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Study of Non-Alcoholic Fatty Liver Disease with Special Reference to Liver Enzyme and Radiological Finding

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ABSTRACT

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Background: *Non-alcoholic fatty liver disease (NAFLD) is a distinct hepatic condition characterized by abnormal fat accumulation in liver cells; histologically resembling alcohol induced liver damage. The term NAFLD is used to describe a wide array of fatty liver changes from simple steatosis to steatohepatitis, cirrhosis and hepatocellular carcinoma (HCC), in the absence, of excessive alcohol intake.* ***Methods:*** *312 suspected patients of NAFLD above the age group of 15 and irrespective of sex were screened during the study. Total 60 patients were selected according to the inclusion and exclusion criteria designed for our study. Further clinical (history, BMI, BP,etc.), biochemical (blood sugar profile, lipid profile, serum transaminases, Serum uric acid etc.), histopathological (liver biopsy) and radiological profiling (USG) was done.*

Result : *Our 60 recruited patients had a mean age of 52.53±11.68 years with 21 (35%) male subjects and 39 (65%) female subjects. We found that fatigue, malaise and abdominal pain were the commonest whereas heart burn as the second commonest complain among the study group. Further clinical examination of 26 (43.3%) patients with RUQ abdominal pain revealed that 14 (53.8%) had abdominal tenderness, 10 (38.5%) had abdominal tenderness with hepatomegaly and 2 (7.7%) had no significant clinical findings. Our study revealed mean BMI to be 27±6.32 kg/m2 with more than half of our patients were pre-obese (33.3%) and obese (28.3%). Lipid profiling revealed 13 (21.7%) patients had hypertriglyceridemia. Serum transaminases revealed 22 (36.7%) and 39 (65%) had raised SGPT/ALT and SGOT/AST levels respectively. Ultrasonographically, 30 (50%) had grade-I, 23 (38.3%) had grade-II and 7 (11.7%) had grade-III fatty liver. Due to low patient compliance, only 3 (5%) had their liver biopsy done which revealed steatosis and dense fibrosis.*

Conclusion: *Current absence of specific treatment further for NASH and NAFL emphasizes the need of healthy diet, yoga and daily exercise in order to control insulin resistance/metabolic syndrome.*

Key Words: *Non-alcoholic fatty liver disease, metabolic syndrome.*

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INTRODUCTION

The term Non-alcoholic steatohepatitis (NASH) was first introduced in 1980, Ludwig and colleagues described a cohort study of middle-aged patients with elevated serum liver enzyme, histology changes resembling alcoholic hepatitis in patient with no or insignificant alcohol intake on liver biopsy. Since then it has been realized that NASH is a part of wider group of conditions, now called as non-

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alcoholic fatty liver disease (NAFLD).[1]

NAFLD encompasses a spectrum of liver pathology with different clinical prognoses. The simple accumulation of triglyceride within hepatocytes (hepatic steatosis) is on the most clinically benign extreme of the spectrum. On the opposite, most clinically ominous extreme, are cirrhosis and primary liver cancer.[2]

Non-alcoholic steatohepatitis (NASH) is part of the spectrum of NAFLD and is defined as steatosis with hepatocellular ballooning, Mallory's hyaline with or without fibrosis plus lobular inflammation.[3] NASH itself is also a heterogeneous condition; sometimes it improves to steatosis or normal histology, sometimes it remains relatively stable for years, but sometimes it results in progressive accumulation of fibrous scar that eventuates in cirrhosis.[2] NASH can progress to cirrhosis and is associated with hepatocellular carcinoma.[4]

NAFLD affects 10 to 24% of the general population in various countries and can affect any age group. Most relevant studies have reported NAFLD to be more common in men than women and have described a later peak in prevalence in women[5], suggesting a relationship to sex hormones and menopause. NAFLD is also increasingly seen in paediatric population particularly obese children.[6]

In terms of epidemiology, several studies have tried to quantify the true worldwide incidence of NAFL/NASH; however, due to extreme variations in study parameters and available testing, a clear and reliable occurrence rate is not currently available.[7] It is no surprise that the prevalence of NAFLD is increasing worldwide with each passing year, given the current trends in dietary irresponsibility and preponderance of a sedentary lifestyle.[7] Lifestyle is an important factor, and increased consumption of high-fructose corn syrup and sugar-containing sodas, coupled with a sedentary lifestyle, has been associated with higher rates of NAFLD and specifically NASH.[8] NAFLD is strongly associated with overweight/obesity and insulin resistance. Truncal obesity is more strongly associated with NAFLD.[9] However, it can also occur in lean individuals and is particularly common in those with a paucity of adipose depots (i.e. lipodystrophy).

Additionally, there has been a linear rise of NAFLD with that of diabetes and metabolic syndrome.[10] NAFLD is considered to be the hepatic manifestation of the metabolic syndrome as defined by the presence of 3 or more of the following: abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) levels, hypertension, and an elevated fasting plasma glucose. Metabolic Syndrome particularly insulin resistance is a forerunner of NAFLD. Other metabolic abnormalities include Type 2 DM, hyperuricemia and PCOS (Polycystic ovarian syndrome).

The mechanisms underlying the pathogenesis and progression of NAFLD are not entirely clear. The best-understood mechanisms pertain to hepatic steatosis. This is proven to result when hepatocyte mechanisms for triglyceride synthesis (e.g. lipid uptake and de novo lipogenesis) overwhelm mechanisms for triglyceride disposal (e.g. degradative metabolism and lipoprotein export), leading to accumulation of fat (i.e. triglyceride) within hepatocytes. Obesity stimulates hepatocyte triglyceride accumulation by altering the intestinal microbiota to enhance both energy harvest from dietary sources and intestinal permeability. Reduced intestinal barrier function increases hepatic exposure to gut-derived products, which stimulate liver cells to generate inflammatory mediators that inhibit insulin actions. Obese adipose depots also produce excessive soluble factors (adipokines) that inhibit tissue insulin sensitivity. Insulin resistance promotes hyperglycaemia. This drives the pancreas to produce more insulin to maintain glucose homeostasis. However, hyperinsulinemia also promotes lipid uptake, fat synthesis and fat storage. The net result is hepatic triglyceride accumulation (i.e., steatosis).

The study was mainly aimed to study the prevalence of NAFLD in mixed population of Bihar with varying food habits, for identification of risk factors and/or other comorbidities which are directly or indirectly responsible for causation of fatty liver disease as well as to raise awareness among general population regarding avoidance of sedentary lifestyle and benefits of healthy diet, yoga and exercise in prevention of insulin resistance /metabolic syndrome.

METHODS

The study was conducted in Katihar Medical College and Hospital from December 2015 till May 2017. 312 suspected patients of NAFLD above the age group of 15 and irrespective of sex were screened during the study. Total 60 patients were picked from medicine outdoor and indoor departments of Katihar Medical College. They were selected according to the inclusion and exclusion criteria designed for our study.

Inclusion Criteria includes

1. All cases suspected to be having NAFLD from symptomatic point of view.
2. All the consecutive cases of increased liver enzymes in medicine clinical outdoor and indoor departments of the hospital
3. All the consecutive cases of fatty liver noticed in ultrasonography in the radiology department without any significant history of alcohol intake.
4. Patients not taking alcohol.
5. Obese patients (particularly central obesity) with or without diabetes.
6. Type 2 DM
7. Presence of insulin resistance/metabolic syndrome.
8. Patients with dyslipidemia.
9. Patients of malnutrition with fatty liver.

Exclusion Criteria includes

1. Pregnant women with fatty liver.
2. Patients of alcoholic hepatitis/alcoholic steatohepatitis.
3. Patients suffering from viral hepatitis (Hepatitis B or C)

History and Clinical Examination the Cases

The history taking, clinical examination and biochemical investigations of cases in the present study were done. A

thorough history was taken with special emphasis to exclude history of significant alcohol intake which was defined as intake less than 20gm per day (in females) and less than 30gm per day (in males). Systemic data collections were carried out by review of all medical records. BMI (It was calculated and is defined as weight (KG)/ height (m2): Normal: 18.5 – 24.9 kg/m2, Preobese: 25 – 29.9 kg/m2 and Obese: ≥30kg/m2 was termed (as defined by WHO and CDC).

Biochemical Profiling

Diabetes Mellitus was defined as presence of FBS ≥ 126mg/dl and RBS ≥ 200mg/dl or higher. According to ATP III guidelines Dyslipidemia was defined as presence of one of the following: LDL > 160mg/dl, Total cholesterol ≥ 200mg/dl, Triglyceride > 150mg/dl, HDL < 40mg/dl and Insulin Resistance Syndrome was defined as presence of more than 3 of the following: Abdominal obesity, defined as a waist circumference > 102cm (40 in) in men > 78cm (35in) in women, Triglyceride > 150mg/dl, HDL cholesterol < 40mg/dl in men and < 50mg/dl in women, BP ≥ 130 / ≥ 85 mmHg, FBS ≥ 110mg/dl.

Investigations

Other investigations performed were Hb% (Cyan Haematin method), Viral markers: HbsAg and Anti HCV (ELISA), FBS and RBS (God-Pod method), Hb1Ac (Direct Enzymatic Assay), Lipid Profile: Total Cholesterol (CHOD-PAP method), LDL (by calculation), HDL (Phosphotungstate method), VLDL (by calculation), Triglyceride (GPO-POD method), Serum uric acid (Uricase method), LFT: Serum Bilirubin (Mallory Evelyn Modificands. Punto final), Serum SGOT/AST and SGPT/ALT (IFCC without Pyridoxal phosphate kinetic UV), USG whole abdomen and Liver biopsy.

RESULTS

Our study of 60 NAFLD patients revealed that the mean age was 52.53±11.68 years most of our patients were of 5th, 6th and 7th decade of life (Table 1). There was a noticeable prominent female predominance i.e. 39 (65%) out of 60 NAFLD subjects (Table 1), with male: female ratio being 1:1.86. Majority of our patients 50 (83%) had more than one complaints (Table 2) with commonest complain being fatigue, malaise and abdominal pain whereas heart burn was the second commonest complain. Further clinical examination of NAFLD patients with RUQ abdominal pain i.e. 26 (43.3%) there were 14 (53.8%) patients who had associated abdominal tenderness only and 10 (38.5%) patients who had abdominal tenderness along with hepatomegaly. Our study of risk factors among the selected 60 NAFLD subjects revealed that 30% had diabetes mellitus, 20% had hypertension, 13% had hypertriglyceridemia, 10% had hypothyroidism, 10% had malnutrition, 7% had hyperuricemia, 5% had diabetes mellitus with hypertriglyceridemia, 3% had hypertension with hypertriglyceridemia and 2% had hypertension with dyslipidemia (Table 3). BMI as per WHO recommendation distributed our 60 patients into 10% (6 patients) malnourished, 28.3% (17 patients) normal, 33.3% (20 patients) pre-obese and 28.3% (17 patients) obese (Table 4). Mean BMI of our study group was 27±6.32 kg/m2. Diabetic profiling with Fasting Blood Sugar (FBS) and Postprandial Blood Sugar (PPBS) revealed that 18 (30%) patients had FBS in diabetic range whereas 11 (18%) patients had PPBS in diabetic range. Mean FBS and PPBS were 112.98±40.99 mg/dL and 149.43±66.04 mg/dL respectively. Lipid profiling of our 60 NAFLD subjects revealed that 92% had Total Cholesterol (LPC) within normal range with mean LPC being 167.65±31.84 mg/dL, 95% had LDL (LPL) within normal range with mean LPL being 93.03±27.01 mg/dL, 77% had HDL (LPH) within normal range with mean LPH being 45.93±8.93 mg/dL and 80% had Triglyceride (LPT) within normal range with mean LPT being 145.5±69.54 (Table 5). Serum transaminases of 60 NAFLD patients revealed 22 (36.7%) and 39 (65%) had raised SGPT/ALT and SGOT/AST levels. The mean SGPT/ALT values were 40.4±23.54 IU/L and mean SGOT/AST values were 45.6±20.7 IU/L. However, there were 38 (63.3%) patients who had normal SGPT/ALT levels and 21 (35%) patients who had normal SGOT/AST levels. Radiological investigation (USG) of selected 60 NAFLD patients revealed 30 (50%) patients showed grade-1 fatty liver, 23 patients (38.3%) had grade-2 fatty liver and 7 patients (11.7%) showed grade-3 fatty liver (Table 6). Low patient compliance and associated limitations of liver biopsy lead to only 3 (5%) patients given consent for liver biopsy which revealed steatosis and dense fibrosis.

Table 1: Age & Gender Distribution of Patients for NAFLD

	No of Patients			% of Patients	
Age (Yrs)	Male	Female	Total	Male	Female
21-30	0	2	2	0	5.1
31-40	2	4	6	9.5	10.3
41-50	5	13	18	23.8	33.3
51-60	8	7	15	38.1	17.9
61-70	4	11	15	19	28.2
71-80	1	2	3	4.8	5.1
81-90	1	0	1	4.8	0
TOTAL	21	39	60	100	100

DISCUSSION

The prevalence of NAFLD in our study population was 19.23% approximately. There are only few studies regarding the prevalence of NAFLD in India. Some studies have shown that the prevalence of NAFLD in the general population is upto 30%. In a recent study by Michael H. Le et al. the prevalence of NAFLD in US has been found to be 30.0%, as suggested by results from investigations relying on imaging studies.

Table 2: Nature of Complaints As Reported By NAFLD Patients

Nature of Complaints	No. of Patients	% of Patients (rounded off)
Single complaints	10	17%
More than one complaint	50	83%
TOTAL	60	100%

Table 3: Aetiological incidence distribution of NAFLD patients

Aetiology	No of patients			% of patients		Total (RO)
	Male	Female	Total	Male	Female	
Hypertension	4	8	12	19	20.5	20
Diabetes Mellitus	10	8	18	47.6	20.5	30
Hypothyroidism	2	4	6	9.5	10.3	10
Hyperuricemia	0	4	4	0	10.3	7
Hypertriglyceridemia	4	4	8	19	10.3	13
Malnutrition	0	6	6	0	15.4	10
DM Type2 + Hypertriglyceridemia	0	3	3	0	7.7	5
HTN + Dyslipidemia	1	0	1	4.9	0	2
HTN + Hypertriglyceridemia	0	2	2	0	5	3
TOTAL	21	39	60	100	100	100

Table 4: BMI distribution of NAFLD patients

BMI	No of patients			% of patients Total (RO)
	Male	Female	Total	
<18.5	1	5	6	10
18.5 - 24.9	5	12	17	28.3
25.0 - 29.9	9	11	20	33.3
30.0 - 39.9	6	11	17	28.3
TOTAL	21	39	60	100

The patients in our study were in the age group 20-85years (mean age 52.53 years). In our study most of the patients were of 5th, 6th and 7th decade of life. A study Kalra S et al. the prevalence of NAFLD increased with increasing age, with 239(45.8%) identified patients in age group of 25-50 years and 283(54.2%) were aged 51-55 years (OR:0.71, 95%CI: 0.54-0.92, p=0.005); with highest prevalence recorded in 61-70 year age group, at 61.8%.Such an age distribution in our NAFLD patients was due to the fact that most of our patients were of working age group (within 50 years). In our study NAFLD was found to be more common in women (39 out of 60) with male: female ratio being 1:1.86. According to study done by D.H Akbar & A.H Kawther, showed that there was a significant preponderance of NAFLD in female with their male: female ratio being 1:2.6.Most of the male patients in our study group were employees and most of them had a history of alcohol consumption, thus they could not qualify for the diagnosis of NAFLD, whereas the females, mostly housewives had sedentary lifestyle with no history of alcohol intake. Majority of our patients 50(83%) had more than one complaint and 10(17%) presented with a single complaint. In our study fatigue, malaise and abdominal pain were found to be the commonest presentation. Heart burn was the second commonest presentation.

Table 5: BMI distribution of NAFLD patients

LPT	No of Patients			% of patients
	Male	Female	Total	Total
65-149	15	25	40	66.7
150-199	3	5	8	13.3
200-455	3	9	12	20
TOTAL	**21**	**39**	**60**	100

Table 6: BMI distribution of NAFLD patients

Radiology findings	No. of patients			% of patients		
	M	F	T	M	F	T
Grade-I	10	20	30	47.6%	51.3%	50%
Grade-II	8	15	23	38.1%	38.5%	38.3%
Grade-III	3	4	7	14.3%	10.2%	11.7%
Total	21	39	60	100	100	100

Clinical findings of our study showed: 26 patients had RUQ abdominal discomfort/pain. 14 patients had RUQ abdominal discomfort with tenderness. 10 patients had RUQ abdominal discomfort and tenderness with hepatomegaly. Our study showed commonest clinical finding was abdominal tenderness. Study done by Girish K Pati, Shivaram P Singh they found that most patients with NAFLD were usually asymptomatic, or may present with fatiguability, heaviness and discomfort on the right side of upper abdomen. Approximately more than half of our patients were pre-obese (33.3%) and obese (28.3%). Rests of the patients were well within the normal range of BMI (38.3%). Singh et al. in their study in Odisha (n=632) found 61.7% obese NAFLD patients with mean BMI of 26.1 kg/m^2. Our study showed that 21 patients (35%) had diabetes mellitus type 2.Similarly in a study conducted by Bano et al. in Rawalpindi (Pakistan) they found that among 103 cases of NAFLD there were 34% cases of DM type 2. Our study had 13 (21.7%) out of 60 patients had hypertriglyceridemia. Likewise, in a study conducted by Nusrat A et al. they found that out of their 200 diabetic patients, 42 (21%) had TG (Triglycerides) >500 and 4 (2%) had TG=500 whereas out of their 200 non-diabetic group, no patient had TG (Triglycerides) ≥500. 22 (36.7%) patients had raised SGPT levels and 39 (65%) patients had raised SGOT levels in our study group. However, there were 38 (63.3%) patients who had normal SGPT levels and 21 (35%) patients who had normal SGOT levels. Sharavanan TKV et al. found that the liver enzymes are a poor measure

of NAFLD. Although elevation of serum transaminases are common in NAFLD, normal values can be found in upto 78% of their patients in the presence of histologic findings. In our study 30 out of 60 patients (50%) showed grade-1 fatty liver, 23 patients (38.3%) had grade-2 fatty liver and 7 patients (11.7%) showed grade-3 fatty liver in the radiological (ultrasonography) findings. Mahaling DU et al they found that out of their 70 cases which were diagnosed as NAFLD on ultrasonography, grade I NAFLD cases were 47.15%, grade II were 42.85% and grade III were 10%. Only 3 patients (5%) in our study group had their liver biopsy due to lack of consent by the patient/patient party mainly due to illiteracy, low social economic status and biopsy related complications. Histopathological findings showed steatosis and dense fibrosis.

CONCLUSION

We planned this study to estimate the prevalence of NAFLD in patients who attended medical OPD & IPD of Katihar Medical College & Hospital, where we excluded patients of alcohol consumption, HbsAg positive, Anti HCV positive, known chronic liver disease, drug induced liver disease and pregnant women with fatty liver disease. Imaging studies (Ultrasonography) played a key role in the diagnosis of NAFLD. We screened 312 suspected patients and selected 60 patients who were fatty liver positive on ultrasound abdomen leading to a prevalence rate of 19.23%.

Diabetes mellitus and hypertriglyceridemia was found to be a major risk factor in our study group. Raised serum transaminases were found 65% (SGOT/AST) and 36.7% (SGPT/ALT) in our study group. However, there are studies showing normal serum transaminases in NAFLD groups with histological findings. Thus, proving them to be non-reliable as biochemical marker. Finally, in our current scenario the absence of specific treatment for NASH and NAFL further emphasizes the need of healthy diet, yoga and daily exercise in order to control insulin resistance/metabolic syndrome.

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