STUDY ON NONALCOHOLIC STEATOHEPATITIS (NASH) IN PATIENTS OF OBESE, TYPE 2 DIABETES MELLITUS

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ABSTRACT

BACKGROUND

Nonalcoholic steatohepatitis (NASH) represents only a part of a wide spectrum of non-alcoholic fatty liver disease (NAFLD) and its prevalence is only 2-3% in the general population. Diabetes mellitus increases the risk for severe necroinflammation. The diagnosis rests on the hallmark histological features. Liver biopsy is essential for positive diagnosis and prognostication of NASH. The aim of this study was to evaluate the correlation between NASH and risk factor like diabetes, BMI and other risk factors.

MATERIALS AND METHODS

36 patients with histologically confirmed NASH with elevated liver aminotransferase and negative markers for other diseases admitted to our institution from Sept-2012 to August-2014, were included in the study, meeting our inclusion & exclusion criteria. Investigations were done & data was collected. Data were pooled & interpreted using standard statistical methods.

RESULTS

Twenty out of thirty-six patients had diabetes in our study i.e. 55.6% were diabetes. 22 out of 36 patients i.e. 61.1% had BMI >28 kg/m^2. the mean waist circumference in our study was 93.13 Cm. 15 out of 24 female patients i.e. 62.5% females had WC>88 cm and 8 out of 12 male patients i.e. 66.7% males had WC >102 cm., 20 out of 36 patients i.e. 55.6% patients fulfilled at least 3 out of 5 criteria and therefore had insulin resistance syndrome or metabolic syndrome.

CONCLUSION

Patients with NASH are typically asymptomatic unless cirrhosis develops. 97.22% patients were dyslipidaemics. NASH may be considered an additional features of insulin resistance & metabolic syndrome. Age, gender, waist circumference, BMI, ALT, AST: ALT ratio, serum triglyceride levels, HTN & BAAT score are independent predictors of NASH.

KEYWORDS

NASH Nonalcoholic Steatohepatitis AST Transaminase, Diabetes Mellitus HDL High Density Lipid LDL Low Density lipid TG Triglyceride, NAFLD- Nonalcoholic Fatty Liver Disease.

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BACKGROUND

Nonalcoholic steatohepatitis (NASH) is a liver disease characterized by steatosis and periportal and lobular inflammation. In its initial phases, during which fat accumulates in the liver, no clinical symptoms are evident. In advanced stages, fibrosis (eventually progressing to established cirrhosis in some patients) is detectable According to Brunt et al[1] histologically, along with a mixed inflammatory cell infiltrate, glycogen nuclei, and Mallory's hyaline. Because its adequate diagnosis requires histological evaluation of the liver, the prevalence of NASH is probably underestimated.

Two types of NASH exist: primary NASH (which is associated with metabolic syndrome-related conditions, such as obesity, type 2 diabetes, and hyperlipemia) and secondary NASH (which occurs after obesity-related intestinal surgery, rapid weight loss in the obese, total parenteral nutrition, treatment with drugs such as amiodarone or perhexiline maleate, lipodystrophy, or Wilson's disease). The actual prevalence of NASH in type 2 diabetes and obesity is unknown. It is estimated that 75% of type 2 diabetic patients present some form of non-alcoholic fatty liver of different degrees.

As far as obesity is regarded, steatosis has been reported in 70% of obese and 35% of lean patients and NASH in 18.5% of obese and 2.7% of lean patients in a consecutive study

The presence of obesity or type 2 diabetes, high (at least two times that of normal) levels of alanine aminotransferase (ALT) and triglycerides, hypertension, and an aspartate aminotransferase/ ALT ratio greater than unity may justify performing a biopsy, since prognostic information is greater in these subgroups of patients.

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In case of NASH the patient has an increased risk that the process will develop into hepatic cirrhosis, terminal hepatic failure, or hepatocellular cancer. In addition to the clinical studies, the following facts also suggest an existing relationship between the two entities-

a. The components of the metabolic syndrome (obesity, insulin resistance, dyslipidaemia, and- in a certain aspect- hypertension) constitute the risk factors of primary NASH;
b. Common features seen in the presumed pathologic mechanism: insulin resistance, disorders of the lipid metabolism, obesity, and the role of the adipocytokines;
c. The beneficial effect on NASH exerted by certain medicines used in the treatment of insulin resistance. Due to the dramatic increase in the prevalence of obesity, the number of patients with metabolic syndrome complicated by NASH is increasing continuously according to Garcia-Monzon et al[2]

MATERIALS AND METHODS

Study Design- Prospective, open labelled, single centric, parallel design study. Study site - Tertiary care hospital from Berhampur. MKCG MCH.

Study Duration- This study is conducted during the period of 2012 to 2014.

36 Patients with histologically confirmed NASH who had elevated liver aminotransaminases, negative serologic markers of viral or autoimmune hepatitis and no findings in favour of metabolic liver disease were enrolled. A careful history was taken regarding alcohol intake.

Inclusion Criteria were-

1. Patients of either sex.
2. Age more than 20 years
3. Elevated liver aminotransaminases.
4. Histologic confirmation of nonalcoholic steatohepatitis.

A careful history was taken with special attention to alcohol intake and ultrasonography was performed in all enrolled patients.

Exclusion Criteria were-

1. History of alcohol intake.
2. Recent gastrointestinal surgery
3. Pregnancy
4. Usage of drugs known to result in steatosis, including glucocorticoids, synthetic oestrogens, tamoxifen, amiodarone, Calcium-channel blockers, and methotrexate.
5. Positive serologic markers of viral or autoimmune hepatitis (including HBsAg, HCV antibody (ELISA), HIV antibody (ELISA), antinuclear antibodies, anti-smooth muscle antibodies, and anti-liver/kidney microsomes type 1 antibodies).
6. Findings in favour of metabolic liver diseases, including Wilson's disease and hemochromatosis and positive alpha-1 antitrypsin.

Out Of 100 patients, who were primarily studies for elevation of serum aminotransaminases in the beginning, 50 patients fitted into the inclusion criteria, except pathologic confirmation, consented to undergo liver biopsy. The pathologic diagnosis of NASH was confirmed in 36 patients and these patients were analysed, the rest were excluded from the study.

In patients with history of type II diabetes mellitus a relevant history was elicited, that is the duration of illness and the drug history. The duration and dosage of these drugs was also noted.

By standard means the weight in kgs. and height in meter of all the patients was measured. Body Mass Index was calculated by the formula as per Quetelet Index.

B. M. I = Weight in Kg./ (height in meters)^3

The grading and staging of all biopsy specimens were determined based on the method proposed by Brunt et al. Overweight was defined as a BMI between 25 and 29.9 kg/m2, and obesity as BMI equal or above 30 kg/m^2. Criteria for diagnosis of diabetes mellitus.

Symptoms of diabetes (polyuria, polydipsia, weight loss) plus random blood glucose concentration>11.1 mmol/L (200 mg/dl) or fasting plasma glucose > 7.0 mmol/L (126 mg/dl) or HbA1C >6.5% or Two hour plasma glucose >11.1 mmol/L (200 mg/dl) during an oral glucose tolerance test.

The above is as per the guidelines of American Diabetes Association 2011.

Dyslipidaemia and insulin resistance was defined according to guidelines of ATP III. Thus, patients with one of the criteria of LDL-C >160 mg/dL, total cholesterol > 200 mg/dL, triglycerides >150 mg/dL, or HDL-C<40 mg/dL were considered dyslipidemic. Insulin resistance was defined with presence of three of the following:

1. Abdominal obesity, defined as a waist circumference in men >102 cm (40 in) and in women >88 cm (35 in)
2. Triglycerides >150 mg/dL
3. HDL cholesterol <40 mg/dL in men and <50 mg/dL in women or specific medication
4. Blood pressure >130/ >85 mmHg or specific medication
5. Fasting glucose >100 mg/dL or specific medication or previously diagnosed type II diabetes.

Aims and Objectives-

To study the correlation of NASH with various risk factors like diabetes, BMI and other risk factors like hypertriglyceridemia, hypertension.

1. To evaluate the predictors of NASH.
2. To study the prognosis of NASH.

RESULTS

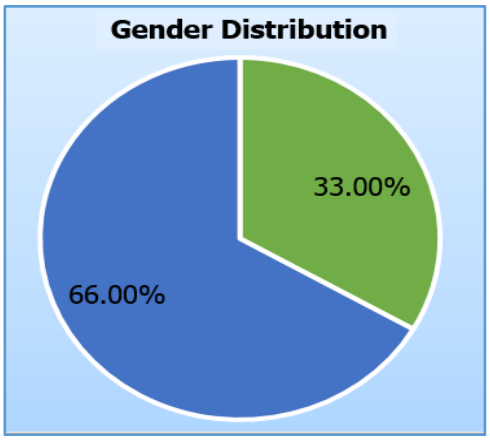

Figure 1. Gender Distribution

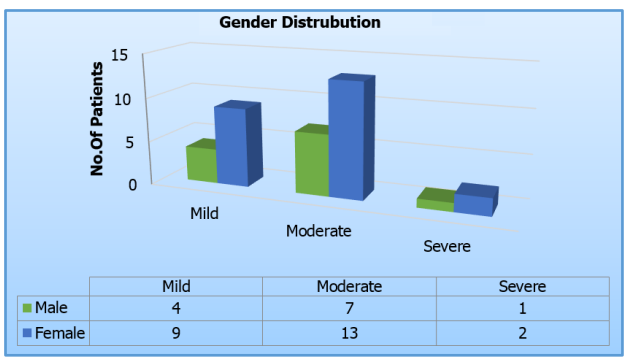

Figure 2. Severity among Different Age

24 out of 36 patients i.e. 66.67% were females and hence a female preponderance was found.

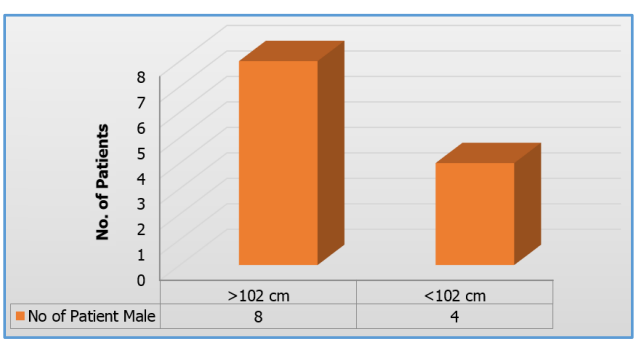

Figure 3. Waist Circumference

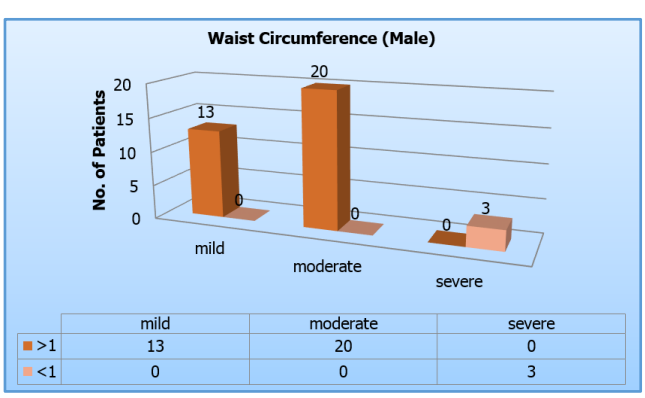

Figure 4. Severity Grading

8 out of 12 patients i.e. 66.7% of the male patients had waist circumference > 102 cm.

NASH			
Waist Circumference (Female)	**Mild**	**Moderate**	**Severe**
≥88 cm	11%	92.30%	100.00%
<88 cm	88.90%	7.70%	0.00%

Table 1. WC in Different Stages

Waist Circumference (Female)	No. of Patients (Female)	% of Patients
>88 cm	15	62.50%
<88 cm	9	37.50%

Table 2. Waist Circumference in Females

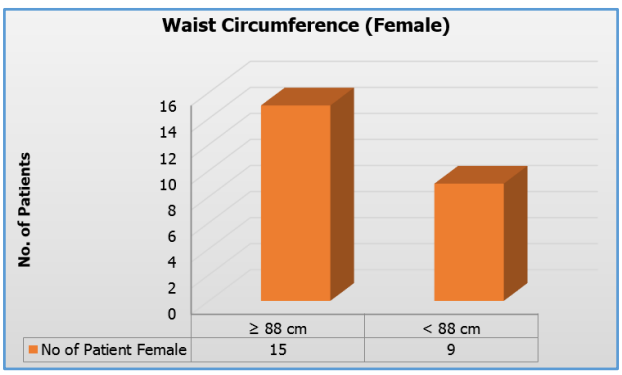

Figure 5. Waist Circumference in Female

15 out of 24 females i.e. 62.5% females had waist circumference >88 cm.

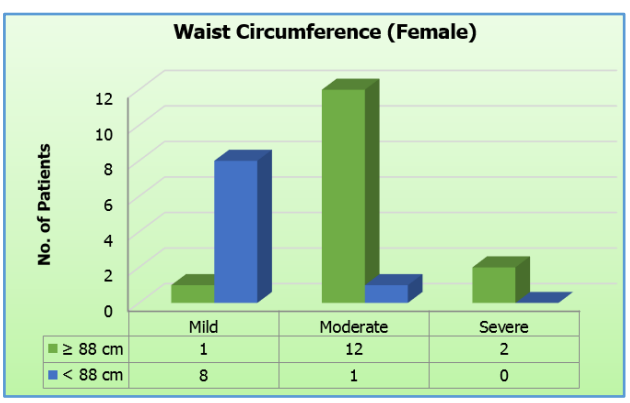

Figure 6. WC in Different Grading

BMI	Mild	Moderate	Severe
> 28 kg/m²	5	14	3
≤28 kg/m²	8	6	0

Table 3. Grading

BMI	No. of Patients	% of Patients
< 25 kg/m²	2	5.60%
≥ 25 -≤ 28 kg/m²	12	33.30%
> 28 kg/m²	22	61.10%

Table 4. BMI

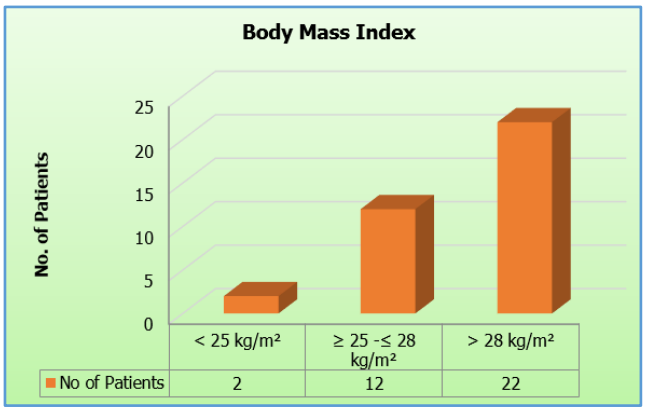

Figure 7. Grading

34 out of 36 patients had a BMI >25 kg/m^2 i.e. 94.4% patients were overweight.

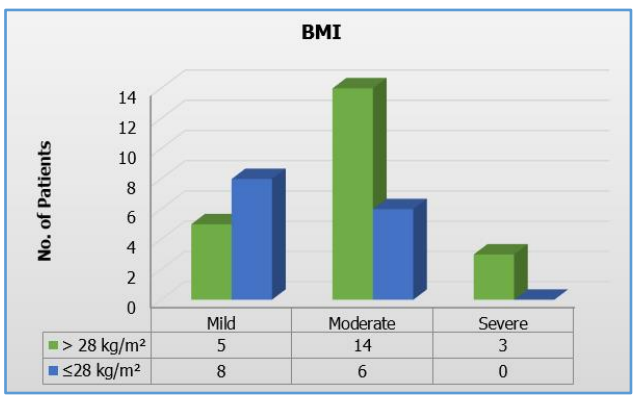

Figure 8. BMI

	NASH		
Type 2 DM	**Mild**	**Moderate**	**Severe**
Present	61.50%	45.50%	100.00%
Absent	38.50%	55.00%	0.00%

Table 5. Grading

Type 2 DM	No. of Patients	% of Patients
Present	20	55.60%
Absent	16	44.40%

Table 6. Type 2 DM

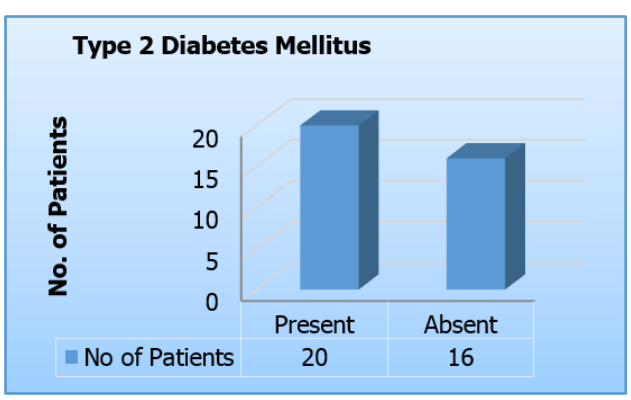

Figure 9. Type 2 DM

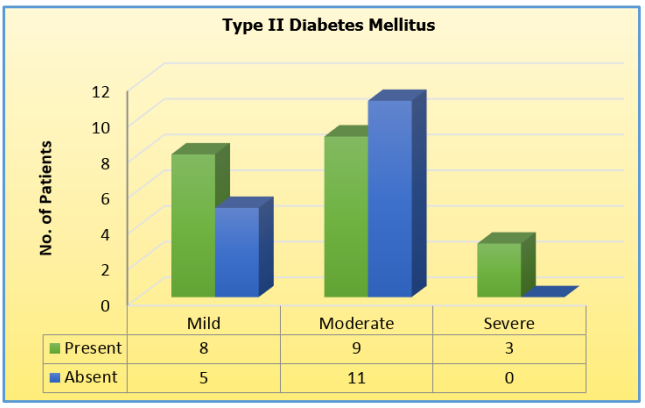

Figure 10. Type 2 DM in Different Stages

20 out of 36 patients i.e. 55.6% patients were type 2 DM.

Insulin Resistance	NASH		
	Mild	**Moderate**	**Severe**
Present	30.80%	65.00%	100.00%
Absent	69.20%	35.00%	0.00%

Table 7. Insulin Resistance in Different Grading

Insulin Resistance	No. of Patients	% of Patients
Present	20	55.60%
Absent	16	44.40%

Table 8. Insulin Resistance

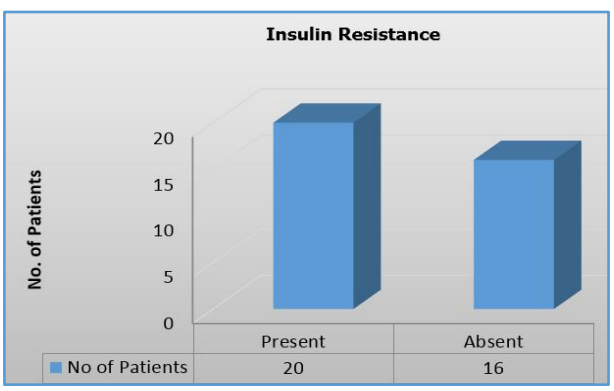

Figure 11. Insulin Resistance

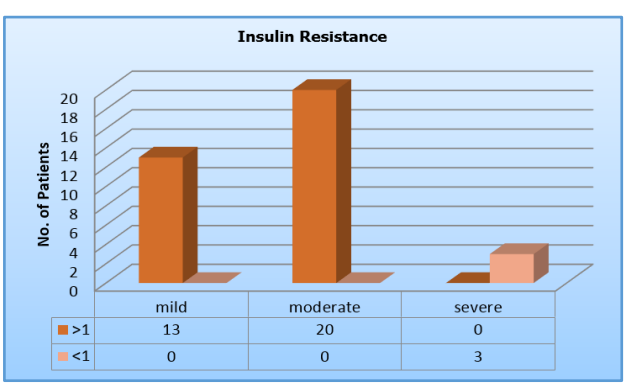

Figure 12. Insulin Resistance in Different Stages

20 out of 36 patients i.e. 55.6% patients had insulin resistance syndrome or metabolic syndrome.

	NASH		
Triglyceride levels	**Mild**	**Moderate**	**Severe**
≥ 150 mg/dl	69.20%	100.00%	100.00%
< 150 mg/dl	30.80%	0.00%	0.00%

Table 9. Triglyceride Levels in Different Stages

Triglyceride Levels	No. of Patients	% of Patients
Elevated (>150 mg/dl)	32	88.90%
Normal	4	11.10%

Table 10. Triglyceride Levels

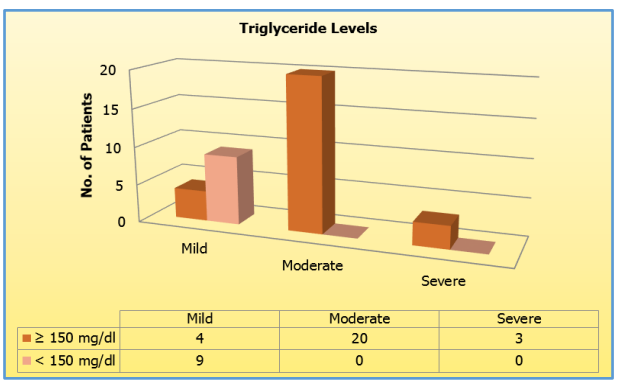

Figure 13. Triglyceride in Different Stages

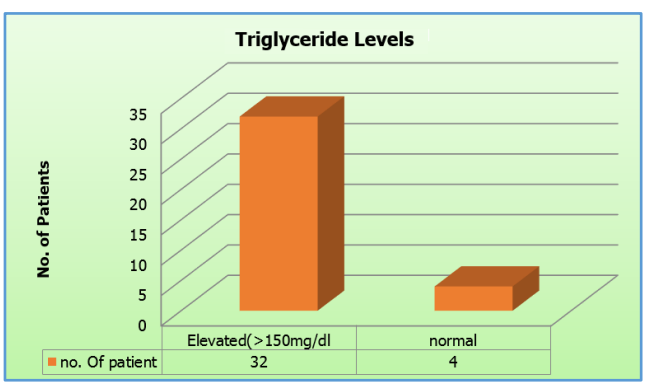

Figure 14. Triglyceride Levels

32 out of 36 patients i.e. 88.9% patients had hypertriglyceridemia.

Serum Cholesterol	No. Of Patients	% of Patients
<200 mg/dl	20	55.60%
>200 mg/dl[16]	16	44.40%

Table 11. Serum Cholesterol

Serum Cholesterol	NASH		
	Mild	**Moderate**	**Severe**
≥ 200 mg/dl	30.80%	55.00%	33.30%
< 200 mg/dl	69.20%	45.00%	66.70%

Table 12. Serum Cholesterol in Different Stages

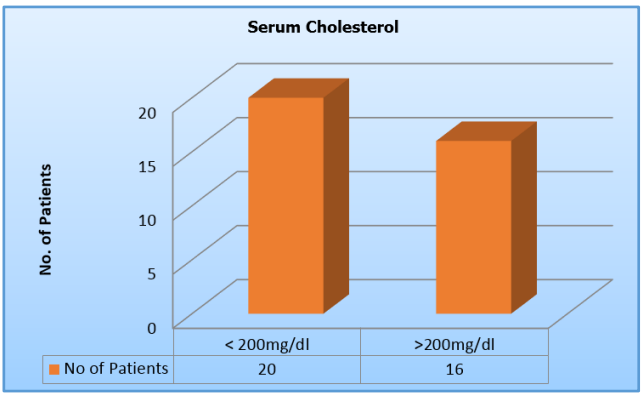

Figure 15. Serum Cholesterol

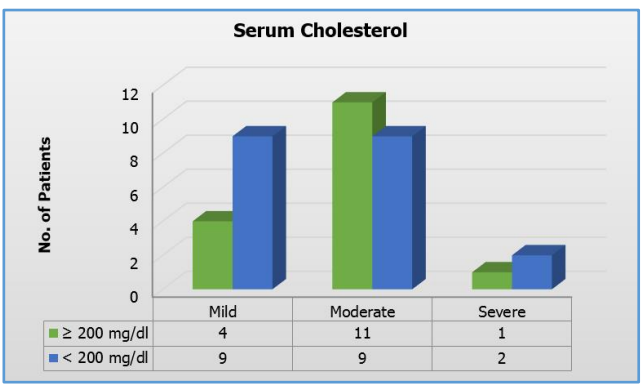

Figure 16. S.Cholesterol in Different Staging

32 out of 36 patients i.e. 88.9% patients had hypercholesterolemia.

AST:ALT Ratio	NASH		
	Mild	**Moderate**	**Severe**
< 1	100.00%	100.00%	0%
> 1	0%	0%	100.00%

Table 13. Ratio in Different Grading

AST:ALT Ratio	No. of Patients	% of Patients
< 1	33	91.70%
> 1	3	8.30%

Table 14. AST:ALT Ratio

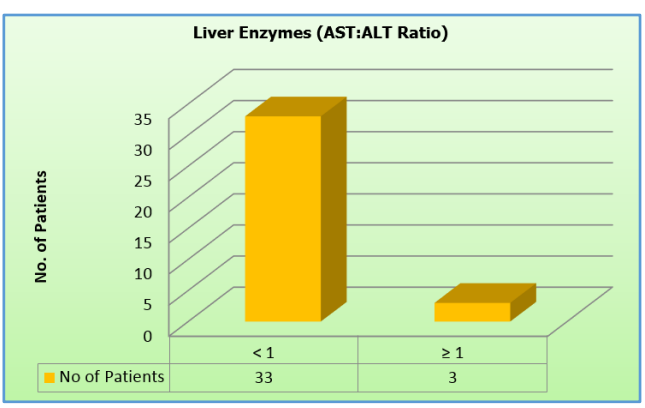

Figure 17. AST: ALT Ratio

AST: ALT ratio was<1 in 33 out of 36 patients i.e 91.7% patients.

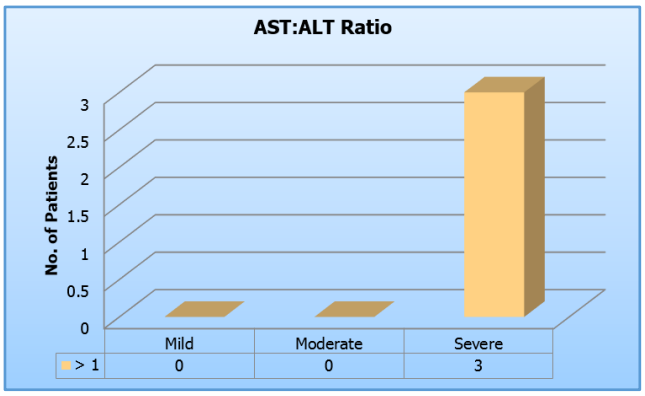

Figure 18. AST: ALT Ratio

DISCUSSION

36 patients with persistently raised liver enzymes with exclusion of other liver disorders were prospectively enrolled.

Gender- Majority of the patients i.e. 66.67% were females, and the female to male ratio was 2:1.

In our study also there is a female preponderance with 66.67% i.e. 24 out of 36 patient being females.

Thus our study shows that female gender is associated with severe steatohepatitis.

In our study 69.23%, 65% and 66.67% of the patients are females as compared to 30.77%, 35% ,33.33% males in mild, moderate and severe NASH respectively. Thus, female gender is an independent predictor of liver damage in patients with NASH with increasing severity being more common in females.

DM- 20 out of 36 patients in our study had Type II DM. i.e. 55.6% patients were Type II DM.

In our study 15% of the diabetics and none of the non-diabetics had severe steatohepatitis.

This shows that diabetes increases the risk for severe necroinflammation.

Rodriguez Hernandez et al[4] in 2008 said that diabetes mellitus was correlated with histological hepatic change

AST, ALT- In our study all the patients had elevated liver aminotransaminases.

The mean ALT levels in our study was 75.5 ± 27 U/L. The mean AST levels was 66.8 ± 29.51 U/L. Similarly, the mean ALT and AST levels were 80.9+32.0 U/L & 66.9 ± 28.9 U/L respectively in the Iranian study.

In our study 3 patients had AST: ALT ratio>1. Three patients had evidence of cirrhosis on histology. This explains that AST: ALT ratio which is < 1 in NASH is reversed as NASH progresses towards cirrhosis. Thus AST: ALT ratio >1 is a predictor of advanced fibrosis & cirrhosis. Gholam et al[2] said that elevated transaminase levels correlated with NASH.

In our study the mean AST & ALT levels were 51.54 ± 14.8 U/L & 60.77 ± 12.7 U/L respectively in mild NASH, 63.95 ± 19.34 U/L & 76.75 ± 27.68 U/L respectively in moderate NASH, 145.33 ± 6.11 U/L and 124.67 ± 6.43 U/L respectively in severe NASH.

This shows that as the severity of NASH increased, the AST & ALT levels increases. Thus elevated transaminase levels correlated with NASH. Shi et al[5] denoted that elevated serum levels of ALT is an independent predictor of degree of inflammation.

Our study shows that ALT levels are increased as the severity of NASH increase.

Thus this shows than ALT is an independent predictor of steatohepatitis.

BMI- In 22 out of 36 patients i.e. 61.1% patients the BMI was more than 28 kg/m^2

In our study mean weight was 78.06 + 12.52 kg, mean height was 1059 ± 0.07 m, mean BMI was 30.80 + 4.44 kg/m^2.

Obesity is the condition most often associated with NASH. As in most studies 100% patients with NASH were also obese.

In our study 33.33% patients had BMI between 25-28 kg/m^2 and 61.1% patients and BMI more than 28 kg/m^2.

Thus 94.4% of patients were overweight with NASH. Singh et al in 2008 signified that BMI is an independent predictor of liver damage in patients with NASH.

In our study 3 patients out of 36 had severe steatohepatitis with BMI more that 28 kg/m^2 none of the patients with BMI less than 28 kg/m^2 had severe steatohepatitis. Thus BMI can be used as an independent predictor of severity of NASH.

Waist Circumference (WC)- Mean waist circumference of the patients was 93.14 cm ± 10.46 cm in our study.

Mean waist circumference in males was 100.33 cm and in females was 85.46 cm. 15 out of 24 female patients i.e. 62.5% females had WC>88 cm and 8 out of 12 male patients i.e. 66.7% males had WC >102 cm.

Singh et al[6] identified WC as an independent predictor of the degree of liver necroinflammation.

The mean WC in patients with mild NASH was 86.77 ± 12.62 cm, in moderate NASH it was 95.25 ± 7.73 cm and in severe NASH it was 96.00 ± 6.56 cm. Thus it shows that in patients with severe steatohepatitis WC is more as compared to mild & moderate steatohepatitis. 2 out of 15 females with WC>88 cm had severe NASH and none of the females with WC<88 cm. had severe NASH.

1 out of 8 males with WC >102 cm had severe NASH and none of the males with WC <102 cm had severe NASH.

Thus it shows that WC is an independent predictor of degree of necroinflammation.

Dyslipidaemia was defined according to guidelines of ATP III. Patients with one of the criteria of LDL cholesterol >160 mg/dl, total cholesterol>200 mg/di triglycerides>150 mg/dl or HDL cholesterol <40 mg/dl were considered dyslipidaemics.

16 out of 36 patients, i.e. 44.4% had S. cholesterol levels>200 mg/dl,

4 out of 24 female patients, i.e. 16.7% HDL cholesterol>50 mg/dl,

32 out of 36 patients, i.e. 88.9% Triglyceride >150 mg/dl,

In our study 35 out of 36 patients i.e. 97.22%, were dyslipidaemics.

Insulin Resistance (IR)- Gholam et al[2] said that individuals with NASH had a high level of insulin resistance. In our study, out of 24 females had WC > 55 cm 8 out of 12 males had WC > 102 cm, 32 out of 36 patients had TG > 150 mg/dl 4 out of 12 males had HDL Cholesterol <40 mg/dl 4 out of 24 females had HDL Cholesterol< 50 mg/dl out of 36 patients had BP > 130 /> 85 mm Hg 20 out of 36 patients had type II DM.

Thus, 20 out of 36 patients i.e. 55.6% patients fulfilled atleast 3 out of 5 criteria and therefore had insulin resistance syndrome or metabolic syndrome Bahrami et al[7] found the rate of insulin resistance was 54.7% in patients with NASH. Similarly, in our study all patients with severe NASH had insulin resistance.

Cirrhosis- As expected, measures of hepatic functional capacity do not become abnormal until cirrhosis and liver failure set in. The serum albumin level become abnormal before the serum bilirubin levels does.

In our study out of 36 liver biopsies done, severe necroinflammatory activity was seen in 3 cirrhotic patients. 3 patients in our study had hypoalbuminemia, reversal. of A: G ratio, hyperbilirubinemia.

NASH can cause fibrosis & progressed to cirrhosis. It has been shown that this progress is seen in 8.26% of patient.

In our study 3 patients out of 36 i.e. 8.33%. had cirrhosis.

CONCLUSION

1. ----- NASH represents a part of a wide spectrum of NAFLD. It could be one of the common causes of cryptogenic cirrhosis.
2. The occurrence of NASH is more in the 5th decade.
3. Patient with NASH are typically asymptomatic unless cirrhosis develops.
4. Risk factors associated with NASH include obesity, type II DM and hypertriglyceridemia.
5. NASH may be considered an additional features of insulin resistance & metabolic syndrome.
6. Age, gender, waist circumference, BMI, ALT, AST: ALT ratio, serum triglyceride levels, HTN & BAAT score are independent predictors of NASH.
7. Distinction between NASH and steatosis cannot be made reliably on clinical ground or imaging. Diagnosis can be made with certainty only by examination of liver histology. Characteristic features include fatty change, inflammation, hepatocellular injury with ballooning degeneration and mallory bodies and/or fibrosis.

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