver as well as the non alcoholic nature of the disease. A liver biopsy is a gold standard, but it is invasive with associated risk. Sonography is the cheapest of all the imaging modalities and is widely available. Ultrasonographic (US) features include the presence of a bright hepatic echo pattern (compared with the kidneys), deep attenuation, vascular blurring either singly or in combination to diagnose hepatic steatosis. These features have a diagnostic sensitivity and specificity of greater than 82% [10]. The diagnosis and determination of the degree of steatosis using ultrasonography may be correlated with the metabolic profile of patients as well as the degree of CV risk. Accumulating evidence suggests that the link between these two disorders involves components of atherogenesis and inflammation and may play a role in patient outcomes and treatment [11]. Hence, we aimed to determine the association of the severity of US NAFLD with the cardiometabolic profile of patients.

MATERIALS AND METHODS

This descriptive cross-sectional study was conducted in the Department of Radiology, Sri Venkateshwaraa Medical College Hospital and Research Centre, Puducherry, India. The study was conducted for six months from January to June 2021. All the eligible 100 subjects visited during the study period were included in the study by convenient sampling. Study was approved by the Institutional Review Board and the Ethics Committee of the hospital and informed consent was obtained from each participant.

Inclusion criteria

- Male and female patients of age range 18-55 years.
- The patients diagnosed with NAFLD based on history and ultrasound imaging.

Exclusion criteria

- Patients with established liver disease or focal hepatic lesions such as hepatitis, cirrhosis, or nodules/masses.

- A history of significant alcohol consumption.
- Patients with any history of taking drugs or supplements that may influence the lipid profile and liver enzymes.

Demographic and Metabolic Profiles

Age, gender, Body Mass Index (BMI), duration of diabetes, co-morbidities like Coronary Artery Disease (CAD), diabetic neuropathy, diabetic nephropathy were collected from the patient records. Data on metabolic parameters like TG (mg/dL), TC (mg/dL), Low Density Lipoprotein (LDL) (mg/dL), High Density Lipoprotein (HDL) (mg/dL), HbA1c, ALT (U/L), Aspartate Aminotransferase (AST) (U/L) and Fasting Blood Sugar (FBS) (mg/dL) were collected from the laboratory.

Ultrasonographic (US) Grading of NAFLD

Transabdominal imaging was done using Siemens acuson X300, a curvilinear transducer with a frequency of 3 MHz. Imaging of the liver was done without compounding and tissue harmonic imaging. A blinded radiologist and one of the authors interpreted the US images of all the patients. The imaging-based grading of NAFLD was done as follows: Grade I (mild)- increased parenchymal echogenicity with visible periportal and diaphragmatic echogenicity; Grade II (moderate)- increased parenchymal echogenicity with obscuration of the echogenic walls of the portal vein branches, without obscuration of the diaphragm and Grade III (severe)- increased parenchymal echogenicity with imperceptible periportal echogenicity and obscuration of the diaphragmatic outline [11].

STATISTICAL ANALYSIS

Descriptive statistics were done for numerical parameters as mean and standard deviation and qualitative parameters as frequency and proportion. All quantitative data like metabolic and glycaemic control-related values were cross-checked for the normal distribution between the severity of NAFLD and then applied. One-way ANOVA test to compare means and provided the statistical significance for the same. The p-value <0.05 was considered statistically significant. Data were analysed by using coGuide software, V.1.03 [12].

RESULTS

A total of 100 patients were included in the final analysis. The mean age of the patients was 46.87±7.3 years, of which 28% were aged upto 20 years, 42% were aged between 25-35 years and 30% were aged 35 years and above, and 65% were males, and 35% were females. The mean BMI was 26.37 (kg/m^2). The majority of the participants (45%) had BMI within 23-24.9 kg/m^2. The mean duration of diabetes was reported to be 13 years among the participants [Table/Fig-1].

The most common co-morbidity among the study participants was hypertension reported in 55%, followed by CAD in 43%, Cardiovascular Disease (CVD) in 32%, diabetic neuropathy in 28%, and diabetic nephropathy in 22% [Table/Fig-2].

The mean of TG (mg/dL), TC (mg/dL), LDL (mg/dL), HDL (mg/dL), HbA1c (%), ALT (U/L), AST (U/L) and FBS (mg/dL) was 197.7, 141.32, 133.53, 38.84, 5.272, 32.4, 27.02 and 116.12, respectively [Table/Fig-3].

The severity of NAFLD was mild in 57 (57%), moderate in 31 (31%), and severe in 12 (12%) [Table/Fig-4].

There was statistically significant difference in TG (mg/dL) (p-value <0.001), TC (mg/dL) (p-value <0.001), HbA1c (%) (p-value <0.05) and ALT (U/L) (p-value 0.034) across the groups. There was no significant difference in LDL (mg/dL) (p-value 0.65), HDL (mg/dL) (p-value 0.92), FBS (mg/dL) (p-value 0.3) and AST (U/L) (p-value 0.05) [Table/Fig-5].

Parameters	Summary
Age (in years)	46.87±7.3 (20 to 48)
Age group (in years)	
<25	28 (28%)
25-35	42 (42%)
>35	30 (30%)
Gender	
Male	65 (65%)
Female	35 (35%)
BMI	26.37±4.57
<18.5 kg/m^2	12 (12%)
18.5-22.9 kg/m^2	31 (31%)
23.0-24.9 kg/m^2	45 (45%)
≥25 kg/m^2	12 (12%)
Duration of diabetes (in years)	13±3.7

[Table/Fig-1]: Descriptive analysis of demographic parameters in the study population (N=100).

Co-morbidities	Frequency (%)
Hypertension	55 (55%)
CAD	43 (43%)
CVD	32 (32%)
Diabetic neuropathy	28 (28%)
Diabetic nephropathy	22 (22%)

[Table/Fig-2]: Summary of co-morbidities (N=100).

Parameters	Mean±SD
Triglycerides (TG) (mg/dL)	197.7±41.01
Total cholesterol (TC) (mg/dL)	141.32±36.02
LDL (mg/dL)	133.53±39.48
HDL (mg/dL)	38.84±7.65
HbA1c	5.272±1.21
ALT (U/L)	32.4±11.9
AST (U/L)	27.02±5.27
FBS (mg/dL)	116.12±33.2

[Table/Fig-3]: Descriptive analysis of metabolic parameters, glycaemic parameters, and fasting lipid profile (N=100).

Severity of NAFLD	Frequency (%)
Mild	57 (57%)
Moderate	31 (31%)
Severe	12 (12%)

[Table/Fig-4]: Distribution of study participants as per Severity of NAFLD (N=100).

Variable	Mild NAFLD (n=57)	Moderate NAFLD (n=31)	Severe NAFLD (n=12)	p-value
Triglycerides (TG) (mg/dL)	141.32±36.02	162.46±38.81	220.72±33.89	<0.001
Total cholesterol (TC) (mg/dL)	197.7±41.01	240.15±42.29	261.85±35.48	<0.001
LDL	141.8±36.3	147.6±38.0	150.5±39.0	0.65
HDL	30.5±6.1	30.0±5.2	30.2±5.6	0.92
HbA1c	5.2±3.11	6.2±1.9	7.1±1.5	0.04
ALT (U/L)	33.09±19.38	37.39±13.91	48.33±23.10	0.034
AST (U/L)	21.18±5.99	23.89±7.12	25.4±8.1	0.05
FBS (mg/dL)	102.15±29.01	105.08±22.18	116.6±43.30	0.3

[Table/Fig-5]: Association between severity and clinical and metabolic parameters (N=100).
ANOVA test p-value

DISCUSSION

The results of the present study showed that metabolic parameters like TG, TC, HbA1c, and ALT increase with the increase in severity of NAFLD. Similar to the findings of the present study, a previous study showed a positive correlation between elevated serum TG, high BMI range, and evidence of impaired fasting glucose with NAFLD, which showed a trend towards MS [13,14]. An overproduction of triglyceride and glucose was observed in fatty liver associated with MS [15,16]. This can eventually cause hyperinsulinemia, insulin resistance, and disorders of the CV system [17]. Elevated TG level was the only factor that showed significant association with liver inflammation grade in a previous study [18]. An increase in TG level in NAFLD subjects was found to be due to the saturation of fatty acid oxidation and higher secretion of Very Low Density Lipoprotein (VLDL) [19]. In the present study, an increase in TC level was observed with an increase in severity of NAFLD, similarly the study by Cuenza LR et al., reported a significant association of TG with the severity of fatty liver on US grading [11].

An earlier study from China also showed a significant association between elevated serum HbA1c level and risk of NAFLD [20]. It has been found that NAFLD occurs in around 20% obese and 5% overweight patients and has a 2.6-fold association with diabetes. Obesity is present in the majority of individuals with NAFLD and was noted to be an independent risk factor strongly associated with the progression of the disease [13].

Continuous elevation of ALT has been used to find out the presence of NAFLD. In addition, an increase in aminotransferase was found to have a significant association with higher BMI, increase in waist circumference, elevated levels of TG and fasting insulin as well as lower levels of HDL in circulation, and occurrence of high BP and T2DM [21,22]. Elevated levels of ALT in circulation have been considered as a specific sign of liver injury because this enzyme is mainly located in the liver cytosol and has a lesser presentation in other sites. Whereas enzyme AST has both mitochondrial and cytosolic forms and is found in the skeletal muscle, liver, heart, brain, kidneys, pancreas, lungs, and white and red blood cells [23].

A recent meta-analysis has shown that CV events affect the outcome of NAFLD patients and such patients have an increased risk of both fatal and non fatal CV events compared with those without NAFLD. A further increase in the risk of CV events was observed among patients with greater severity of the liver disease [24]. Persistent inflammation and oxidative stress cause microvascular damage and impaired endothelial dysfunction which causes an increase in CV risk in NAFLD patients [25]. An increase in the prevalence of arterial rigidity and hypertension has been observed in those patients [26]. Similarly, in this study more than half (55%) of the patients had hypertension. Also, CAD was present in 43% of NAFLD patients. It has been observed that there is an increased risk of CAD in NAFLD patients compared to the general population as well as an increased risk of mortality from CV disease [27].

Limitation(s)

Firstly, the study was conducted in a single center which can affect the generalisability of results. Second, the grading of severity was not done by histological examination, which is the gold standard technique. Ultrasound was preferred as it was noninvasive compared to histopathological examination.

CONCLUSION(S)

All the metabolic parameters increase with the increase in severity of NAFLD. A significant difference was observed for TG, TC, HbA1c and ALT. Early diagnosis helps in identifying patients at high risk and prevents adverse CV events. In future a comparative cross-sectional study or a case control study can be conducted to confirm the findings of this study.

REFERENCES

[1] Spiro H. Clinical Gastroenterology. New York: McGraw-Hill; 1993. Pp. 1059-108.
[2] Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: Impact of ethnicity. Hepatology. 2004;40(6):1387-95.
[3] Nomura H, Kashiwagi S, Hayashi J, Kajiyama W, Tani S, Goto M. Prevalence of fatty liver in a general population of Okinawa, Japan. Jpn J Med. 1988;27(2):142-49.
[4] Sherif ZA, Saeed A, Ghavimi S, Nouraie SM, Laiyemo AO, Brim H, et al. Global epidemiology of nonalcoholic fatty liver disease and perspectives on US minority populations. Dig Dis Sci. 2016;61(5):1214-25.
[5] Machado M, Marques-Vidal P, Cortez-Pinto H. Hepatic histology in obese patients undergoing bariatric surgery. J Hepatol. 2006;45(4):600-06.
[6] Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: An autopsy study with analysis of risk factors. Hepatology. 1990;12(5):1106-10.
[7] Clark JM, Diehl AM, Brancati FL. Nonalcoholic fatty liver disease and the risk of type 2 diabetes in the United States. Diabetes. 2001;50:A38.
[8] Day CP. Natural history of NAFLD: Remarkably benign in the absence of cirrhosis. Gastroenterology. 2005;129(1):375-78.
[9] Sanyal AJ, Banas C, Sargeant C, Luketic VA, Sterling RK, Stravitz RT, et al. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. Hepatology. 2006;43(4):682-89.
[10] Mishra P, Younossi ZM. Abdominal ultrasound for diagnosis of nonalcoholic fatty liver disease (NAFLD). Am J Gastroenterol. 2007;102(12):2716-17.
[11] Cuenza LR, Razon TL, Dayrit J. Correlation between severity of ultrasonographic nonalcoholic fatty liver disease and cardiometabolic risk among Filipino wellness patients. J Cardiovasc Thorac Res. 2017;9(2):85-89.
[12] BDSS Corp. Released 2020. coGuide Statistics software, Version 1.0, India: BDSS corp. Available from: https://www.coguide.in. [Last accessed on 2021 Sep 28].
[13] Nseir W, Hellou E, Assy N. Role of diet and lifestyle changes in nonalcoholic fatty liver disease. World J Gastroenterol. 2014;20(28):9338-44.
[14] Gill C, Vatcheva KP, Pan JJ, Smulevitz B, McPherson DD, Fallon M, et al. Frequency of Nonalcoholic Fatty Liver Disease and Subclinical Atherosclerosis Among Young Mexican Americans. Am J Cardiol. 2017;119(11):1717-22.
[15] Jimba S, Nakagami T, Takahashi M, Wakamatsu T, Hirota Y, Iwamoto Y, et al. Prevalence of non alcoholic fatty liver disease and its association with impaired glucose metabolism in Japanese adults. Diabet Med. 2005;22(9):1141-45.
[16] Yki-Järvinen H. Non alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. Lancet Diabetes Endocrinol. 2014;2(11):901-10.
[17] Targher G, Byrne CD. Nonalcoholic fatty liver disease: A novel cardiometabolic risk factor for type 2 diabetes and its complications. J Clin Endocrinol Metab. 2013;98(2):483-95.
[18] Madan K, Batra Y, Datta Gupta S, Chander B, Anand Rajan KD, Tewatia MS, et al. Non alcoholic fatty liver disease may not be a severe disease at presentation among Asian Indians. World J Gastroenterol. 2006;12(21):3400-05.
[19] Zimmermann A, Zimmermann T, Schattenberg J, Pöttgen S, Lotz J, Rossmann H, et al. Alterations in lipid, carbohydrate and iron metabolism in patients with non alcoholic steatohepatitis (NASH) and metabolic syndrome. Eur J Intern Med. 2011;22(3):305-10.
[20] Ma H, Xu C, Xu L, Yu C, Miao M, Li Y. Independent association of HbA1c and nonalcoholic fatty liver disease in an elderly Chinese population. BMC Gastroenterol. 2013;13(1):01-06.
[21] Ioannou GN, Weiss NS, Boyko EJ, Mozaffarian D, Lee SP. Elevated serum alanine aminotransferase activity and calculated risk of coronary heart disease in the United States. Hepatology. 2006;43(5):1145-51.
[22] Clark J. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol. 2003;98(5):960-67.
[23] Giboney P. Mildly elevated liver transaminase levels in the asymptomatic patient. Am Fam Physician. 2005;71(6):1105-10.
[24] Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. J Hepatol. 2016;65(3):589-600.
[25] Pereira ENGDS, Silvares RR, Flores EEI, Rodrigues KL, Ramos IP, da Silva IJ, et al. Hepatic microvascular dysfunction and increased advanced glycation end products are components of non alcoholic fatty liver disease. PLoS One. 2017;12(6):e0179654.

[26] Steffen H, Demir M, Lang S, Schulte S, Töx U. High rate of undetected arterial hypertension in patients with non alcoholic steatohepatitis (NASH). J Hypertens. 2010;28:e557.

[27] Mahfood Haddad T, Hamdeh S, Kanmanthareddy A, Alla VM. Nonalcoholic fatty liver disease and the risk of clinical cardiovascular events: A systematic review and meta-analysis. Diabetes Metab Syndr Clin Res Rev. 2017;11:S209-16.

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