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A CLINICAL PROSPECTIVE STUDY TO ESTIMATE THE RELATIONSHIP BETWEEN NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND METABOLIC SYNDROME

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Abstract

Background: Non-Alcoholic Fatty Liver disease (NAFLD) is emerging as the most common liver disease in industrialized and many developing countries. Prevalence of NAFLD is rising due to the change in lifestyle habits, diet and obesity and is increasingly recognized as a major contributor to the burden of chronic liver disease world-wide. NAFLD appears to be the hepatic manifestation of the metabolic syndrome as they have common pathogenesis arising from insulin resistance, central adiposity & chronic low-grade inflammation. It includes a spectrum of diseases that ranges from simple steatosis or steatosis with mild inflammation to steatohepatitis which in turn can progress to cirrhosis in 15 to 20 percent of the patients Progression is often silent. The major features of metabolic syndrome include central obesity, fasting Hyperglycemia, hypertriglyceridemia, low levels of high density lipoproteins (HDL), and hypertension. Therefore, this study deals with the correlation between NAFLD and metabolic syndrome and its component and its various complications. To Study the association between Non-Alcoholic Fatty Liver Disease and Metabolic Syndrome. To estimate the prevalence of Non-alcoholic fatty liver disease among metabolic syndrome subjects. To correlate the components of metabolic syndrome with Non-alcoholic fatty liver disease.

Material and Methods: A cross sectional hospital-based study was conducted on a total of 100 subjects at kempegowda institute of medical sciences, Bangalore from November 2018 to November, 2020. Subjects who are above the age of 18 years fulfilling the International Diabetic Federation (IDF) criteria for metabolic syndrome were included. Exclusion criteria were taken care of. A detailed history, clinical examination was done on the subjects, later they were subjected to necessary investigations like Ultrasound Abdomen. Liver Function Tests, HBsAg, HCV Antibodies, Lipid profile and Blood sugar levels. NAFLD was diagnosed using the Ultrasonography. Results were interpreted. **Results:** In our study, prevalence of NAFLD in Metabolic syndrome was 88%. There is positive correlation of

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NAFLD with MS and its components such as waist circumference, fasting blood sugars and dyslipidaemia. About 20% of the NAFLD subjects manifested with severe liver disease in the form of NASH/cirrhosis which was alarming and was associated positively with the severity of various components of metabolic syndrome like waist circumference and dyslipidaemia.

Conclusion: The need of screening MS patients for undiagnosed NAFLD has been reinforced by this study.

Keywords: Metabolic syndrome; Non-alcoholic fatty liver disease; cirrhosis.

Introduction

Nonalcoholic fatty liver disease is emerging as the most common liver disorders in industrialized countries and many developing countries. NAFLD is probably the most common liver disorder in the world affecting 2.8%-24 % of the general population.[1]

It exists as a histologic spectrum ranging from simple steatosis or steatosis with mild inflammation (types 1 and types 2 NAFLD) to more severe steatohepatitis (types 3 and 4 NAFLD or Non-alcoholic steatohepatitis (NASH). Types 1 and 2 NAFLD infrequently progress to cirrhosis but types 3 and 4 NAFLD progress to cirrhosis in as many as 15-20 % patients. Progression is often silent and paradoxically it is often associated with normalization of the aminotransferases. In addition to the usual complications of cirrhosis and portal hypertension, hepatocellular carcinoma is now recognized as a late complication of NAFLD. NASH related cirrhosis is an increasing indication for Liver transplantation.[2]

The leading causes of death overall are coronary artery disease (10%), extrahepatic malignancy (5%), and cirrhosis-related death (2%).[2]Survival in NAFLD is influenced by its association with the metabolic syndrome.

Metabolic syndrome: The metabolic syndrome is a cluster of cardiometabolic conditions, generally characterised by an expansion of the adipose visceral tissue, -which include type 2 Diabetes mellitus, atherogenicdyslipidaemia (low HDL and high triglycerides) and high blood pressure.[3,4] This multi-system condition has adverse effects on many organs, the liver being one of them.[5]

Metabolic syndrome has become one of the major public health challenges worldwide.[6]

It was first described as a cluster of metabolic abnormalities, with insulin resistance as the central pathophysiological feature, and was labelled as „Syndrome X".[7]

This syndrome affects 1 in 5 people worldwide, with the prevalence mirroring the rapid rise in obesity.[8] Prevalence of MS in Europe varies from 12-26% depending on geographical area, urbanization and ethnic mix.[9] Studies in Asia, suggest the prevalence is 5 to 20% with an overall global prevalence of 16% of the adult population.[10] Prevalence in India appears to be highest at around 26% of the adult urban population and prevalence appears to be increasing as obesity rates and urbanization increase.[5]

The prevalence of NAFLD pooled for Asian countries was estimated to be 27.4 %. Even in Rural regions of India including parts of Maharashtra and Haryana the prevalence of NAFLD had increased to 28.1% in 2015 to 30.7% in 2016 respectively. over the past three decades changing lifestyles and dietary habits have set the stage for the obesity and NAFLD epidemic in Asia.[11] NAFLD is estimated to affect as many as a third population and up to 70% of diabetic and obese subjects in the united states.[12] As a result of obesity pandemic in many parts of the world, the global burden of NAFLD is projected to increase over the next decade,

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raising concerns that an increasing proportion of the population will develop cirrhosis and end stage liver disease with age.[13]

NAFLD appears to be the hepatic manifestation of metabolic syndrome, and is increasingly recognised as a major contributor to the burden of chronic liver disease world-wide. Metabolic syndrome and non-alcoholic fatty liver disease appear to have a common pathogenesis, arising from insulin resistance, central adiposity and chronic low grade inflammation. Treatment of metabolic syndrome may have a significant impact on progression of non-alcoholic fatty liver disease, and therapeutic options treating the underlying cause of metabolic syndrome (weight loss and insulin sensitising drug therapy) appear to be valid options in treating liver disease to prevent progression to fibrosis and cirrhosis.[5]

Objectives

1. To Study the association between Nonalcoholic Fatty Liver Disease and Metabolic Syndrome.
2. To estimate the Prevalence of Nonalcoholic fatty liver disease among metabolic syndrome subjects.
3. To correlate the components of metabolic syndrome with Nonalcoholic fatty liver disease.

Material and Methods

Duration of Study: November 2018 to November 2020

Place of Study: Dept. of General Medicine, Kimsh, Bangalore

Type of study: Observational

Inclusion Criteria:

1. Subjects with metabolic syndrome (defined by IDF criteria) who are above the age of 18 years

Patients fulfilling IDF criteria for metabolic syndrome (as mentioned below):

According to new International Diabetic Federation **(IDF) criteria,**[9] for a person to be defined as having the metabolic syndrome they must have:

Central obesity – defined as waist circumference >/= 90cm for men and >/= 80 cm for women (Indian population).

Plus any two of the following four factors

1. Raised triglyceride (TG) level >/= 150mg/dl or specific treatment for this lipid abnormality.
2. Reduced High Density Lipid (HDL) cholesterol <40mg/dl in males and <50mg/dl in females, or specific treatment for this lipid abnormality.
3. Raised arterial blood pressure (B.P) systolic > 130mm of Hg, diastolic > 85mm of Hg or treatment for previously diagnosed hypertension.
4. Raised Fasting Blood Glucose (FBG) >100mg/dl or previously diagnosed type 2 diabetes.

Exclusion Criteria:

1. Alcohol consumption greater than or equal to 20 g/d in women and 30 g/day in men.
2. Known hepatic diseases, HbsAg, HCV positive subjects.
3. Subjects on medications like corticosteroids amiodarone, tamoxifen, methotrexate or high dose estrogens, anti-HIV drugs.

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4. Subjects who have undergone Jejunoileal bypass or extensive small bowel resections.
5. Pregnancy.

Methods: Subjects who are above the age of 18 years who fulfill the inclusion (metabolic syndrome) and exclusion criteria were enrolled into the study.

International Diabetic Federation (IDF) Criteria was used for defining the metabolic syndrome

A detailed history, clinical examination emphasizing on waist circumference Blood pressure measurement following standard methods was done on the subjects, later they were subjected to necessary investigations and results were interpreted.

a) Waist circumference was measured midway between the lower rib and iliac crest.
b) Blood pressure - was recorded as the mean of three measurements taken at 1 min intervals using standard sphygmomanometer.
c) Fasting glucose and Fasting lipid profile were measured after overnight fast in whole blood using hexokinase-based assay and CHOD-PAP immune-colorimetric assay respectively.

The following investigations were done on the subjects:

a) Ultrasound Abdomen
b) Liver Function Tests
c) HBsAg, HCV Antibodies
d) Fasting Lipid profile
e) Blood sugar levels

Ultrasonography detects steatosis by echogenicity and sound attenuation with defined Criteria as mentioned above.

Method of Statistical Analysis: The following methods of statistical analysis have been used in this study.

Statistical Analysis: Statistical Package for Social Sciences [SPSS] for Windows, Version 22.0. Released.

2013. Armonk, NY: IBM Corp., was used to perform statistical analyses.

Descriptive Statistics: Descriptive analysis of all the explanatory and outcome parameters was done using mean and standard deviation for quantitative variables, frequency and proportions for categorical variables.

Results

Table 1: Gender wise distribution of study subjects:

Variable	Category	n	%
Sex	Males	41	41%
	Females	59	59%

A total of 100 patients were included in the study out of which 41(41%) were male and 59 (59%) were female.

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Table 2: Age Wise Distribution of Study Subjects

Variable	Category	n	%
Age	31-40 years	9	9%
	41-50 years	26	26%
	51-60 years	29	29%
	61-70 years	28	28%
	> 70 years	8	8%
		Mean	SD
	Mean & SD	55.97	11.07
	Range	31 - 78	

Majority of the patients in this study were middle aged with a mean age of 55+/-11 years. Here, 29% subjects taken were between the age group 51-60 years, 28% were from the age group 61-70 years and 26% were from the age group 41-50 years. Only 9% of the subjects were below the age of 40 and 8% above the age of 70. There-fore maximum study subjects were from 41-70 years but the subjects were taken ranging from the age 31 to 78 years.

Table 3: Age Wise Distribution of NAFLD and Non-NAFLD Groups

Mean Age (in yrs.) comparison between NAFLD & Non NAFLD groups using Mann Whitney Test						
Variable	**Category**	**NAFLD (n=88)**		**Non NAFLD (n=12)**		**P-Value**
		Mean	**SD**	**Mean**	**SD**	
Age	Mean & SD	55.24	11.24	61.33	8.28	0.06
	Range	31 - 78		48 - 72		

In this study, mean age of prevalence of NAFLD was 55.24+/-11.24. The age of the subjects, who had NAFLD ranged from 31-78 years whereas, the mean age of the non-NALFLD subjects was 61.33+/-8.28. The age of these subjects ranged from 48-72 years. Though prevalence of NAFLD showed an onset at lower age as compared to Non NAFLD subjects it wasn't significant.

Table 4: Prevalence of NAFLD among Metabolic Syndrome Subjects

Variable	Category	n	%
NAFLD	Present	88	88%
	Absent	12	12%

In this study out of 100 subjects of metabolic syndrome, 88 subjects had Non- Alcoholic Fatty liver disease detected by the ultrasonography and 12 subjects had normal liver. Thus making the prevalence of NAFLD in metabolic syndrome to be 88 percent in this study.

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Table 5: Comparison between the Components of Metabolic Syndrome and NAFLD

Components of Metabolic Syndrome and NAFLD among Study subjects					
Variable	Present (n=55)		Absent (n=9)		P-Value
	Mean	SD	Mean	SD	
Waist Circumference [a]	112.06	13.84	103.75	8.83	0.02*
FBS [a]	171.39	71.33	107.75	27.71	<0.001*
TG a	177.93	91.70	114.42	52.04	0.002*
HDL [a]	36.28	6.64	34.75	9.02	0.38
	n	%	n	%	
HTN [b]	65	73.9%	10	83.3%	0.48

*- Statistically Significant

Note: a. P-Value derived by Mann Whitney Test; b. P-value derived by Chi Square Test In this study: The mean waist circumference in the NAFLD group was 112.06 +/- 13.84 and in the non NAFLD group it was 103.75 +/- 8.83 which is significantly higher in the NAFLD group. (P value-0.02).

The mean FBS in the NAFLD group was 1721.39 +/-71.33 and in the non-NAFLD group it was 107.75 +/-27.71 which were significantly higher in the NAFLD group. (P value-<0.001).

The mean triglycerides values in the NAFLD group was 177.93+/-91.70 and in the non NAFLD group it was 114.42+/-52.04 which was significantly higher in the NAFLD group.(P value-0.002).

The mean value of HDL in the NAFLD group was 36.28 +/-6.64 and in the non-NAFLD group it was 34.75+/-9.02 and there was no statistically significant difference between the two groups. Here among the 88 NAFLD subjects 65 subjects (73.9%) had hypertension and in the 12 non NAFLD subjects, 10 had hypertension (83.3%) making any difference in the two groups statistically insignificant. Thus, we observed a significant positive correlation between Components of metabolic syndrome namely waist circumference, triglyceride levels and fasting blood glucose levels with NAFLD.

Table 6: Association between Other Comorbidities and NAFLD

Association between Other comorbidity conditions and presence of NAFLD among study subjects using Chi Square Test						
Comorbidity Conditions	**Category**	**NAFLD Present (n=88)**		**NAFLD Absent (n=12)**		**P-Value**
		n	**%**	**n**	**%**	
Diabetes Mellitus	Absent	14	15.9%	4	33.3%	0.14
	Present	74	84.1%	8	66.7%	
Hypertension	Absent	23	26.1%	2	16.7%	0.48
	Present	65	73.9%	10	83.3%	
Hypothyroidism	Absent	72	81.8%	11	91.7%	0.39
	Present	16	18.2%	1	8.3%	
Ischemic Heart Disease	Absent	71	80.7%	10	83.3%	0.83
	Present	17	19.3%	2	16.7%	

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Chronic Kidney Disease	Absent	82	93.2%	10	83.3%	0.24
	Present	6	6.8%	2	16.7%	
COPD	Absent	79	89.8%	12	100.0%	0.25
	Present	9	10.2%	0	0.0%	
Cerebrovascular Accident	Absent	83	94.3%	11	91.7%	0.72
	Present	5	5.7%	1	8.3%	
Dyslipidaemia	Absent	9	10.2%	2	16.7%	0.50
	Present	79	89.8%	10	83.3%	
Obs. Sleep Apnoea	Absent	82	93.2%	11	91.7%	0.85
	Present	6	6.8%	1	8.3%	
Bronchial Asthma	Absent	85	96.6%	11	91.7%	0.41
	Present	3	3.4%	1	8.3%	
Dilated Cardiomyopathy	Absent	84	95.5%	12	100.0%	0.45
	Present	4	4.5%	0	0.0%	

In this study, it's observed that 84.1 % of the NAFLD subjects had Diabetes mellitus and 66.7% of the non NAFLD subjects had diabetes mellitus, though the prevalence of diabetes mellitus was higher in NAFLD subjects it was not found to be statistically significant when compared to non NAFLD subjects.

Here among the 88 NAFLD subjects 65 subjects (73.9%) had hypertension and in the 12 non NAFLD subjects, 10 had hypertension (83.3%) making any difference in the two groups statistically insignificant. Similarly, Hypothyroidism was present in 18.2% of NAFLD subjects and 8.3% of the non NAFLD subjects; Ischemic heart disease was present in 19.3% of NAFLD subjects and 16.7% of the non NAFLD subjects; COPD was present in 10% of NAFLD subjects;

Dyslipidaemia was present in 89.8% of the NAFLD subjects and 83.3% of the non- NAFLD subjects and dilated cardiomyopathy was present in 4.5% of NAFLD subjects. Although the above comorbidities were more prevalent in the NAFLD group but there was no statistically significant difference between the two groups (NAFLD and non-NAFLD group).

Whereas, it is observed that chronic kidney disease was seen in 6.8% of the NAFLD subjects and 16.7% in the non-NAFLD subjects; cerebrovascular accident was seen in 5.7% of the NAFLD subjects and 8.3% in the non-NAFLD subjects; the prevalence of OSA was found to be 6.8% in NAFLD and 8.3% in non-NAFLD subjects; bronchial asthma was found in 3.4% of the NAFLD subjects and 8.3% in non-NAFLD subjects and the above comorbidities didn't show higher prevalence in the NAFLD group.

Table 7: Comparison of LFT Parameters and NAFLD

Comparison of mean values of LFT parameters between subjects with and without NAFLD using Mann Whitney Test						
Parameters	**NAFLD**	**N**	**Mean**	**SD**	**Mean Diff**	**P-Value**
TB (mg/dl)	Present	88	0.815	0.517	0.353	0.009*
	Absent	12	0.463	0.214		
DB (mg/dl)	Present	88	0.358	0.342	0.108	0.19

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	Absent	12	0.250	0.250		
AST (IU/ml)	Present	88	37.011	18.984	13.261	0.03*
	Absent	12	23.750	9.845		
ALT (IU/ml)	Present	88	35.830	20.472	13.747	0.02*
	Absent	12	22.083	10.457		
TP (mg/dl)	Present	88	7.233	6.598	0.625	0.87
	Absent	12	6.608	0.665		
S ALB (mg/dl)	Present	88	3.501	2.747	-0.474	0.003*
	Absent	12	3.975	0.738		

When comparison was made between the various parameters of Liver function test in subjects with NAFLD and non NAFLD subjects it was found that: The mean value of total bilirubin was 0.815+/-0.517 in NAFLD subjects and 0.463+/-0.214 in non NAFLD subjects and was significantly higher in NAFLD subjects. (P value-0.009).

The mean value of DB in NAFLD subjects was 0.358+/-0.342 and the mean value in non NAFLD subjects was 0.250+/-0250 and was higher in the NAFLD subjects but was not found to be statistically significant.

The mean value of AST was 37.01+/-18.94 in NAFLD Subjects and 23.75+/-9.84.5 in non-NAFLD subjects which was significantly higher in the NAFLD subjects with a P value-0.03.

The mean value of ALT was 35.830+/-20.472 in NAFLD subjects and 22.083+/-10.457 in non-NAFLD subjects and showed statistically significant elevated values among NAFLD subjects compared to Non NAFLD (P value-0.02).

The mean value of S. albumin was 3.501+/-2.747 in NAFLD Subjects and 3.975+/-0.738 in non-NAFLD subjects and was significantly lower in NAFLD subjects. (p value -0.003). The mean value of TP in NAFLD was 7.23+/-6.598 and in non-NAFLD it was 6.608+/-0.665 and the mean difference wasn't found to be statistically significant.

Therefore, we see that there was a statistically significant correlation between LFT parameters namely total bilirubin and AST, ALT, S. albumin and NAFLD. The rest of the parameters of LFT didn't show positive correlation with NAFLD.

Table 8: Prevalence of NASH

Prevalence of **NASH among *NAFLD subjects			
Variable	**Category**	**n**	**%**
NAFLD to NASH	NAFLD	70	79.5%
	NASH	18	20.5%

This table shows the prevalence of NASH/ CIRRHOSIS among NAFLD subjects. Among 88 subjects who had NAFLD, 18 subjects were found to have NASH. Therefore 20.5 % of the NAFLD subjects had NASH/ cirrhosis and (18% of the MS patients had NASH/Cirrhosis) here on *NAFLD refers to the Non-NASH NAFLD subjects and **NASH refers to the subjects with cirrhosis.

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Table 9: Age Wise Comparison between NAFLD and Nash/Cirrhosis Groups

Mean Age (in years) comparison between NAFLD & NASH/CIRRHOSIS groups using Mann Whitney Test						
Variable	**Category**	**NAFLD (n=70)**		**NASH (n=18)**		**P-Value**
		Mean	**SD**	**Mean**	**SD**	
Age	Mean & SD	53.61	11.16	61.56	9.36	0.004*
	Range	31 - 78		42 - 75		

The mean age of prevalence of NAFLD (non-cirrhosis) subjects in this study was found to be 53.61+/-11.16 and the mean age of the cirrhotic subjects was found to be 61.56+/-9.36 which was higher in the NASH OR CIRRHOSIS group and was statistically significant (p value0.004) implying that the prevalence of cirrhosis increases with the age and disease progresses with the age.

Table10: Gender Wise Comparison between NAFLD and Nash/Cirrhosis Groups

Gender wise comparison of prevalence of NAFLD in Metabolic Syndrome and presence of NASH among NAFLD subjects using Chi Square Test							
Variables	**Category**	**Males**		**Females**		**χ^2 Value**	**P-Value**
		n	**%**	**n**	**%**		
NAFLD in MS	Present	36	87.8%	52	88.1%	0.003	0.96
	Absent	5	12.2%	7	11.9%		
NASH in NAFLD	NAFLD	29	80.6%	41	78.8%	0.038	0.85
	NASH	7	19.4%	11	21.2%		

In this study, when gender wise comparison was done between NAFLD and non-NAFLD group among the Metabolic Syndrome subjects there was no major statistical (P value-0.96) difference and was equally prevalent in both the genders although it was a female predominant study. Female subjects taken were 59 and male subjects taken were 41 and 88.1% and 87.8% respectively were found to have NAFLD. Also, when comparison was made between the two genders between the NAFLD and the NASH/cirrhosis groups among the study subjects there was no significant difference between the two genders. Here 21.2% of the female NAFLD subjects had NASH/Cirrhosis and 19.4% of the male NAFLD subjects had NASH. (Chi square -0.038 and P value-0.85). Thus, depicting no correlation of single gender with NAFLD and also its progression to cirrhosis.

Table 11: Comparison of Components of Metabolic Syndrome between NAFLD and Nash/Cirrhosis Subjects

Comparison of mean values of different components pertaining to Metabolic syndrome b/w NAFLD & NASH subjects using Mann Whitney Test						
Components	Category	N	Mean	SD	Mean Diff	P-Value
WC	NAFLD	70	111.36	14.75	-3.42	0.03*
	NASH	18	114.78	9.33		
FBS	NAFLD	70	174.83	77.32	16.83	0.99
	NASH	18	158.00	39.22		

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TG	NAFLD	70	181.91	97.80	24.15	0.76
	NASH	18	158.72	62.46		
HDL	NAFLD	70	38.43	7.19	5.04	0.003*
	NASH	18	32.28	6.72		

In this study, it was found that the mean value of WC among NAFLD subjects was 111.36+/14.75 and among NASH subjects it was 114.78 +/-9.33. (Mean diff - -3.42 and p value- 0.03) which was significantly higher among NASH/cirrhosis subjects showing positive correlation with severity of NAFLD.

The mean value of FBS among NAFLD subjects 174.83+/-77.32 and in cirrhosis subjects it was 158+/-39.22 and it was lower in the cirrhosis subjects probably due to progression of the liver disease where liver healthy liver takes oart in gluconeogenesis and glycogenolysis.

The mean value of HDL among NAFLD subjects was 38.43+/-7.19 and among NASH subjects was 32.28+/-6.72 and was significantly lower among NASH subjects (P value- 0.003) showing positive correlation of low levels of HDL with severity of NAFLD.

The mean value of TG in NAFLD subjects was 181.91+/-97.80 and in NASH subjects it was 158.72+/-62.42 which was lower in the NASH subjects.

Table 12: Comparison of LFT Parameters between NAFLD and Nash/Cirrhosis Subjects

Comparison of mean values of LFT parameters between NAFLD & NASH subjects using Mann Whitney Test						
Parameters	Category	N	Mean	SD	Mean Diff	P-Value
TB (mg/dl)	NAFLD	70	0.768	0.480	-0.232	0.13
	NASH	18	1.000	0.621		
DB (mg/dl)	NAFLD	70	0.326	0.332	-0.157	0.02*
	NASH	18	0.483	0.360		
AST (IU/ml)	NAFLD	70	37.643	19.986	3.087	0.79
	NASH	18	34.556	14.666		
ALT (IU/ml)	NAFLD	70	34.486	19.049	-6.570	0.34
	NASH	18	41.056	25.213		
TP (mg/dl)	NAFLD	70	7.506	0.375	1.334	0.03*
	NASH	18	6.172	0.714		
S ALB(mg/dl)	NAFLD	70	3.767	0.017	1.300	<0.001*
	NASH	18	2.467	0.490		

In this study, when LFT parameters were compared between Non-NASH NAFLD and NASH/cirrhosis using Mann Whitney test the following were observed:

The mean value of TB was 0.768+/-0.480 in NAFLD and1.0 +/-0.621 in NASH which was higher in NASH but difference wasn't statistically significant. The mean value of DB was 0.326+/-0.332 in NAFLD subjects and was 0.483+/-0360 in NASH subjects (mean diff- -0.157 & P value -0.02), was significantly higher in NASH subjects thus showing positive correlation of direct bilirubin with severity of NAFLD.

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The mean value of AST and ALT were 37.643+/-19.986 and 34.486+/-19.049 respectively in NAFLD subjects. The mean value of AST and ALT were 34.556+/-14.666 & 41.056+/25.213 respectively in NASH subjects, the mean difference of which was not statistically significant but noticeably ALT was higher in NASH patients.

The mean value of TP was 7.506+/-0.375 in NAFLD subjects and was 6.172+/-0.714 in NASH group which showed statistically significant difference between the two groups with NASH having lower levels of Total protein. (Mean diff- 1.334 & P value-0.03). Thus, showing positive correlation between the synthesis of total protein and severity of NAFLD.

The mean value of S. Albumin was 3.767+/-0.017 in NAFLD group and was 2.467+/-0.490 in NASH subjects which showed statistically significant lower values in the NASH/cirrhosis group (P value-0.001). Again, showing positive correlation between the low serum albumin levels and the severity of NAFLD.

Table 13: Comparison of Association of Other Comorbidities among NAFLD and Nash/Cirrhosis Subjects.

Association between Other comorbidity conditions and Presence of NAFLD & NASH among study subjects using Chi Square Test						
Comorbidity Conditions	Category	NAFLD (n=70)		NASH (n=18)		P-Value
		n	%	n	%	
Diabetes	Absent	13	18.6%	1	5.6%	0.18
	Present	57	81.4%	17	94.4%	
Hypertension	Absent	17	24.3%	6	33.3%	0.44
	Present	53	75.7%	12	66.7%	
Hypothyroidism	Absent	60	85.7%	12	66.7%	0.06
	Present	10	14.3%	6	33.3%	
Ischemic Heart Disease	Absent	55	78.6%	16	88.9%	0.32
	Present	15	21.4%	2	11.1%	
Chronic Kidney Disease	Absent	64	91.4%	18	100.0%	0.20
	Present	6	8.6%	0	0.0%	
COPD	Absent	63	90.0%	16	88.9%	0.89
	Present	7	10.0%	2	11.1%	
Cerebrovascular Accident	Absent	67	95.7%	16	88.9%	0.27
	Present	3	4.3%	2	11.1%	
Dyslipidaemia	Absent	9	12.9%	0	0.0%	0.11
	Present	61	87.1%	18	100.0%	
Obs. Sleep Apnoea	Absent	65	92.9%	17	94.4%	0.81
	Present	5	7.1%	1	5.6%	
Bronchial Asthma	Absent	67	95.7%	18	100.0%	0.37
	Present	3	4.3%	0	0.0%	
Dilated Cardiomyopathy	Absent	68	97.1%	16	88.9%	0.13
	Present	2	2.9%	2	11.1%	

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In this study, It was found that type 2 DM was found in 81.4% of the NAFLD subjects and 94.4 % of the NASH subjects which showed high prevalence in NAFLD subjects but showed higher prevalence in NASH subjects thus showing a positive correlation with the severity of NAFLD but wasn't statistically significant (P value-0.18)

Hypertension showed higher prevalence in NAFLD and was found in 75.7% of the (non-NASH) NAFLD subjects and in 66.7% of NASH/cirrhosis subjects and did not show any positive correlation with the severity of NAFLD.

Hypothyroidism was present in 14.3 % of the NAFLD subjects and 33.3% of the NASH subjects and was more prevalent in NASH subjects. No statistical significance was seen between hypothyroidism and severity of NAFLD.

IHD was seen in 21.4% of the NAFLD subjects and 11.1% of the NASH subjects and was more common in the non-NASH NAFLD group and showed no statistical significance. CKD was found in 8.6 % of the NAFLD subjects and was not found in any of the NASH study subjects here in this study COPD was found in as few as 10% subjects in NAFLD and 11.1% of the NASH subjects but no statistical correlation could be derived between COPD and severity of NAFLD.

CVA was seen in 4.3% of the NAFLD subjects and 11.1% of the NASH subjects and was markedly more common in NASH as compared to NAFLD subjects as a vascular complication but the correlation of CVA with severity showed no statistical significance.

Dyslipidaemia was seen in 87.1% of the NAFLD subjects and was present in 100% of the NASH group thus more prevalent in NASH group but p value was 0.11 making it statistically not significant OSA was present in 7.1% of the NAFLD subjects and 5.6% of the NASH subjects and showed no correlation between OSA and severity of NAFLD.

Dilated cardiomyopathy was seen in 2.9% of NAFLD subjects and 11.1% of the NASH subjects and was more prevalent in NASH subjects as a cardiovascular complication but statistical significance wasn't found.

Discussion

NAFLD is known to be associated with various metabolic abnormalities including central obesity, type 2 Diabetes mellitus, Dyslipidaemia and hypertension which are well established cardiovascular risk factors and collectively termed as "Metabolic syndrome". Liver ultrasonography is frequently used to assess fatty infiltration. In this study using the above two concepts various conclusions pertaining to our aims and objectives were made.

It is still not known whether NAFLD is a cause or consequence of metabolic dysfunction, thus making this study one of its kind. It has also been hypothesized that NAFLD may be hepatic manifestation of Metabolic syndrome.[5]

In this Cross-sectional study a total of 100 subjects above 18 years of age fulfilling the IDF criteria of metabolic syndrome were taken. Exclusion criteria were taken care of. Required investigations were done as already mentioned which included ultrasonography to detect NAFLD. Further the results and conclusion were interpreted as follows.

In this study maximum distribution of the study subjects with metabolic syndrome was between the ages 41-70 years. The highest no of subjects were between 51-60 years with a prevalence of 29% in this age group (mean age 55.9). The mean age of prevalence of NAFLD was 55.24+/-11.24 and the mean age of prevalence of NASH was 61.56+/-9.36. Similarly, in

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a prospective study by Priyanka jain et al it was found that distribution of NAFLD was higher in patients with age group greater than 55 which means NAFLD increases with increasing age[16]. According to study by Agrawal R et al,[17] the mean age for maximum prevalence of NAFLD was found to be 41.29+/-10.32 and also more than 65% were males and the rest females. But In the present study, we had 59 females and 41 males fulfilling the criteria for metabolic syndrome. The female predominance may be due to the higher prevalence of alcoholism in males than in females in our country. Nonetheless the prevalence of NAFLD was 87.8% in males and 88.1% in females and there was no significant difference between the two genders.

Also, when comparison was made between the two genders in view of prevalence of NASH among the study subjects there was no significant difference between the two genders.

Here 21.2% of the female NAFLD subjects had NASH/Cirrhosis and 19.4% of the male NAFLD subjects had NASH. (Chi square -0.038 and P value-0.85).Thus, depicting no correlation of single gender with NAFLD. In contrast, according to Agrawal PK et al the prevalence of NAFLD was found to be higher among male population as compared to female population.[15] Also according to a prospective study done by hui-yuncheng et al the peak prevalence of NAFLD occurred earlier in men(40-49 years) than for women(>50years).the prevalence of NAFLD was significantly higher in males than in females prior to age 50 and higher in females than in males after age of 50. Estrogen is speculated to be able to suppress visceral fat accumulation and to increase subcutaneous fat accumulation.[18]

In this study, it was found that the prevalence of NAFLD in metabolic syndrome was as high as 88%. Out of the 100 metabolic syndrome patients who were classified according to the IDF CRITERIA, 88 patients showed features of NAFLD on ultrasonography. This was in accordance with the previous studies which have established strong association of metabolic Syndrome with NAFLD.[14]

Surprisingly, the prevalence of severe disease in the form of cirrhosis / NASH was 20.5% among the NAFLD subjects who had metabolic syndrome. Thus, making prevalence of NASH in Metabolic syndrome to 18% which is significantly high and alarming.

In Agrawal PK et al (2017) study, there was Moderate prevalence of MS and NAFLD among The rural population and higher prevalence of MS in NAFLD group. (42.74% v/s17.32%).[15]

In the study by Patell R et al (2014) it was found that Prevalence of NAFLD in obese population was as high as 80% and there were significant differences in clinical anthropometric, laboratory findings between NAFLD and non NAFLD group.[19]

According to study by Gaharwar R et al (2015), 51.4% of NAFLD cases had MS.MS had positive correlation with grading of NAFLD.[14] Agrawal R et al, in their study found that The prevalence of MS in NAFLD Was as high as 78.22% and predicted strong correlation between the components of MS and NAFLD.[17] Zhang T et al in their large-scale prospective cohort study from northern urban Han Chinese population found that the incidence of MS in NAFLD group was higher than in non NAFLD group. NAFLD was found to be an independent risk factor for prediction of MS.[20] Uchil D et al studied the components of metabolic syndrome as risk factors for NAFLD and found increased prevalence of the risk factors in NAFLD group.[21] Tominaga K et al (2008) conducted a study in paediatric age group, the trend test revealed a strong dose response relationship(p <0.001), Between paediatric NAFLD and the number of the proposed components of

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Paediatric metabolic syndrome in japan (Mets –JC).They concluded in their study that the prevalence of NAFLD in children and adolescents is closely related to Metabolic syndrome, insulin resistance and Waist circumference.[22]

In studies with paired biopsies (one biopsy performed after the period of follow up), the disease progressed in 32-41%, remained stable in 34-50%, and improved in a minority of the patients with NAFLD. A recent survey indicates that NAFLD may account for approximately 80% of cases with elevated liver enzyme levels in the American population, and that 1 in 4 or 5 American adults actually have NAFLD. Similar data have been obtained in the Japanese,[23] and the Italian,[24] populations. Although in most cases fatty liver does not progress to more severe liver diseases, approximately 20% to 30% of patients have histologic signs of fibrosis and necroinflammation, indicating the presence of non-alcoholic steatohepatitis (NASH).[25] These patients are at higher risk of developing cirrhosis, terminal liver failure, and hepatocellular carcinoma,[26] Furthermore Hsiao et al demonstrated that the presence of severe fatty liver correlated significantly with the prevalence and degree of hypertension, abnormal glucose and triglyceride metabolism.[27]

In the present study, the mean waist circumference was 112.06+/-13.84 in the NAFLD group and 103+/-8.83 in the non NAFLD group which was significantly higher in the NAFLD group. This is in consistent with the other different studies. Patell R et al in their case control study concluded that the prevalence of NAFLD increases from 57.5 % to 74 % in obese persons.[19] In A study by Gaharwar R et al subjects with greater WC had higher grade of fatty liver.[14] it was proposed that the abdominal fat is directly associated with disease state. Waist circumference was an independent determinant of hepatic necro inflammation degree.[28] Accordingly, Soler et al did the abdominal USG on 69 patients and reported that WC was significantly higher in NAFLD subjects.[29]

The mean value of FBS in NAFLD group was 171.39+/-71.33 and in non NAFLD group it was 107.75+/-27.71 which was statistically significant (p-value-0.001) and was higher in NAFLD group. Also in this present study triglyceride levels were significantly higher in the NAFLD group (p-value-0.002). It was noted that 84.1% of the NAFLD subjects had TYPE 2 DM and 89.8% had Dyslipidaemia in the NAFLD group. In the study by Priyanka jain et al also 88% of the NAFLD subjects had T2DM.[16] our findings are consistent with various other studies mentioned above suggesting an association between high blood sugar levels and development of NAFLD in MS. In the study by Gaharwar R et al the prevalence of hypertriglyceridemia and low HDL levels was greater in the NAFLD subjects.[14] Cotrim et al reported the prevalence of hyperlipidaemia in 66.8% of the Subjects with NAFLD in brazil.[30]

Recent studies have shown NAFLD strongly associated with increased risk of cardiovascular disease, there being independent association between hepatic steatosis, carotid atherosclerotic plaques and endothelial dysfunction.[31] In the present study too we found that the Prevalence of cardiovascular complications like Hypertension, IHD, DCM, hypothyroidism was more in the NAFLD subjects with MS but we could not establish statistical significance between the NAFLD and non NAFLD groups. One study by Tanne et al reported higher prevalence and severity of NASH in subjects with severe OSA,[32] suggesting that intermittent hypoxia may play a role in NASH pathogenesis. Such significant difference wasn't noticed in the present study. Lie et al investigated by meta-analysis the association between MS and risk of stroke

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compared to individuals without MS,[33] patients had a 1.6 fold increased risk of stroke and in this way there could be indirect association of stroke with NAFLD but our present study didn't show any significance difference between NAFLD and non NAFLD groups.

In the present study, the prevalence of Hypertension in NAFLD was 73.1%. Cotrim et al reported 64% hypertension prevalence among NAFLD patients steatohepatitis.[30] Hypertension especially systolic hypertension is also an independent NAFLD predictor.[24]

In this study, the comparison of the various LFT parameters between NAFLD and non NAFLD subjects was done .The mean TB was higher in the NAFLD group and was statistically significant. The mean values of AST and ALT was also higher in the NAFLD group and was statistically significant. Significantly low levels of S. Albumin were associated with subjects with NAFLD. This was in accordance with most of the similar studies already mentioned. NAFLD is presently recognized as one of the most common causes of altered liver tests of end stage liver disease requiring liver transplantation.[3]

When the comparison between the non-cirrhosis NAFLD and the NASH/ cirrhosis was done with respect to the parameters of MS, It was found that the waist circumference was significantly higher in the NASH subjects and the HDL levels were lower among the NASH subjects and was statistically significant thus showing positive correlation of the above two parameters with severity of the non-alcoholic liver disease.

Again the comparison between the various LFT parameters between non cirrhosis NAFLD and cirrhosis subjects showed statistically significant lower levels of total protein and serum albumin in the NASH subjects probably attributed to decreased synthetic function of the cirrhosed liver thus showing positive correlation with the lower levels and the severity of NAFLD. Also, there was a statistically significant higher level of DB among the NASH when compared to NAFLD subjects in our study thus showing positive correlation with severity.

In the present study, It was found that comorbidities like diabetes, hypothyroidism, IHD, DCM, CVA, Dyslipidaemia were more prevalent in the cirrhosis subjects compared to noncirrhosis NAFLD subjects though statistical significance for its positive correlation couldn't be obtained.

So, we conclude here that, the presence of multiple metabolic disorders is associated with a potentially progressive, severe liver disease. The increasing prevalence of obesity, coupled with diabetes, dyslipidaemia, hypertension, and ultimately the metabolic syndrome puts a very large population at risk of forthcoming liver failure in the next decades.[34]

Rapid development, urbanisation and consequent change in diet and physical activity levels has led to a rapid growth in obesity and prevalence of MS. The commensurate rise in NAFLD worldwide is consequent on these changes. Whilst fatty liver disease is less of a burden of total liver disease worldwide, compared to viral hepatitis and alcohol, it is likely to grow in prevalence, especially in the developing world, unless major improvements in the prevention and management of Metabolic syndrome are developed.

However, it is not known whether NAFLD is a cause or a consequence of metabolic dysfunction. A better understanding of the mechanisms responsible for the pathogenesis and pathophysiology of NAFLD will potentially identify both novel biomarkers for metabolic risk and unique targets for therapeutic intervention.

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Conclusion

- Prevalence of NAFLD was significantly higher in metabolic syndrome subjects in comparison to general population.
- The prevalence of NAFLD was 88% in metabolic syndrome subjects.
- There was a statistically significant association between NAFLD and components of Metabolic Syndrome namely waist circumference, fasting blood sugars and hypertriglyceridemia.
- The prevalence of type 2 diabetes mellitus, Dyslipidaemia, cardiovascular diseases, hypothyroidism was also higher in NAFLD subjects though statistical significance couldn‟t be established.
- As high as 20.5% of the NAFLD subjects had severe progressed disease in the form of cirrhosis which is an alarming percentage?
- There was a significant difference in the LFT parameters like TB, AST, ALT and Serum albumin between NAFLD and non NAFLD subjects.
- The prevalence of severity of NAFLD correlated directly with the severity of components of MS namely Waist circumference and dyslipidaemia.
- Also, severity of NAFLD correlated with prevalence of comorbidities like Diabetes mellitus, hypothyroidism, Cardiovascular diseases and dyslipidaemia but statistically significant correlation couldn‟t be obtained.
- Early detection and treatment of NAFLD in Metabolic Syndrome subjects can prevent development of complications in them due to the combined effects of both diseases.

Thus, need for screening MS subjects for undiagnosed NAFLD has been reinforced by this study.

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