ejpmr, 2018,5(6), 386-392

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

STUDY OF NON ALCOHOLIC FATTY LIVER DISEASE & ITS ASSOCIATION WITH METABOLIC SYNDROME IN A TERTIARY CARE CENTRE OF NORTH KARNATAKA

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Article Received on 25/03/2018 **Article Revised on 15/04/2018** **Article Accepted on 05/05/2018**

ABSTRACT

Background: Non alcoholic fatty liver disease (NAFLD) is Associated with Obesity, Insulin Resistance, and type 2 diabetes. The spectrum of NAFLD ranges from simple fatty liver (hepatic steatosis), with benign prognosis, to a potentially progressive form, non alcoholic steatohepatitis (nash), which may lead to liver fibrosis and cirrhosis, resulting in increased morbidity and mortality. So these patients can be treated earlier and prevented from going into cirrhosis. **Objectives:** 1. To study the clinical profile of patients of NAFLD with varying degrees of severity as diagnosed by ultrasonography. 2. To study the correlation between the NAFLD and metabolic syndrome along with its individual components. **Methodology:** this study was done from January 2016 to June 2017.the study was an observational study of patients diagnosed as NAFLD, attending opd and indoor patients of the Department of General Medicine, Hanagal Shri Kumareshwar Hospital attached to Snmc, Bagalkot. NAFLD was diagnosed on the basis of ultrasound assessment of the liver. All patients diagnosed as NAFLD were investigated for metabolic syndrome according to the ncep atp 3 criteria and a relationship between NAFLD and metabolic syndrome was studied. **Conclusion:** our study reveals higher proportion of all the components of metabolic syndrome in cases of NAFLD. Therefore whenever these parameters are encountered in the clinical setting, patients must be evaluated for the presence of NAFLD by abdominal ultrasonography. The best way to prevent NAFLD is primary prevention; to identify and treat the risk factors.

KEYWORDS: Non alcoholic fatty liver disease, Metabolic syndrome, Tertiary care centre.

INTRODUCTION

NAFLD is a condition defined by excessive fat accumulation in the form of triglycerides (steatosis) in the liver (> 5% of hepatocytes histologically). A subgroup of NAFLD patients have liver cell injury and inflammation in addition to excessive fat (steatohepatitis). The latter condition, designated NASH, is virtually indistinguishable histologically from alcoholic steatohepatitis (ASH). The term Non alcoholic steatohepatitis (NASH) is a form of liver disease observed in middle aged patients with abnormal liver biochemical test results and histologic evidence of alcoholic hepatitis but with no history of alcohol absue.[1]While the simple steatosis seen in NAFLD does not correlate with increased short-term morbidity or mortality, progression of this condition to that of NASH dramatically increases the risks of cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[2]

This increased prevalence relates directly to the obesity epidemic seen in these populations. In the United States, NASH is thought to occur in 3% of the general population, with fibrosis due to NASH being seen in >40% of obese patients. The spectrum of NAFLD includes simple hepatic steatosis, which, over time, can progress to NASH, with the subsequent development of fibrosis and cirrhosis. It is now known that many patients with hitherto identified "cryptogenic" cirrhosis in fact have liver disease on the basis of NASH, with the resolution of the steatosis once patients become catabolic due to cirrhosis.[3]

Non-alcoholic liver disease is an important cause of liver disease in India. Epidemiological studies suggest its prevalence in around 9% to 32% of general population, but with a higher prevalence in overweight / obesity and diabetes.[4]

Most cases of NAFLD are discovered in the fourth to sixth decades of life, although NAFLD is also described, with increasing frequency, in obese children and adolescents, as well as in older adults. NAFLD may be present long before a diagnosis is established. In early clinical studies, the majority of patients with NAFLD were female; however, subsequent data have suggested that men may be affected as often as women and may be

at greater risk for advanced forms of NAFLD, including NASH. The prevalence of NAFLD appears to vary by ethnicity. In the Dallas Heart Study, Hispanics demonstrated the highest prevalence (45%) of NAFLD, compared with 33% for whites and 24% for African Americans. The reasons for racial and ethnic disparities in the prevalence of NAFLD is not known but may be related, at least in part, to racial differences in body fat distribution and the prevalence of the metabolic syndrome, which is greatest in people of Hispanic descent. Other studies have also shown that African Americans and Mexican Americans have higher frequencies of unexplained serum aminotransferase elevations than do whites. Familial clustering of NAFLD may occur, which likely reflects both genetic and environmental predisposition to the metabolic conditions associated with NAFLD.[1]

Most patients who come to medical attention with NAFLD are identified as a result of incidentally discovered elevated liver enzymes (ALT, AST). When patients are symptomatic, symptoms include fatigue or a vague right upper quadrant discomfort. ALT is generally higher than AST, and aminotransferases are only mildly (1.5–2 times the upper limit of normal) elevated. Recent studies have shown that many patients can have advanced fibrosis with NASH and even cirrhosis due to NASH with normal liver enzymes, indicating that the prevalence of the disease is likely to be even greater than was previously suspected.[5]

NASH is frequently seen in conjunction with other components of the metabolic syndrome (hypertension, diabetes mellitus, elevated lipids, and obesity), with NAFLD being considered the hepatic manifestation of this syndrome. Insulin resistance is the underlying link between these various disorders and numerous studies have shown that virtually all patients with NASH have insulin resistance. Abnormal ferritin values are seen in 50% of patients with NASH, and an elevated ferritin level may be a marker of insulin resistance in NASH.[5]

MATERIALS AND METHODS

This prospective study comprised of 65 cases diagnosed as NAFLD, and fulfilling the inclusion/exclusion criteria were included. This is a one and a half year study, done from January 2016 to June 2017 of patients attending out patient department and indoor patients of the Department of General medicine in Hanagal Shri Kumareshwara hospital and research centre, S. Nijalingappa medical college, Bagalkot.

INCLUSION CRITERIA FOR THE STUDY GROUP

1. Age: More than 18 years.
2. All patients diagnosed as NAFLD by abdominal ultrasonography.

EXCLUSION CRITERIA FOR THE STUDY GROUP

1. Age < 18 years and >85 years.
2. History of jaundice or HBs antigen positivity.
3. History of alcohol intake more than 30 grams/day in males and more than 20 grams/day in females.
4. History of following drug intake- steroids, synthetic oestrogens, heparin, calcium channel blockers, amiodarone, valproic acid, antiviral agents.

SAMPLE SIZE

Based on study done by Gaharwar R et al, consider the proportion of fatty liver as 60%. Taking 95% of confidence level & 12% of absolute precision using OPEN EPI version 2.3.1 software, the sample size is calculated to be 65.

Subjects are included in the study according to the standard criteria accepted by the American gastroenterology association i.e., An increase in hepatic echogenicity as a reference, the presence of enhancement and lack of differentiation in the periportal intensity and the vascular wall due to great hyperechogenicity in the parenchyma.

All patients will undergo ultrasound (USG) of the abdomen to detect fatty changes in the liver, performed by a experienced radiologist, using a high-resolution B-mode ultrasonography system, having an electric linear transducer mid frequency of 3–5 MHz. The scanning was done for an average of 20 minutes; Fatty liver was defined as the presence of an ultrasonographic pattern consistent with bright liver, with evident ultrasonographic contrast between hepatic and renal parenchyma, vessel blurring, and narrowing of the lumen of the hepatic veins in the absence of findings suggestive of chronic liver disease.

NAFLD was defined as any degree of fatty liver in the absence of alcohol intake.

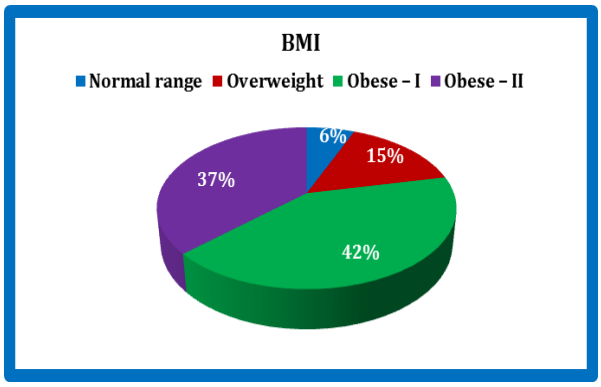
Detailed history, anthropometry and clinical examination is carried out after taking informed consent of the patient. All patients in the study underwent routine investigations including complete blood counts, blood sugar, liver function tests, HBsAg, anti HCV, and lipid profile.

RESULTS

In the present study, 38 (58.5%) were males and 27 (41.5%) were females. Majority i.e., 28 (43.1%) study subjects were in the age group of 51-60 years. The mean age was 54.14+10.11 years with a range from 32 to 78years. The mean age of males and females were 53.58+11.49 years and 54.93+7.89 years respectively. Majority (59.3%) of the subjects were males in all the age groups except for the age group 51-60 years.

Among the study subjects majority i.e. 27 (41.5%) belonged to obese class I, followed by 24 (36.9%)

belonged to obese class II, 10 (15.4%) belonged to overweight and only 4 (6.2%) belonged to normal BMI according to WHO classification for BMI. Mean weight, height and BMI of the patients with its standard deviation were 67.86±10.86Kgs, 154.34±6.25cms and 28.39±3.70Kg/m^2 respectively.



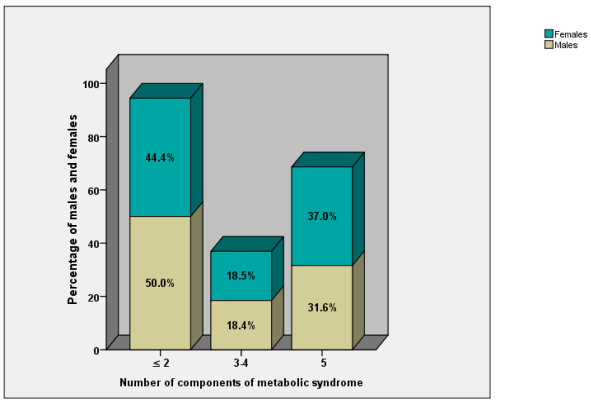
Graph 1: Distribution of study subjects according to Body mass indexWHO Asia-Pacific guideline[1]

Among the study subjects50/65, 76.9% had abnormal waist circumference among whom majority i.e., 52.0% were females; 39/65, 60.0% had raised triglyceride levels of≥150mg/dL or were on specific treatment; 52/65, 80.0% had low HDL levels and both males and females contributed equally for low HDL levels; 23/65, 35.4% had raised blood pressure of ≥ 130/85 mm of Hg or were known hypertensives and 33/65, 50.8% had fasting blood glucose of ≥100 mg/dL or were known diabetics. Mean waist circumference, triglycerides, HDL levels of the study subjects with its standard deviation were 94.68±10.42cms, 163.95±59.38 mg/dL, 35.63±7.56 mg/dL respectively. Mean systolic, diastolic and fasting blood sugar of the patients with its standard deviation were 125.57±11.22 mmHg, 83.26±7.63 mmHg and 141.02±73.75 mg/dL respectively.

Table 1: Distribution of study subjects based on the components of metabolic syndrome.

Components of Metabolic Syndrome	n (%)
Waist circumference Males ≥ 90cms Females≥ 80cms	24 (48.0) 26 (52.0)
Triglycerides ≥150mg/dL or on specific treatment	39 (60.0)
HDL Cholesterol Men < 40mg/dL Women < 50mg/dL	26 (50.0) 26 (50.0)
Blood pressure ≥ 130/85 mm of Hg (or known Hypertensives)	23 (35.4)
Fasting glucose ≥100 mg/dL (or known diabetics)	33 (50.8)

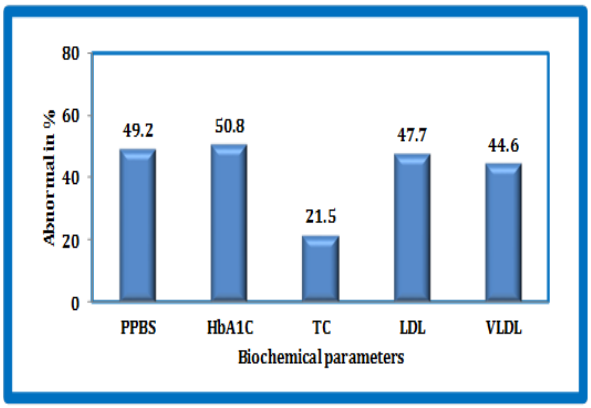
Majority i.e., 31 (47.7%) of the subjects had at least two components of Metabolic syndrome out of five, followed by 22 (33.8%) had all the five components and 12 (18.5%) had 3-4 components. Among those with 3-5 components of metabolic syndrome, majority were females.



Graph 2: Distribution of study subjects based on other Anthropometric Measurements

Mean and standard deviation of hip circumference of the study population was 101.71±6.34 cms. Median value of Waist Hip Ratio was 0.91 and it ranged from a minimum of 0.79 to 1.19. Majority of patients i.e., 39 (60.0%) had abnormal Waist Hip Ratio.

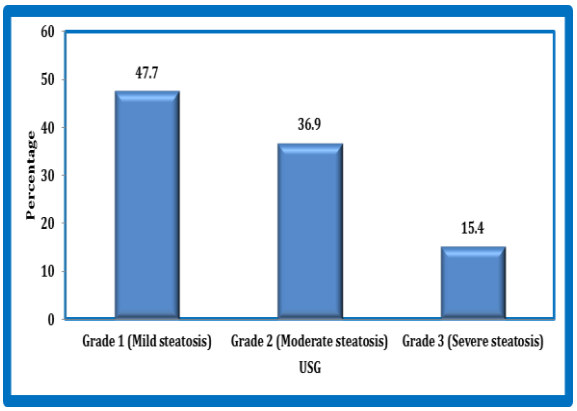
Among the study population, the proportion of study subjects with normal and abnormal PPBS and HbA1C values were nearly same. 21.5% of them had abnormal total cholesterol, 47.7% had abnormal LDL values and 44.6% had abnormal VLDL values.Means and standard deviations of PPBS, HbA1C, Total cholesterol, LDL and VLDL were 212.91±101.42mg/dL, 7.34±2.41%, 158.72±42.48mg/dL, 109.12±33.37mg/dL and 33.37±12.33mg/dL respectively.



Graph 3: Distribution of study subjects based on other biochemical parameters

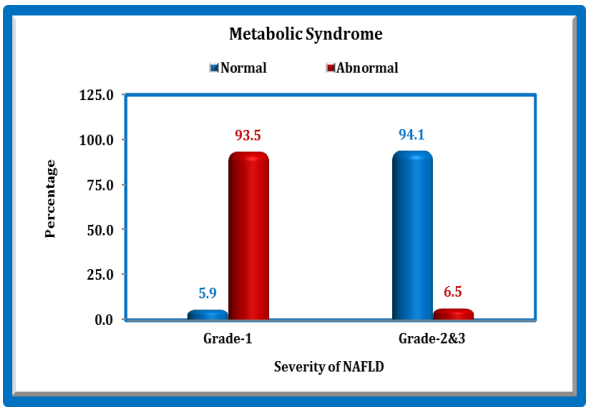
Among the study population, 13 (20.0%) of them had raised SGOT levels, 21 (32.3%) had raised SGPT levels and 26 (40.0%) had raised ALP values. Mean and standard deviation of SGOT, SGPT and ALP were

124.00±30.71 U/L, 88.00±34.43 U/L and 287.00±144.46 U/L respectively.



Graph 4: Distribution of study subjects based on the severity of NAFLD

The above table and graph represents that, most (31/65, 47.7%) of the study subjects had grade 1 (mild steatosis), followed by 24/65, 36.9% had grade 2 (moderate steatosis) and 10/65, 15.4% had grade 3 (severe steatosis).



Graph 5: Association of severity of NAFLD with Metabolic syndrome

Among the study subjects with metabolic syndrome, majority i.e., 32 (94.1%) had grade 2 and 3 NAFLD and among those with no metabolic syndrome, majority i.e., 29 (93.5%) had grade 1 NAFLD. Metabolic Syndrome was significantly associated with occurrence of NAFLD (P<0.05).

DISCUSSION

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease since its prevalence is estimated to be 20-30% in general population of Western countries. Studies introduced that NAFLD may progress to cirrhosis, liver failure, and hepatocellular carcinoma. It has been shown that NAFLD is strongly associated to the features of metabolic syndrome. Insulin resistance is a key pathogenic factor in both NAFLD and metabolic syndrome. Available data from clinical, experimental and epidemiological studies indicate that NAFLD may be the hepatic manifestation of metabolic syndrome.[6]

The metabolic syndrome is a clustering of risk factors that greatly increases an individual's probability for developing atherosclerotic cardiovascular disease (ASCVD), type 2 diabetes mellitus and chronic kidney disease. The predominant underlying risk factors appear to be abdominal obesity, atherogenic dyslipidaemia, hypertension, elevated plasma glucose, a prothrombotic state, and a proinflammatory state.[6]

Pande A and Pande V noted mean age of study participants as 53.70±7.22 years which is similar to the present study findings with the mean age of 54.14 + 10.11 years.[7] The mean age of males and females were 53.58+11.49 years and 54.93+7.89 years respectively which is comparable to study findings of Gaharwar R *et al.*, which showed mean age in males and females as 49.06 years and 49.20 years respectively.[8] Majority i.e., 28 (43.1%) of the current study subjects were in the age group of 51-60 years which are in parallel to the findings by Gupta M *et al.*, where he recorded 45-54 years age group predominated the prevalence of NAFLD.[9]

15.4% were overweight and 78.4% were obese in the present study which is nearly similar to the findings by Asati P *et al.*, wherein 25% of patients were overweight, 61% were obese.[10] Mean weight, height and BMI of the patients were 67.86±10.86 Kgs, 154.34±6.25 cms and 28.39±3.70 Kg/m^2 respectively whereas according to Schild BZ*et al.*, in his study at Brazil, the mean weight, height and BMI was 123.14 ± 25.40 kg, 1.67 ± 0.09 m was 56.24 ± 9.30 kg/ m^2. The difference may due to different study settings.[11]

60.0% had hypertriglyceridemia levels of ≥150mg/dL or were on specific treatment; 80.0% had low HDL levels and both males and females contributed equally for low HDL levels; 35.4% had raised blood pressure of ≥ 130/85 mm of Hg or were known hypertensives and 50.8% had fasting blood glucose of ≥100 mg/dL or were known diabetics and 76.9% had abnormal waist circumference. In a study by Gaharwar*et al.*, among patients of fatty liver with metabolic syndrome, 86.1% had hypertriglyceridaemia, Low serum HDL level were seen in 94.44%, 47.2% were hypertensives, 63.8% had diabetes and 77.7% had high waist circumference which are comparable to the current study findings.[8] Mean waist circumference, triglycerides, HDL levels of the study subjects with its standard deviation were, 94.68±10.42 cms, 163.95±59.38 mg/dL, 35.63±7.56 mg/dL respectively. Mean systolic, diastolic and fasting blood sugar of the patients with its standard deviation were 125.57±11.22 mmHg, 83.26±7.63 mmHg and 141.02±73.75 mg/dL respectively. Means of SBP, DBP and FBS were 130.94± 17.32 mmHg, 82.43±8.12 mmHg, 128.18±59.31mg/dl respectively and means of waist circumference, triglycerides and HDL levels were 91.90±9.16 cms, 195.29±95.72mg/dl and 39.12±5.91mg/dl respectively as noted by Asati P *et al.*,[10] which are in parallel to current study findings.

Gaharwar R*etal*., also noted that patients had increased waist circumference with mean of 86.38±9.44cms.[8]

52.3% had the complete diagnosis with ≥3 characteristic features similarly, Sharda M *et al*.,[12] noted that 65.5% of having the complete diagnosis with ≥3 characteristic features and 33% presented with complete diagnosis as stated by Marchesani G *et al*.[13]

Mean and standard deviation of hip circumference of the study population in the present study was 101.71±6.34 cms with a median Waist Hip Ratio was 0.91 ranging from 0.79 to 1.19 whereas according to the findings of BenerA*et al*., mean hip circumference was 113.58 ± 10.27 and mean waist hip ratio 0.94±0.08.[14]

In the current study, 21.5% of them had abnormal total cholesterol, 47.7% had abnormal LDL values and 44.6% had abnormal VLDL values whereas as per findings of Gaharwar R *et al*., 45.71% had hypercholesterolaemia, 34.28% had increased serum LDL levels and 25.71% had increased serum VLDL levels.[8]

According to Asati P *et al*.,the PPBS, Total cholesterol, LDL and VLDL were 193.83±94.60 mg/dL, 201.69±46.87 mg/dL, 119.66±31.11 mg/dL and 30.49±10.33mg/dL which is comparable to our study findings of means and standard deviations i.e., 212.91±101.42 mg/dL, 7.34±2.41%, 158.72±42.48 mg/dL, 109.12±33.37 mg/dL and 33.37±12.33mg/dL respectively.[10]

Mean and standard deviation of SGOT, SGPT were 124.00±30.71 IU/L, 88.00±34.43 IU/L respectively in the present study which was higher compared to the findings of Asati P *et al*., who showed means of 57.1±52.10 and 40.48±27.30 for SGOT, SGPT respectively.[10] Mean ALP levels were seen among those with NAFLD with metabolic syndrome was 287.00±144.46 IU/L similarly among those with NAFLD and DM it was reported by Gupta M *et al*., that it was 100.81±20.66 IU/L.[9]

Most of the present subjects (31/65, 47.7%) of the study subjects had grade 1 (mild steatosis), followed by 24/65, 36.9% had grade 2 (moderate steatosis) and 10/65, 15.4% had grade 3 (severe steatosis) similarly, Ajmal MR *et al*., has noted 50% of those with NAFLD had grade 1 and the rest (36/72) had grade 2 NAFLD, however there were no patients with grade 3 NAFLD wherein minimum members were recorded with grade 3 in our study.[15]Gaharwar R *et al*., recorded 47.15%, 42.85% and 10% of cases having grade I, II, and III fatty liver respectively.[8]

The means of age, height, weight, BMI, hip circumferences of the study participants among the different grades of NAFLD, were nearly same and were not significantly different in the present study (P>0.05). However the height, weight are a part of BMI. BMI has been strongly correlated with weight, but is independent of height[16] and hence increase in weight is observed with increasing grades of NAFLD and mean height was almost similar in all the grades of severity of NAFLD. The means of age were not significantly different among the grades of NAFLD as found by Yang KC *et al*.[17] Means of BMI, Waist Circumference, Triglycerides, were significantly higher with higher grade of severity of NAFLD in a study by Yang KC *et al*., which are similar to current study findings except for BMI which was not significant however the it was slightly more in grade 2 and 3 compared to grade 1.[17] Borai IH *et al*., found that WC and hip circumference were significantly higher among grade 2 and grade 3 compared to grade 1 similar to the current study findings however hip circumference though it was higher in grade 2 & 3 compared to grade 1 it lacked in the statistical significance which may be due to the difference in the ethnicity of the study subjects.[18] Mean Systolic BP, Diastolic BP were higher with mild grade compared to moderate and severe grade as found by Shim MJ *et al*., which was not in convergence with the current study findings which may be due to variations in different tool of measurement, physiological variation, observer variation and different study setting and subjects.[19] Shim MJ *et al* and Yang KC *et al*., have noted that HDL levels were significantly lower in severe grade compared to mild to moderate grades similar to current study.[17,19]

The means of PPBS, HbA1C, LDL and VLDL of the study participants were significantly higher with increasing grades of NAFLD (P<0.05). Total cholesterol levels were significantly higher in grade 2 and grade 3 compared to grade 1 NAFLD (P<0.05). Shim MJ *et al*., found that moderate to severe grade of NAFLD presented higher levels of total cholesterol than the mild NAFLD group.[19] Heidari Z *et al*., noted that patients with Grade II and Grade III NAFLD had significantly higher HbA1c and LDL in comparison with subjects with milder NAFLD.[20] Gupta M *et al*., has noted a relationship between increased PPBS with NAFLD.[9]

The medians of waist hip ratio in grade 1, 2 and 3 NAFLD were 0.88, 9.93 and 0.97 respectively. The medians of waist hip ratio were significantly higher with increasing grades of NAFLD (P<0.05). Bener A *et al*., stated higher mean waist –hip ratio among those Metabolic syndrome[14] and Agrawal R *et al*., has showed a strong relationship was found between NAFLD and metabolic syndrome and the results of other study by the same author has showed direct association of NAFLD with BMI, waist circumference and waist-hip ratio, in addition a positive association was found between grades of fatty infiltration and grades obesity signifying the positive association of NAFLD with obesity.[21, 22]

The mean SGOT, SGPT and ALP levels of the study participants were higher in grade 2 and 3 compared to grade 1. However, the differences in the means of SGOT, SGPT and ALP among different grades of

severity of NAFLD were not statistically significant ($P>0.05$). Shim MJ *et al*., found that moderate to severe grade of NAFLD presented higher levels of AST, ALT, than the mild NAFLD group.[19] The severity of the NAFLD increased, the SGOT and SGPT levels also increased, with *P* value <0.0001 showing statistical significance as reported by Kaur P *et al*.[23] The NAFLD group had significantly higher alkaline phosphatase (ALP) compared to those without NAFLD as noted by Kucukazman M *et al*., similar to our study.[24]

Agrawal R *et al*., has showed a strong relationship was found between NAFLD and metabolic syndrome similar to the current study findings.[21] Wainwright and Byrne have emphasized that NAFLD predisposes to the development of metabolic syndrome features, which can, in turn, increase the risk of development and progression of NAFLD.[25]

CONCLUSION

Our study reveals higher proportion of all components of metabolic syndrome in cases of NAFLD. Therefore whenever these parameters are encountered in clinical setting, patients must be evaluated for the presence of NAFLD by abdominal ultrasonography. Early detection would play a major role in preventive cardiology as its association with metabolic syndrome is frequent and its components are well documented cardiovascular risk factors. The present study reveals that compared to other studies, fatty liver is associated with metabolic syndrome and abnormal parameters correlated with grades of fatty liver. Fibroscan was done for the affordable patients.

A highly individualized approach for the lifestyle modifications and pharmacological therapy based on a thorough assessment of individual metabolic and nutritional status is recommended as the first line of treatment.

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