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ORIGINAL RESEARCH

A study of clinical, biochemical & sonological profile of fatty liver in type 2 diabetes mellitus patients

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ABSTRACT
The prevalence of diabetes is increasing world over and is expected to affect 57 million adults in india by 2025. Apart from kidney, eye, heart and blood vessels, liver is also indirectly related with diabetes mellitus. Virtually the entire spectrum of liver disease is seen in patients with type 2 diabetes Nearly 70-80% of the diabetic subjects have been reported to have hepatic fat accumulation, referred to as NAFLD.[5] There are not enough studies done on the hepatic status of diabetic patients in our country. Hence this study aims to describe the hepatic profile of type 2 diabetic patients. This study aims to correlate the clinical, biochemical, sonological profile of fatty liver in non alcoholic patients with type 2 diabetes mellitus.This study was done at the Kamineni Institute Of Medical Sciences, Narketpally. One hundred and eighteen type 2 diabetic patients diagnosed according to the American Diabetic Association criteria, newly diagnosed or on follow- up were included in the study**. Conclusion:** Non invasive methods are the need of the hour for early and wide screening to detect this disease. Persons with higher BMI are at greater risk of developing NAFLD.No significant correlation was found between age of patient, duration of diabetes fasting blood sugar levels and NAFLD.Liver enzymes were thought to be a potential non invasive strategy for early detection of this disease, but the present study did not find any correlation of the level of liver enzymes and the degree of fatty liver in Indian patients.

INTRODUCTION

The prevalence of diabetes is increasing world over and is expected to affect 57 million adults in india by 2025. Apart from kidney, eye, heart and blood vessels, liver is also indirectly related with diabetes mellitus. Virtually the entire spectrum of liver disease is seen in patients with type 2 diabetes. This includes abnomal liver enzymes, non alcoholic fatty liver disease (NAFLD), cirrhosis, hepatocellular carcinoma, and acute liver failure. In addition, there is an unexplained association of diabetes with hepatitis. Finally, the prevalence of diabetes in cirrhosis is 12.3-57% . Thus, patients with diabetes have a high prevalence of liver disease and patients with liver disease have a high prevalence of diabetes

NAFLD

Ludwig introduced the term Nonalcoholic steatohepatitis (NASH) to describe a form of liver disease that is histologically indistinguishable from alcoholic hepatitis but occurs in people who do not consume excess ethanol.[1] There is renewed interest in Non alcoholic fatty liver (NAFL) recently because of its increased prevalence in diabetes. It has been shown to be a predisposing factor for insulin resistance and hyperinsulinemia, a major cause of cryptogenic cirrhosis and may even lead to hepatocellular carcinoma.[2,3,4]

Nearly 70-80% of the diabetic subjects have been reported to have hepatic fat accumulation, referred to as NAFLD.[5] There are not enough studies done on the hepatic status of diabetic patients in our country. Hence this study aims to describe the hepatic profile of type 2 diabetic patients.

NAFLD represents a spectrum of diseases from simple fatty liver (steatosis), to steatosis with inflammation, necrosis, and possible cirrhosis, that occurs in people who drink little or no alcohol. NAFLD

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affects more women than men and can be found in all age groups diabetes, by most estimates, is now the most common cause of liver disease in the U.S. Cryptogenic cirrhosis, of which diabetes is, by far, the most common cause, has become the third leading indication for liver transplantation.

The liver helps maintain normal blood glucose concentration in the fasting and postprandial states. Loss of insulin effect on the liver leads to glycogenolysis and an increase in hepatic glucose production. So Insulin resistance is the main culprit in the pathogenesis of fatty liver.The precise genetic, environmental, and metabolic factors and sequence of events that lead to the underlying insulin resistance, however, is not fully understood.

Despite down-regulation of the insulin receptor substrate-2-mediated insulin signaling pathway in insulin-resistant states, the up-regulation of SREBP-1c(sterol regulatory element protein 1 c) and subsequent simulation of de novo lipogenesis in the liver leads to increased intracellular availability of triglycerides, promoting fatty liver. This also increases VLDL assembly and deposition in liver.

The insulin-resistant state is also characterized by an increase in pro inflammatory cytokines such as tumor necrosis factor- (TNF-), which may also contribute to hepatocellular injury.

AIM OF STUDY

This study aims to correlate the clinical, biochemical, sonological profile of fatty liver in non alcoholic patients with type 2 diabetes mellitus.

MATERIALS AND METHODS

This study was done at the Kamineni Institute Of Medical Sciences, Narketpally. One hundred and eighteen type 2 diabetic patients diagnosed according to the American Diabetic Association criteria, newly diagnosed or on follow- up were included in the study.

Patients age less than 30 years, with history of any chronic drug intake other than oral hypoglycemic drugs, jaundice, alcohol intake, Hypothroidism,HIV or HBsAg positive were excluded from the study.

An informed consent was taken. The study protocol was approved by the Ethics committee of Kamineni Institute Of Medical College & Hospital, Narketpally..

The type of hypoglycemic drug intake, height and weight were recorded and Body Mass Index (BMI) calculated.

Patients were classified according to BMI as follows: Underweight: BMI <18.5 kg/m2

Normal weight: BMI 18.5 to 24.9 kg/m2 Overweight: BMI 25 to 29.9 kg/m2

Obese: BMI >30 to 34.9 kg/m2 Morbidly obese: >35 kg/m2

Patients were subjected to biochemical investigations to detect the liver enzyme levels, serum bilirubin, serum albumin, serum globulin, serum total proteins and total cholesterol. Serum albumin levels of 3.5 -5.5 mg%, serum globulin of 2-3.5mg%, AST of 0 - 35 IU/L, ALT of 0 - 35 IU/L, Bilirubin levels of 0.3-1 mg%, total cholesterol less than 200mg%, serum total proteins of 5.5- 8mg%, fasting glucose less than 126mg% and a 2hr post prandial glucose of less than 200mg% were taken as normal. Their most recent fasting and post-prandial blood glucose values were recorded to assess the control of diabetes.

All patients were subjected to ultrasonographic examination of abdomen by a qualified radiologist who was masked from the patient's diagnosis or the indication for ultrasound, to assess the liver parenchyma, liver size, gall bladder, biliary and portal system.

The echo texture of the liver parenchyma was graded as follows

Grade 1: A slight diffuse increase in fine echoes in the hepatic parenchyma with normal visualization of the diaphragm and intrahepatic vessel borders.

Grade 2: A moderate diffuse increase in fine echoes with slightly impaired visualization of the intrahepatic vessels and diaphragm.

Grade 3: A marked increase in fine echoes with poor or no visualization of the intrahepatic vessel borders, diaphragm and posterior portion of the right lobe of the liver.[12]

The data was analyzed and statistical conclusions drawn using the SPSS 13.0 software.

OBSERVATIONS AND RESULTS

A total of one hundred and eighteen patients were included in the study, 71(60.2%) females and 47(39.8%) males. The age and sex distribution is shown below.

TABLE NO: 1 AGE & SEX DISTRIBUTION OF PATIENTS: (n=118)

Age Distribution	Female	Male	Total
30-39	6 (5%)	1(0.8%)	7(5.8%)
40-49	16(13.6%)	11(10%)	27(23.6%)
50-59	26(22%)	14(11%)	40(33.5%)
60-69	20(17%)	17(16%)	37(32.5%)
70-79	3(2.6%)	4(3%)	7(5.6%)
Total(n=118)	**71(60.2%)**	**47(39.8%)**	**118(100%)**

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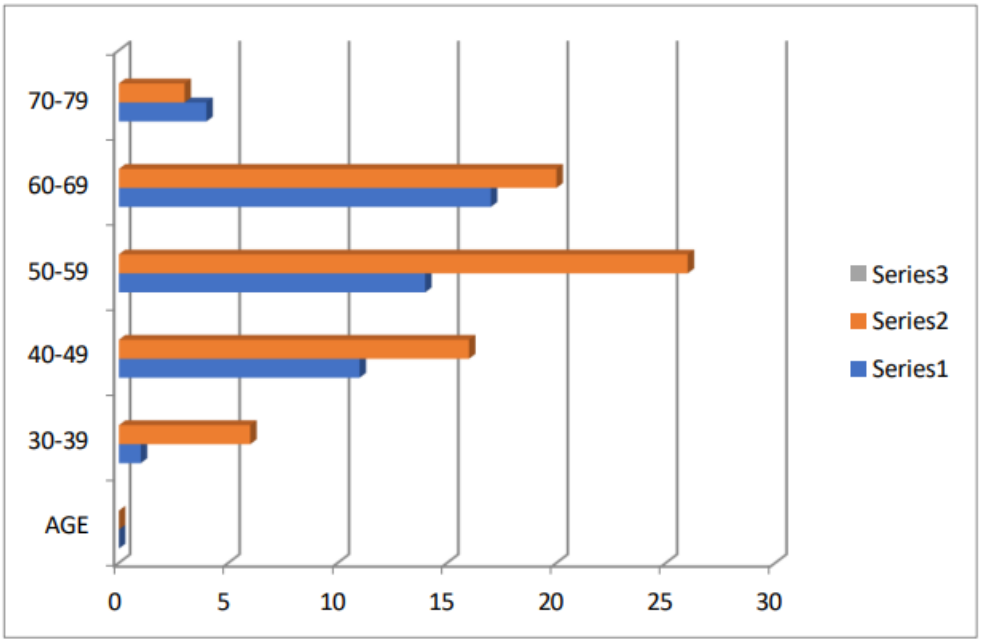

TABLE NO: 2 TYPE OF ANTI-DIABETIC TREATMENT USED BY STUDY PATIENTS: (n =118)

HYPOGLYCEMIC DRUG	NUMBER
METFORMIN	12 (10%)
GLIMEPRIDE	15 (12.5%)
GLIMEPRIDE + METFORMIN	67(57.5%)
OHA + INSULIN	6 (5%)
INSULIN	0 (0%)
NOT ON ANY TREATMENT	18 (15%)

- 67 of 118 patients were on GLIMIPRIDE + METFORMIN.
- Ninety four patients were on oral hypoglycemic drugs, including six patients who were additionally on plain insulin injections. Majority of the patients were either on glimepride alone or combination of both glimepride and metformin. Eighteen patients though diagnosed to have diabetes were not on any drugs at the time of presentation.

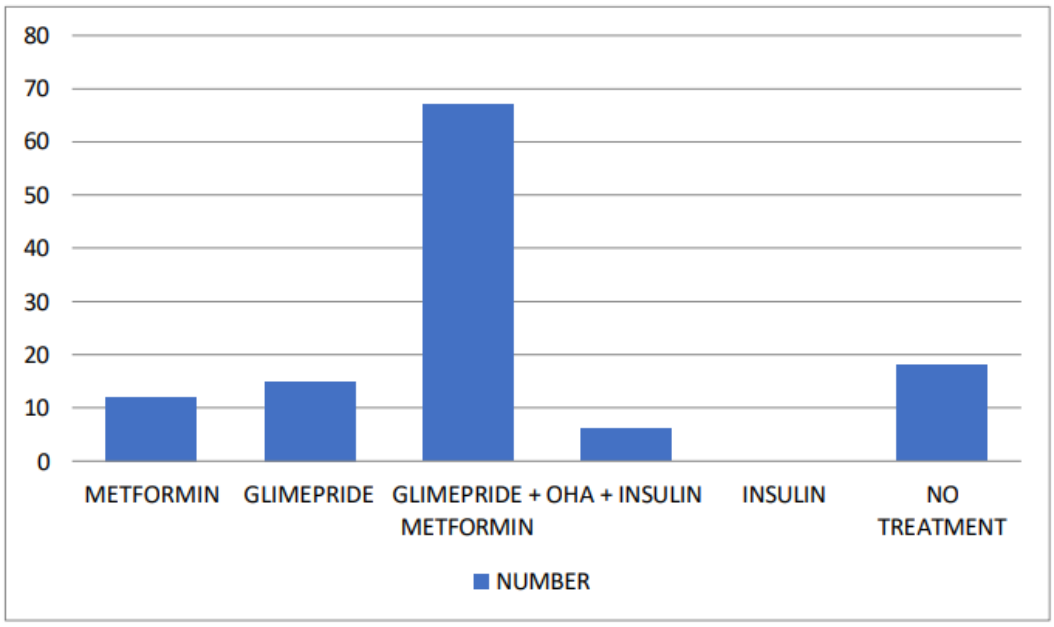

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TABLE NO: 3 DURATION OF DIABETES IN STUDY PATIENTS: (n=118)

DURATION	NUMBER
NEWLY DIAGNOSED (De Novo)	11(10%)
< 5 YRS	66(56%)
≥ 5 YRS	41(34%)

- 11(10%)patients were newly diagnosed.
- 66(56%) patients were diabetic for less than 5 yrs.
- 41(34%) patients were diabetic for more than or equal to 5 yrs.
- NEWLY DISGNOSED(De Novo) are the ones who were diagnosed to be diabetic upon presentation to our hospital.

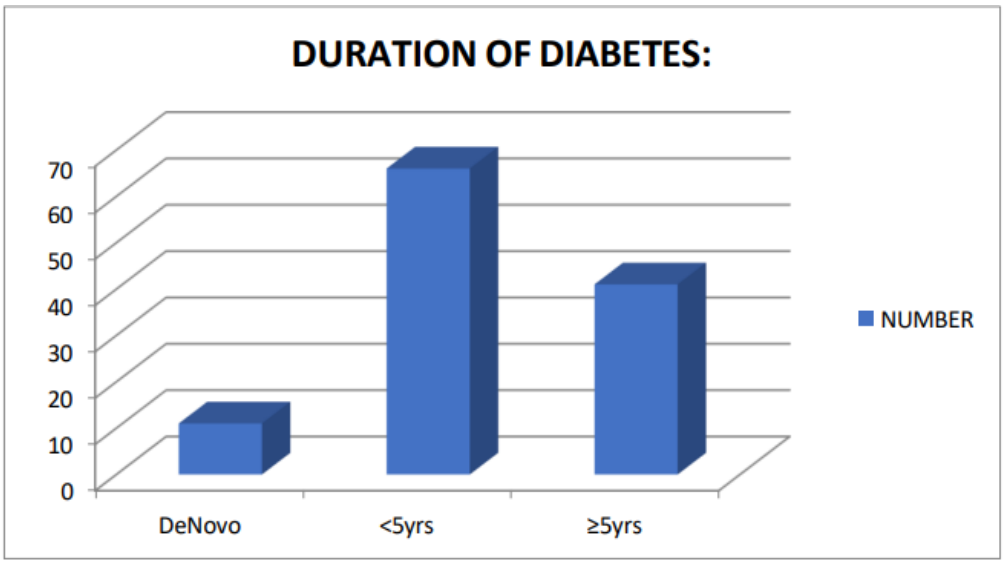

TABLE NO: 4 MEAN VALUES OF BIOCHEMICAL INVESTIGATIONS IN STUDY PATIENTS:(n=118)

INVESTIGATION	MEAN ± SD (n=118)	MAXIMUM	MINIMUM
S Total Proteins	7.0 ± 0.4	7.9	6.0
Serum Albumin	4.1 ± 0.4	4.8	2.4
Serum Globulin	2.8 ± 0.4	3.7	1.2
Serum Bilirubin	0.8 ± 0.3	2.1	0.4
AST	22 ± 8	60	12
ALT	20 ± 8	55	10
ALP	112 ± 18	211	30
FBS	132 ± 45	250	70
PPBS	218 ± 54	330	110
HbA1c	7.5 ± 1.0	10.8	6.5
T.CHOLESTEROL	220 ± 32	328	197
LDL	126 ± 17	172	66
VLDL	28 ± 10	56	12
HDL	66 ± 12	81	31
TRIGLYCERIDES	165± 26	221	137

The total serum proteins were within the normal range for all the patients with a mean value of 7.03 +/- 0.4. low albumin levels, taken as less than 3.5 mg% were found in 4 (3.4%) patients and low globulin level, taken as less than 2 mg% in 2 (1.7%) patients. Liver function tests revealed an elevated AST levels taken as more than 35 IU/L in 8 (6.8%) patients and an elevated ALT levels taken as more than 35 IU/L in 5 (4.2%) patients. An AST/ALT ratio of more than 1 was found in 101 (85.6%) patients. Alkaline phosphatase levels were above 120 IU/L in 37 (31.4%) patients. Age-wise and Sex-wise comparison of the liver function tests revealed no significant difference between the various age classes or between sexes.

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TABLE NO: 5 MEAN FASTING & POST PRANDIAL GLUCOSE IN STUDY PATIENTS: (n=118) MEAN ± SD

BLOOD GLUCOSE	GRADE 1 FATTY CHANGE	GRADE 2 FATTY CHANGE	NO FATTY CHANGE
Fasting blood sugar	132±22	130±24	134±22
Post Prandial Blood Sugar	186±37	230±35	216±36

- Comparing the mean blood glucose values between those with or without fatty liver did not reveal any significant difference.

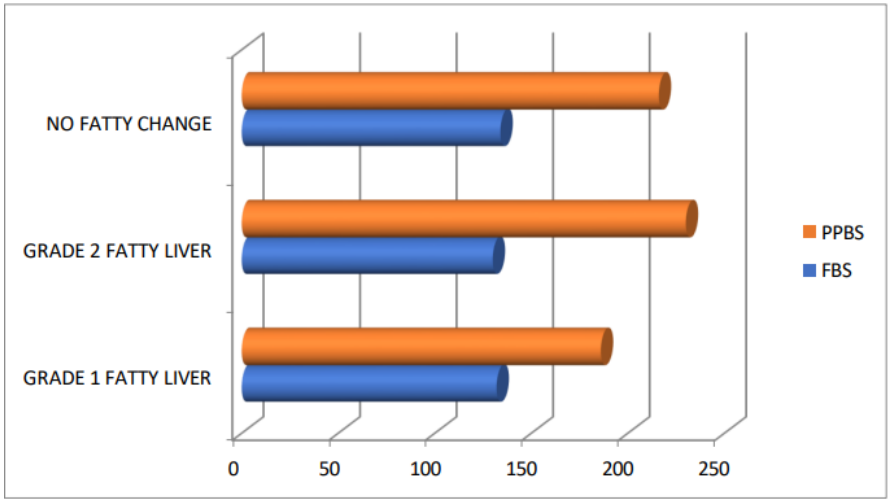

TABLE NO: 6 AGE WISE COMPARISION OF MEAN VALUE OF LIVER FUNCTION TESTS:(n=118) [MEAN ± SD]

Age	30-39yrs	40-49yrs	50-59yrs	60-69yrs	70-79yrs
STP	7.0±0.4	7.0±0.4	7.0±0.4	7.1±0.4	7.1±0.4
S.Albumin	4.0±0.4	4.3±0.4	4.0±0.4	4.0±0.4	4.3±0.4
S.Globulin	2.9±0.4	2.9±0.4	2.9±0.4	2.9±0.4	2.9±0.4
S.Bilirubin	0.9±0.3	0.9±0.3	0.8±0.3	1.0±0.3	1.2±0.3
AST	23±8	22±8	22±8	23±8	31±8
ALT	19±8	19±8	19±8	20±8	25±8
ALP	110±18	127±18	110±18	109±18	119±18

- Age-wise comparison of the liver function tests revealed no significant difference between the various age classes.

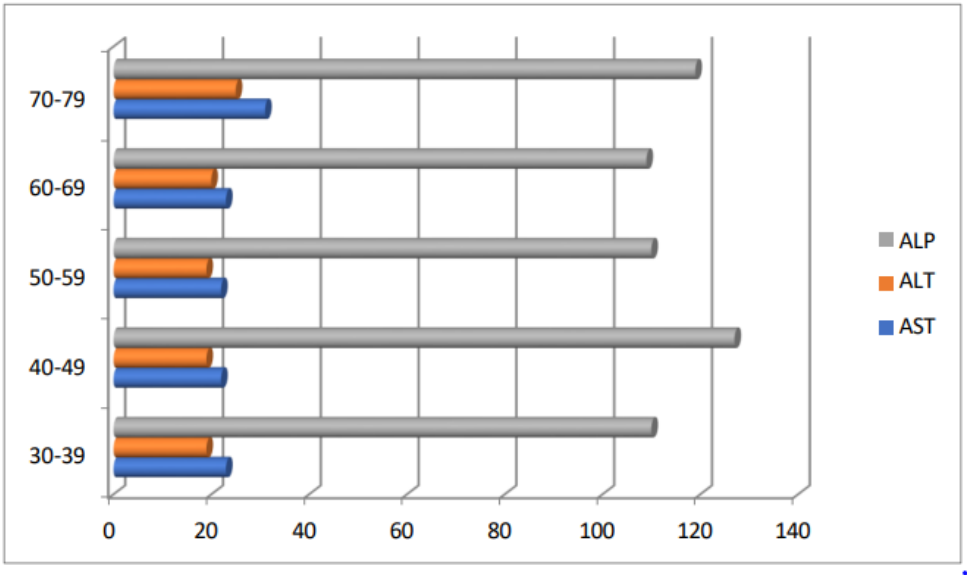

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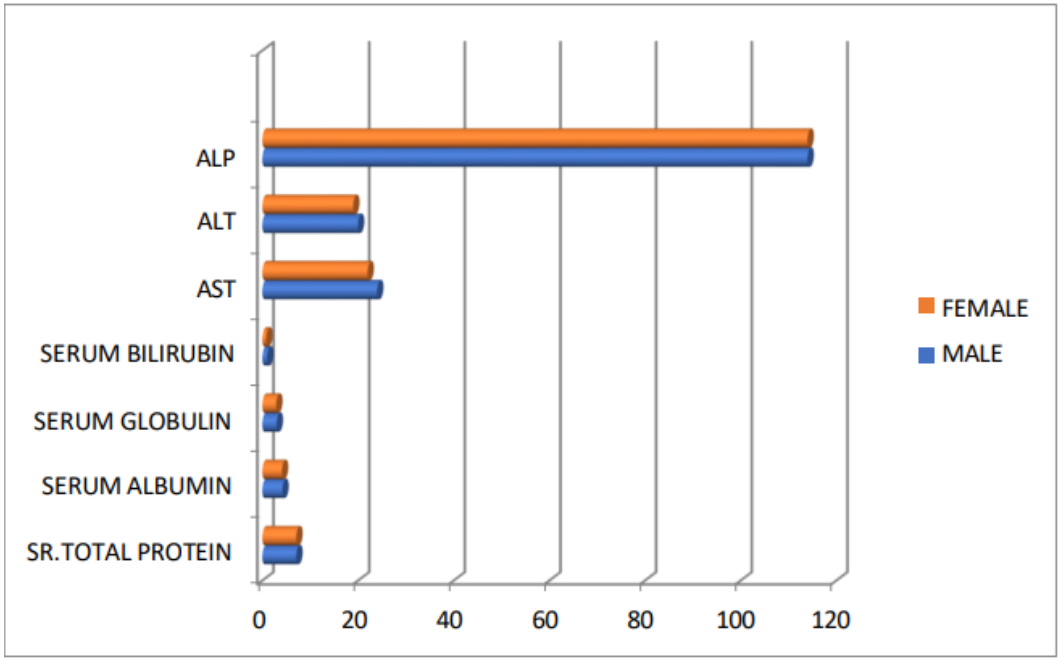
TABLE NO: 7 SEX WISE COMPARISION OF MEAN VALUE OF LIVER FUNCTION TESTS: (n=118)

INVESTIGATIONS	FEMALE	MALE
Serum Total Proteins	7.0±0.4	7.1±0.4
Serum Albumin	4.1±0.4	4.2±0.4
Serum Globulin	2.9±0.4	3.0±0.4
Serum Bilirubin	0.8±0.3	1.0±0.3
AST	22±8	24±8
ALT	19±8	20±8
ALP	114±18	114±18

- Sex-wise comparison of the liver function tests revealed no significant difference between sexes.



Rrecent fasting and 2 hr post prandial blood glucose values were done in all patients, 47 percent had a fasting glucose more than 126 mg% and 61% had a 2 hr post prandial glucose more than 200mg%. There was no significant difference between mean values across gender or age classes. Body mass index measurements revealed that 25 (35.2%) women were over weight (BMI>25) and 5 (7.0%) were obese (BMI>30). The numbers of overweight men were 12 (25.5%). No male patient was found to be obese.Ultra sonographic examination was done in all the patients, fatty liver was found to be more common in females. Overall 60 patients (50.8%) had fatty liver out of the 118 patients screened. Sex wise and BMI class wise distribution is given in tables 5 & 6. Hepatomegaly was identified in 16 (26.6%) patients of whom 11 were males. Asymptomatic gall stones were fouin 11 (18.3%) patients, 6 females and 5 males. Bile duct was found to be dilated (>5mm) in 6 patients, portal vein was normal (<12mm) in size in all the patients

TABLE NO: 8 SEX WISE DISTRIBUTION OF FATTY LIVER BY ULTASONOGRAM:(n=118)

FATTY LIVER	SEX	
	FEMALE(%)(n=71)	MALE(%) (n=47)
Grade 1	35 (49%)	15 (32%)
Grade 2	8(11%)	2(4%)
No Fatty Change	28 (40%)	30 (64%)

- Out of 71 female patients 35 (49%) had Grade 1 fatty change, 8(11%) had Grade 2 fatty change
- Out of 47 male patients 15 (32%) had Grade 1 fatty change ,2(4%) had Grade 2 fatty change

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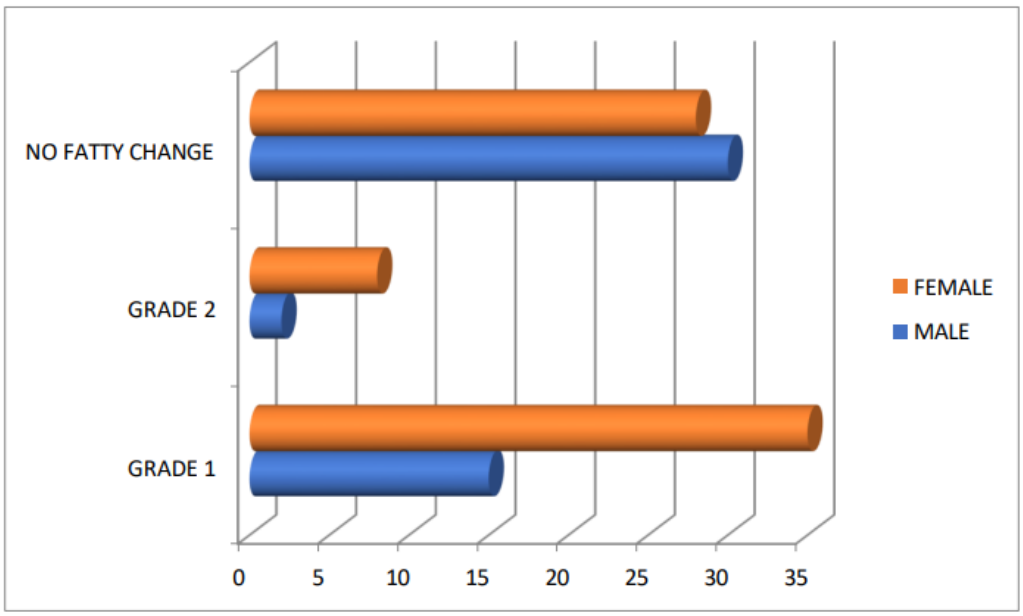

TABLE NO: 9 SEX WISE CORRELATION OF BMI : (n=118)

SEX	Underweight	Normal	Overweight	Obese	Morbidly Obese
MALE (n=47)	1	34	12	0	0
FEMALE (n=71)	1	40	25	5	0

- Body mass index measurements revealed that 25 (35.2%) women were over weight (BMI>25) and 5 (7.0%) were obese (BMI>30).
- The numbers of overweight men were 12 (25.5%) no male patient was found to be obese

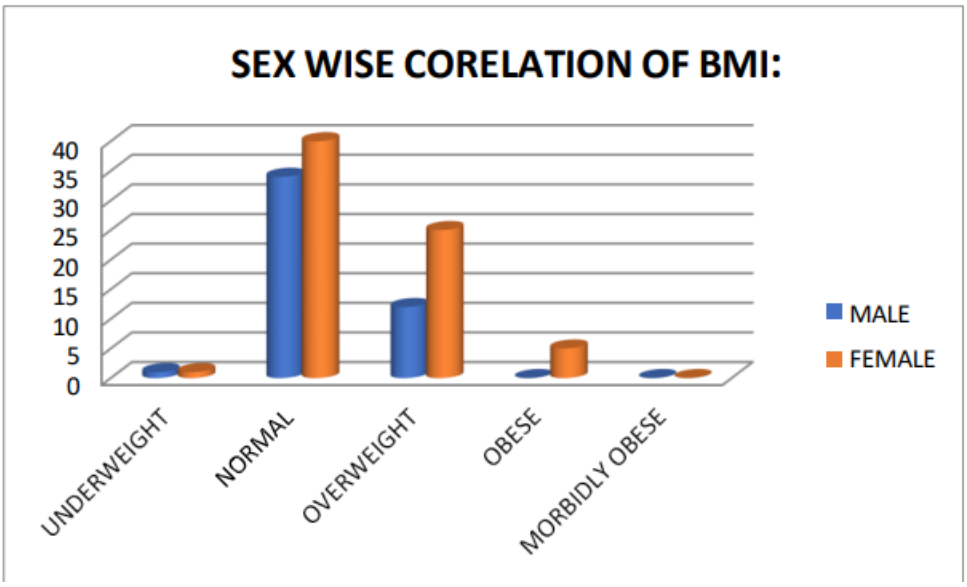

TABLE NO: 10 BMI CLASS WISE DISTRIBUTION OF FATTY LIVER BY ULTRASONOGRAM: (n=118)

Fatty Liver	Underweight (n=2)	Normal (n=58)	Overweight (n= 53)	Obese (n=5)	Morbidly Obese (n=0)
Grade 1	0%	6(28%)	29(55%)	5(100%)	0%
Grade 2	0%	0%	10(19%)	0%	0%
No Fatty Change	2(100%)	42(72%)	14(26%)	0%	0%

- In patients with normal BMI, 16(28%) had Grade 1 fatty change & 0% had Grade 2 fatty change.
- In patients who were Overweight 29(55%) had Grade 1 fatty change & 10(19%) had Grade 2 fatty change.
- In patients who were Obese, 5(!00%) of them had Grade 1 fatty change.

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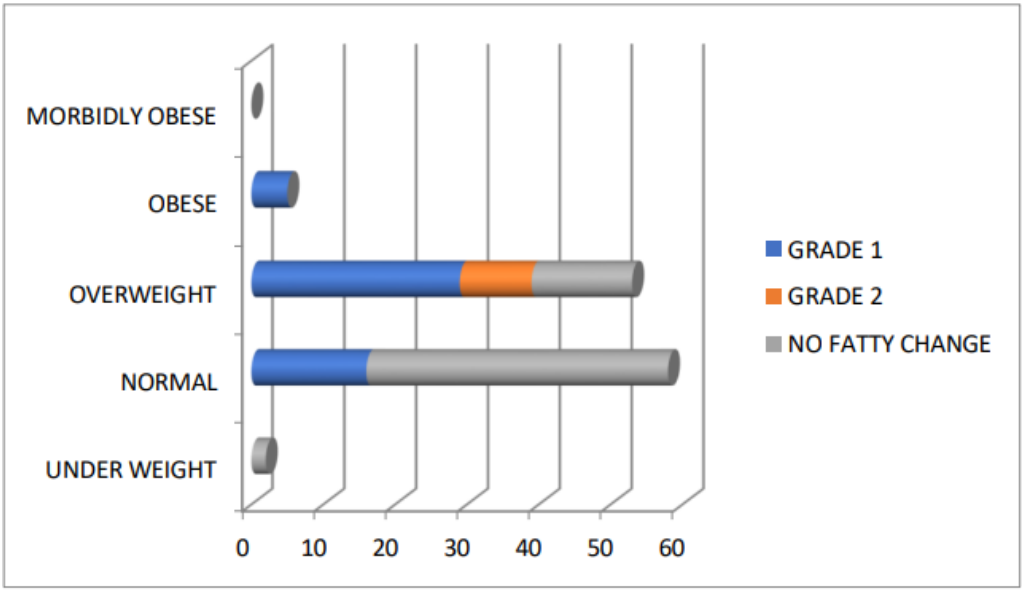

TABLE NO: 11 MEAN VALUES OF LIVER ENZYMES IN CORRELATION WITH GRADE OF FATTY CHANGE: (n=118)

ENZYMES	GRADE 1 FATTY LIVER	GRADE 2 FATTY LIVER	NO FATTY CHANGE
AST	22±8	21±8	21±8
ALT	19±8	17±8	18±8
AST/ALT	1.2±0.2	1.2±0.2	1.2±0.2
ALP	121±18	77±18	110±18

- Our study also did not find a significant elevation of any of the liver enzymes. There was no clinically significant difference between the parameters among patients with fatty liver and those without fatty liver.
- Eighty five percent of the patients in this study had AST/ALT ratio more than one, but it was not found to have any association with fatty liver.

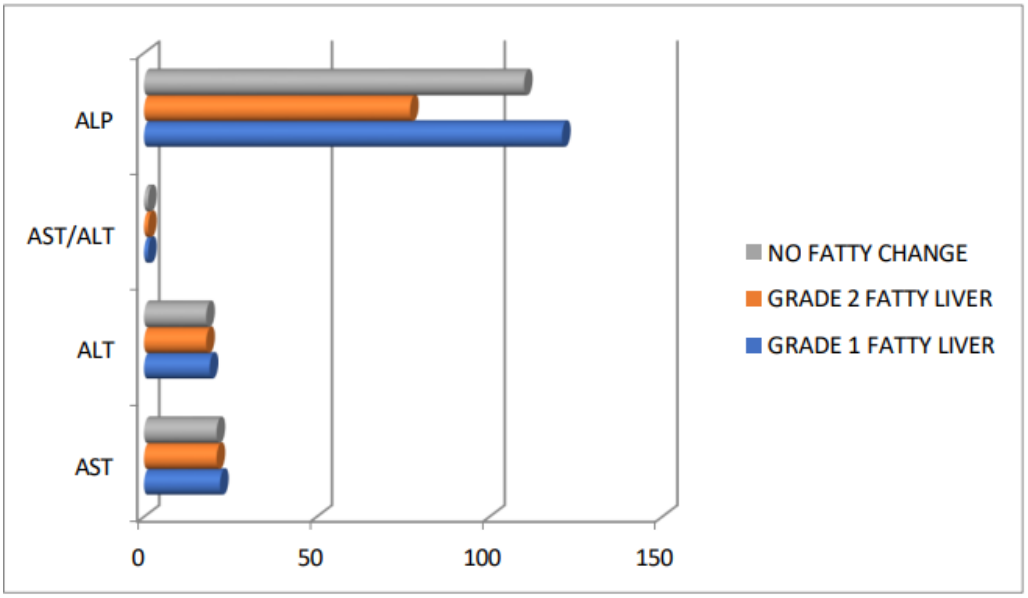

TABLE NO: 12 MEAN FASTING AND POST PRANDIAL BLOOD GLUCOSE IN PATIENTS WITH FATTY LIVER

Blood Glucose	Grade 1 fatty liver	Grade 2 fatty liver	No fatty change
Fasting	132±45	130±45	134±45
2 Hr Post prandial	186±54	230±54	216±54

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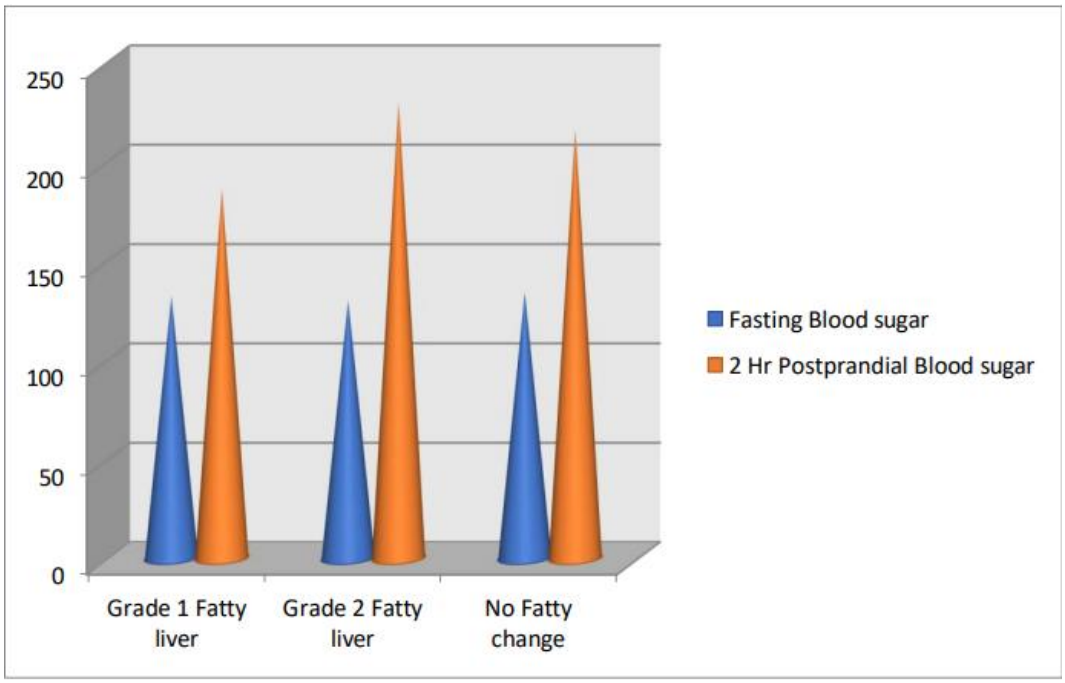

Mean fasting and post prandial blood glucose levels in patients with and without fatty liver did not reveal significant difference.

DISCUSSION

Since clinical symptoms of fatty liver are nonspecific or silent this study does not attempt to define the clinical symptoms of fatty liver. Fatty liver most commonly affects middle-aged women with obesity, altered glucose metabolism and hyperlipidemia.

Age, Gender and Obesity

As reported by Kelly et all[28] there was no difference in the mean age of patients with fatty liver as compared to those with normal liver. Sixty percent of the patients with fatty liver in this study were females but no significant difference in proportion based on gender was found in those with grade 1 fatty liver compared to those without evidence of fatty liver. Obesity was found to have a significant association with fatty liver, in the current study 57% of patients with grade 1 fatty liver had a BMI more than 25kg/m² and 17% patients had grade 2 fatty liver. All 5 patients who were found to be obese had fatty liver.

Liver enzymes

Reid etal[14] and Dixon et al[15]found elevated AST levels in patients with NASH. Laboratory abnormalities identified included a 2-4-fold elevation of serum amino transferase levels while other liver function test results were normal. Agarwal etal[16] and Kelly et al[28] documented elevation of ALT as the biochemical abnormality in patients with NASH. A recent study found that patients with NASH and those with higher grade of histological inflammation had increment of transaminases and albumin levels . The same study showed a correlation of fibrosis with AST and ALT levels. Elariny et al showed that while ALT was associated with NASH and advanced fibrosis, the majority of the patients with either NASH or advanced fibrosis had normal AST.[13] An AST/ALT ratio >1.0 was yet another finding in a study on NASH[15].Contrary to all these a study in 2003 found liver enzymes to be insensitive and unreliable to confirm the diagnosis or stage the extent of fibrosis. Older age, obesity, and diabetes were shown to be predictive of fibrosis.

Our study also did not find a significant elevation of any of the liver enzymes. There was no significant difference between the parameters among patients with grade 1 fatty liver and those without fatty liver. Eighty five percent of the patients in this study had AST/ALT ratio more than one, but it was not found to have any association with fatty liver.The mean duration of Diabetes in persons with NAFLD was 5.47 ± 3.19years and the mean duration of Diabetes in persons with Normal liver in USG was 5.47 ± 3.94 years.No statistically significant relationship was found between the presence of NAFLD, type of Hypoglycemic drugs used and the duration of Diabetes.

The result were similar to the study conducted in Saudi Arabia (Daad H Akbar et al[55]).

The mean Body Mass Index in the Fatty change group was significantly higher than that of the normal group. In the study done by Daad H Akbar et al[55] in Saudi Arabia, Obesity was identified as an independent factor for the development of NAFLD.

CONCLUSION

- Non invasive methods are the need of the hour for early and wide screening to detect this disease. Persons with higher BMI are at greater risk of

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developing NAFLD.

No significant correlation was found between age of patient, duration of diabetes fasting blood sugar levels and NAFLD.Liver enzymes were thought to be a potential non invasive strategy for early detection of this disease, but the present study did not find any correlation of the level of liver enzymes and the degree of fatty liver in Indian patients.

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