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A FOLLOW UP STUDY OF NAFLD PATIENTS TREATED WITH LIFESTYLE MODIFICATION AND DRUGS (VIT E AND ATORVASTATIN)

General Medicine

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ABSTRACT

Background: NAFLD affects more than 20% of population worldwide. There is no nation -wide registry of NAFLD in India. We studied the clinical profile of different spectrum of NAFLD patients. (NAFL, NASH, NASH related cirrhosis, NASH related carcinoma. We also did a follow up of patients with NAFL and NASH treated with lifestyle modifications and vit. E 400mg BD. This study aimed to evaluate the individual and combined performance s of TE and NAFLD fibrosis score in assessing liver fibrosis and cirrhosis. **Materials and Methods:** A prospective observational study was conducted on 88 patients radiological findings (based on USG and FIBROSCAN) suggestive of NAFLD. LSM <7 were classified as NAFL, 7-12 as NASH and LSM>13 as NASH related cirrhosis. Receiver operating characteristic (ROC) curves were obtained. Differences between the areas under the ROC curves (AUCs) were compared. **Observation:** Among observed patients,53.1% were classified as NAFL, 30.3% as NASH, 16.4% as NASH related cirrhosis. In follow up, 70.83% (p=<0.001) of NAFL patients improved in LSM (on fibroscan) whereas 64.28% (p=0.0325) of NASH patients showed improvement.. The optimal cut off values of TE for predicting advanced fibrosis was 8.7 kPa with 74.36 % sensitivity and 93.88% specificity as evidenced by ROC between LSM and NAFLD fibrosis score. **Conclusion**: A statically significant result is seen in followed patients in the form of overall improvement in biochemical and histological profiles. Hence from this study, it can concluded that the first line of treatment of NAFL and NASH should be Lifestyle change, including dietary habits and physical activity and vit. E. TE alone can be used as an important non invasive tool for the diagnosis of NAFLD, as an alternative to liver biopsy. Also it would be an accurate procedure in the follow up of these patients.

KEYWORDS

INTRODUCTION

NAFLD represents a spectrum of liver disease with stages consisting of hepatic steatosis (fatty infiltration only i.e NAFL), steatohepatitis (NASH,which is characterised by inflammation and hepatocellular injury),fibrosis and eventual cirrhosis. Normally, liver contains some fat, but if liver contains more than 5% – 10% percent of the weight then it is called a fatty liver (steatosis).

NAFLD is more common in people who have certain conditions such as obesity, type 2 diabetes, high cholesterol, hypothyroidism, hypopituitarism, sleep apnoea, PCOS (Polycystic ovary syndrome), high triglyceride levels, use of corticosteroids and many others. It can occur in all age groups including children and adults.

Epidemiological studies suugest the prevalence of NAFLD to be around 9-32% in general Indian population with a higher incidence amongst overweight/obese patients. The worldwide prevalence of NAFLD is about 25-30%. The overall prevalence of NAFLD in western countries varies from 15-40 % and in Asian countries 9-40%. Hepatosteatosis develops when the hepatic FFA availability (influx and de novo synthesis with esterification to triglycerides) is greater than FFA disposal (oxidation and secretion) when enhanced FFA influx and de novo lipogenesis overwhelms VLDL secretion and Acyl-CoA oxidation, hepatosteatosis results. In obese patients higher energy intake than energy expenditure that leads to the storage of excess energy as fat in white adipose tissue which leads to local hypoxia and death of adipocytes. All these factors lead to release of proinflammatory cytokines such as NK-κB, tumor necrosis factor α (TNF-α), IL-1β, IL- 6, IL-8 and transforming growth factor-β NAFLD has well established association with insulin resistance. There is also role of genetic factor in pathogenesis. Currently, there are no FDA-approved pharmacologic therapies for NAFL and NASH. Diet and exercise strategies targeting weight loss through an energy deficit remain the cornerstone of disease management. Diet-and exercise-induced weight loss >5% total body weight improves NAFLD and reverses hepatic necro inflammation and fibrosis. Physical activity guidelines for healthy adults—at least 150 min per week of moderate-intensity exercise or 75 min per week of vigorous intensity exercise, with resistance training twice per week on non-consecutive days. vitamin E, in high doses(800 IU/day) has shown histological improvement in the form of reduction in hepatocyte ballooning and lobular inflammation thus reflecting its expected effect as an antioxidant leading to a decrease of oxidative stress-mediated injury.

Methodology

Study Subjects:

The present study was carried out in individuals in department of General Medicine, N.S.C.B. Medical College Hospital, Jabalpur (M.P.) Participants of at least 18 years of age with known or suspected Non alcoholic fatty liver disease (NAFLD) including different spectrum of NAFLD patients [nonalcoholic fatty liver (NAFL), Nonalcoholic steatohepatitis (NASH), NASH-related cirrhosis and NASH related Hepatocellular carcinoma (HCC) were included in the study. The study was approved by institutional review boards and written informed consent was obtained from every participant prior to data collection.

Measurement of liver fat:

1. liver stiffness (ls) measurement :

Transient elastography (FibroScan) is a non-invasive ultrasound technique which is painless, and quick (5–10 min) method for measuring liver stiffness, which is positively correlated with the fibrosis degree. It is based on the principle of Hooke's lawof elasticity Liver stiffness (LS), and shows the resistance of the liver to deformation and expressed in kilopascals (kPa)**.** In this technique. an ultrasound probe emits a vibration that creates a shear wave within the liver. This speed of shear wave is proportional to the stiffness of the tissue, with faster wave progression occurring through stiffer material. LS < 5kPa is normal and excludes ongoing liver disease. LS between 8 and 12.5 kPa are the cut-off values to detect F3 and F4 fibrosis.LS >20 kPa highly correlates with development of portal pressure, and Esophageal varices. In this study, the subjects were divided into spectrum of NAFL (LSM<7kPa), NASH(LSM<7-12 kPa), and NASH related cirrhosis(LSM>13kPa).

2. NAFLD Fibrosis Score

It is a simple non-invasive scoring system using clinical and laboratory variables to find whether advanced fibrosis is present or not in NAFLD patients. This score consists of Age, hyperglycaemia, BMI, platelet count, AST/ALT ratio and albumin. It has a strong PPV (82%) and

NPV (93%) for advanced NAFLD fibrosis. NAFLD-FS received the most extensive validation and recommended for clinical use in the recent US multi society practice guideline on the diagnosis and management of NAFLD. The NAFLD fibrosis score was calculated according to the following formula:-1.675 + 0.037 * age(years) + 0.094 * BMI(kg/m^2) 1.13 * IFG/Diabetes (yes=1, No=0) + 0.99 * AST/ALT Ratio – 0.013 * Platelet(*10^9/L) – 0.66 * albumin (g/Dl)

In this study patients were categorised into 3 categories
Score <- 1.455=less probability of fibrosis
-1.455to 0.675=indeterminate
>0.675=high probability of fibrosis.

Statistical analysis:
The collected data was fed into an excel spreadsheet and then tabulated. Data was statistically analysed using t-test, chi-square test and Karl Pearson_s correlation using SPSS version 20 and Microsoft excel and p<0.05 was considered to be statistically significant.

RESULTS

A total of 88 patients of NAFLD in Department of Medicine, N.S.C.B. Medical College & Hospital , Jabalpur (M.P.) from March 2018 to Aug 2019 who were willing to take part in the study and gave a written informed consent and who satisfied the inclusion and exclusion criteria. In our study,as shown in table no. 1, out of 88 patients diagnosed as NAFLD, 48(54.5%) were classified as NAFL, 24 (27.2%) as NASH and 16 (18.3%) as NASH related cirrhosis. This is in accordance to a study performed by , Anindo Majumdar et al, in 2016 who studied Prevalence of nonalcoholic fatty liver disease in 216 adult population in a rural community of Haryana in which the prevalence of NAFLD was 30.7% (33% in men and 30% in women, *P* 0.71).

Table 1 summarises biochemical and demographic profiles have been divided according to spectrum of NAFLD i.e NAFL, NASH and NASH related cirrhosis. The mean age and BMI in NAFL group was 41.35+/-11.19(yrs) and 25.5+/- 3.1 (kg/m^2). NASH group had mean age 42.79+/- 10.1(yrs) and BMI 28.1 +/- 2.8 (kg/m^2). NASH related cirrhosis had mean age of around 46.06 +/- 14.9 years. Similarly, mean LSM score in NAFL, NASH and NASH related cirrhosis was 5.3 +/- 1 kPa, 9.8 +/-1.8, 43.2+/- 24.2 kPa respectively. Indicating the rise in values of LSM as the degree of fibrosis increases.

Table no-1 Biochemical profiles of subjects according to LSM score

PARAMETER	NAFLD CASES					
	NAFL(n=48)		NASH(24)		NASH REL CIRRHOSIS (16)	
	LSM<7		LSM 7-12		LSM>13	
Age(yrs)	41.35	11.1	42.79	10.1	46.06	14.9
BMI (kg/m2)	25.5	3.1	28.1	2.8	29.4	7.9
SGOT(U/L)	31.8	15.6	59.7	72.5	54.7	43.5
SGPT(U/L)	36.8	20.5	75.3	130.9	45.1	28.8
Total cholesterol (mg/dl)	171.2	50.6	214.8	30.8	195.3	35.3
Triglyceride(mg/dL)	160.1	73.6	226.3	244.6	158.5	90.3
Platelets(lacs/L)	3.097	1.02	2.382	0.85	0.89	0.57
HDL(mg/dL)	40.38	8.79	41.35	9.77	42.12	11.1
LDL(mg/dL)	94.43	38.5	107.62	28.38	97.11	31.2
LSM on Fibroscan(kPa)	5.3	1	9.8	1.8	43.2	24.2

Age distribution:
In this study the majority of patients are in the age group of 41-50 years i.e 38.6% followed by the in the age >50 years (22.8%). The mean age was 42.67 + 11.66 years. Most of the patients in NAFL and NASH group were in the age group 41-50 years. Whereas in NASH related cirrhosis maximum most of the patients were in age group >50 yrs.

Extent of elevation of AST and ALT in patients with NAFLD
In our study the mean AST was 43.56+44.94 in NAFLD patients and mean ALT was 48.82+/-71.91. A mild to moderate (1.5- to 4-fold) elevation of the serum AST or ALT level, or both, is common, there significantly higher levels of ALT, AST and γ-GT in patients with NAFLD, which could be a consequence of hepatic aggression resulting from the infiltration of fatty acids, bringing about inflammatory stimulus.

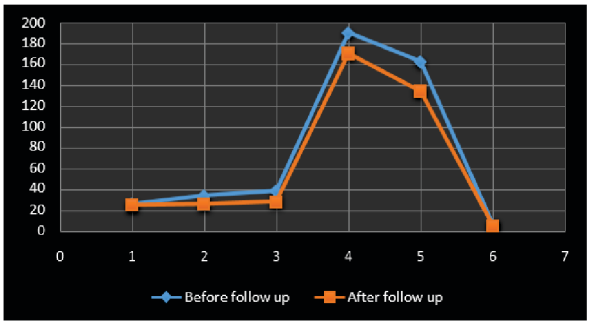
Liver Stiffness (LS) measurement by FIBROSCAN (TRANSIENT ELASTOGRAPHY):
The mean LSM in NAFL patients was found to be 5.3 +/- 1kPa , in NASH patients 9.8 +/- 1.8kPa, in NASH related cirrhosis 43.2 +/- 24.2 k Pa. There is increase in LS values as degree of fibrosis increases.

Out of 88 NAFLD patients,48 and 24 were classified as NAFL and NASH respectively. These patients were advised lifestyle modifications (dietary and exercise). The diet suggested was normocaloric ranging from 1300-1900 Kcal/day with a caloric distribution as follows: 50-65% from carbohydrates, 10-30% from fat and 12-20% from protein. patients were advised aerobic exercises for about 60 mins distributed over a duration of 1 week. Vitamin E was prescribed to only NASH patients in the dose of 400mg BD. Both group of patients were followed up after 3 months with US and Fibroscan.

Among 48 NAFL patients, 2 were lost to follow up. Table 4 and graph 1 compares various parameters in 46 followed up patients.

Table no – 2 Comparison of parameters of NAFL in followed patients (n=46)

Parameters	Before follow up	After follow up	Paired t test	P value
BMI(kg/m2)	25.42 + 3.51	24.71 + 2.56	1.962	0.061
SGOT(U/L)	33.72 + 19.65	25.72 + 5.58	2.341	0.028
SGPT(U/L)	38.03 + 21.13	28.14 + 8.91	3.358	0.003
Total Cholesterol (mg/dl)	189.84+ 54.64	170.27+ 37.30	3.404	0.002
Triglyceride (mg/dl)	162.06+ 66.30	133.9 + 40.26	3.519	0.0018
LSM on Fibroscan	5.97 + 0.56	5.04 + 0.84	5.48	<0.01



Graph no – 1 Comparison of parameters of NAFL Followed Patients (N=46)

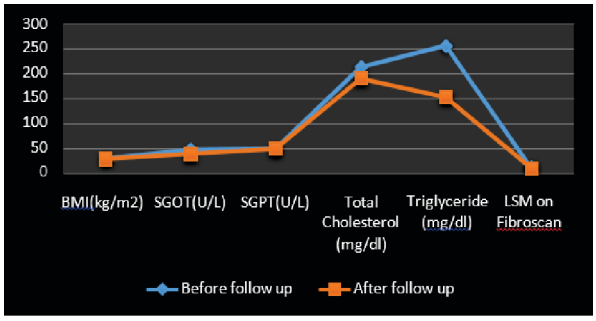
The mean BMI before and after follow up was 25.4 +/- 3.5 kg/m^2 and 24.7 +/- 2.5 kg/m^2 respectively. Mean SGOT before and after follow up was 33.7 +/-19.6 U/L and 25.7 +/- 5.5 U/L respectively. Mean SGPT before and after follow up 38.3 +/- 21.1U/L and 28.1 +/- 8.9U/L respectively. Total cholesterol before and after follow up was 189.8 +/- 54.6 mg/dl and 170.27 +/- 37.3 mg/dl respectively. Total triglycerides were 162.06 +/- 66.3 mg/dl and 133.9 +/- 40.2 mg/dl before and after follow up respectively. Liver stiffness measurement on fibroscan before and after followup was 5.95 +/- 0.56 kPa and 5.04 +/- 0.84 kPa respectively. A statically significant improvement was seen in followed patients in parameters like SGOT (p=0.028), SGPT (p=0.003), total cholesterol (p=0.002), triglycerides (p=0.0018), LSM score (p=0.001). Parameters such as BMI has shown improvement in followed up patients but was not statically significant (p=0.061).

Among 24 patients who were classified as NASH, 1 patient was lost to follow up. Table 3 and graph 2 compares various parameters in 23 followed up patients.

Table no – 3 Comparison of parameters of NASH followed patients (n=23)

Parameters	Before follow up (mean+/-SD)	After follow up (mean+/-SD)	Paired t test	P value
BMI(kg/m2)	28.5786 +/- 2.78	27.2714 +/- 2.47	3.462	0.004
SGOT(U/L)	45.9643 +/- 2.78	37.5286 +/- 15.15	2.504	0.026

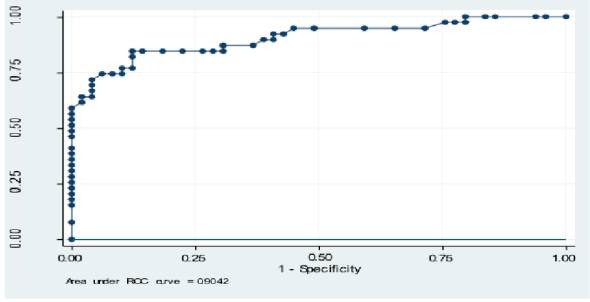
SGPT(U/L)	48.1929 +/- 24.70	47.9714 +/- 23.90	0.041	0.968
Total Cholesterol (mg/dl)	211.5714 +/- 29.07	189.3214 +/- 20.16	3.518	0.004
Triglyceride (mg/dl)	254.9571 +/- 316.55	151.8 +/- 42.44	1.209	0.248
LSM on Fibroscan	10.135 +/- 1.92	9.2 +/-2.393	2.393	0.0325



Graph no - 2 Comparison of Parameters of NASH Followed Patients (N=23)

The mean BMI before and after follow up was 28.5 +/- 2.7 kg/m^2 and 27.2 +/- 2.4 kg/m^2 respectively. Mean SGOT before and after follow up was 45.9 +/- 2.78 U/L and 37.5 +/- 15.1 U/L respectively. Mean SGPT before and after follow up 48.8 +/- 24.7U/L and 47.9 +/- 23.9U/L respectively. Total cholesterol before and after follow up was 211.5 +/- 29.7 mg/dl and 189.3 +/- 20.1 mg/dl respectively. Total triglycerides were 254.9 +/- 316.5 mg/dl and 151.8 +/- 42.4 mg/dl before and after follow up respectively. Liver stiffness measurement on fibroscan before and after followup was 10.2 +/- 1.9 kPa and 9.2+/-2.3 kPa respectively. There was statically significant improvement in BMI (p=0.004), SGOT (p=0.026) total cholesterol(p=0.004) and liver stiffness measurement in fibroscan (p=0.0325).

Parameters such as SGPT and triglycerides has shown improvement in followed up patients but was not statically significant (p=0.96 and 0.248).



Graph No – 3 Roc Between LSM on Fibroscan and NAFLD Fibrosis Score

This ROC shows that at LSM score 8.7 kPa or above fibroscan can detect fibrosis with 74.36 % sensitivity and 93.88% specificity. area under the curve is 0.90 that means in 90 % cases fibroscan correlates with NAFLD fibrosis score with positive likelihood ratio being 12.14 and negativelikelihood ratio being 0.27. Using the area under the ROC curve, 2 cut off points were selected to identify the presence (greater than 0.676) and absence (lower than −1.455) of significant fibrosis.

DISCUSSION:

NAFLD is now considered to be one of the most common forms of chronic liver disease, with a prevalence ranging from 20–30% of adults and 5–17% in children. So, early effective treatment of NAFLD is required to prevent further progression of liver disease to cirrhosis. Due to the association of this disease with overweight, the first step in the treatment has been to prevent obesity, stimulating lifestyle change through physical activity and a healthier diet. Physical exercise, even without weight loss, appears to decrease steatosis. Isolated exercise, without a calorie restriction, has not yet proven effective. In general, the studies seem to show that the decrease in weight is an important factor in reducing NAFLD markers. In this study, a total patients out of 88 patients diagnosed as NAFLD (on the basis of fibroscan, USG and NAFLD fibrosis score) were included. out of these 88 patients, 48(54.5%) were classified as NAFL, 24 (27.2%) as NASH and 16 (18.3%) as NASH related cirrhosis.

Participants were advised lifestyle modification in the form of normocaloric diet ranging from 1300-1900 Kcal/day with a caloric distribution as follows: 50-65% from carbohydrates, 10-30% from fat and 12-20% from protein. Patients were advised aerobic exercises for about 60 mins distributed over a duration of 1 week. Patients were followed up after a duration of 3 months.

Among 48 NAFL patients, 23 were lost to follow up and 25 were followed up. Out of 24 patients who were classified as NASH, 10 patients were lost to follow up and 14 were followed up.

Among 25 followed NAFL patients, a statically significant improvement was seen in followed patients in parameters like SGOT (p=0.028), SGPT (p=0.003), total cholesterol (p=0.002), triglycerides (p=0.0018), LSM score (p=0.001).Parameters such as BMI has shown improvement in followed up patients but was not statically significant (p=0.061).

NASH patients were further advised vitamin E doses 400mg BD along with lifestyle modifications. Mean liver stiffness measurement on fibroscan before and after follow up was 10.2 +/- 1.9 kPa and 9.2+/-2.3 kPa respectively. There was statically significant improvement in BMI(p=0.004),SGOT (p=0.026) total cholesterol(p=0.004) and liver stiffness measurement in fibroscan (p=0.0325) among followed patients. Thus from this study, it can be concluded that, lifestyle change with a healthier diet, gradual weight loss and increased physical activity seem to be the only effective treatment for this disease at present. Diet is characterised by reduced carbohydrate intake, especially sugars and refined carbohydrates (40% of the calories vs. 50–60% in a typical low fat diet), and increased monounsaturated and omega-3 fatty acid intake.

In order to reduce hepatic inflammation, however, at least 7-9 % of weight reduction is required, which, less than half of patients achieves this goal despite dietary counseling and exerciserecommendations. Therefore, additional therapeutic strategy should be developed for the optimal management of hepatic inflammation in NAFLD. Vitamin E significantly reduces ALT levels, LSM values and fibrosis score in NASH patients. But currently vitamin E is not indicated in NAFLD patients without histologic confirmation of inflammation. Hopefully, as seen in this study, vit E due to antioxidant effect would be prescribed to NASH patients in coming future to reduce inflammation.

In this study, we used a simple and validated non invasive scoring system composed of routinely measured and easily available clinical and laboratory variables to discriminate between the presence and absence of advanced fibrosis in patients with NAFLD. This index, which we call the ―NAFLD fibrosis score , was accurate in distinguishing the severity of fibrosis. Using values below the lower or above the higher cut off points, a prediction of absence or presence of advanced fibrosis was made 75% of the individuals. Only few were considered ―indeterminate . This implies that by applying the NAFLD fibrosis score along with fibroscan, could predict fibrosis in patients with 74.36 % sensitivity and 93.88% specificity. Area under the curve is 0.90 that means in 90 % cases fibroscan correlates with NAFLD fibrosis score with positive likelihood ratio being 12.14 and negative likelihood ratio being 0.27, implicating that liver biopsy could be avoided.

CONCLUSION:

The study has shown statistically significant improvement in weight and biochemical parameters as well in followed patients. Treatment with vitamin E has been demonstrated to be effective in reducing having hepatic steatosis and necro-inflammation. We herein have also came to the conclusion that TE positively correlated with NAFLD fibrosis score and combing both can significantly increase the PPV in predicting significant fibrosis compared to TE alone.

Limitations :

1. Liver biopsy could not be done in this study as none of the patient gave consent for the same.
2. This study relied upon self-reporting of physical activity levels

rather than using an objective measure.

3. Limitations of fibroscan such as its use in patients who have ascitis, individuals who are morbidly obese and operator experience.

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