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Metabolic syndrome and non-alcoholic fatty liver disease association-a study in rural tertiary care centre in north India

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Abstract:

Objective: We intended to establish a clinical association between NAFLD and MS. **Materials and Methods:** Weight, height, waist circumference, hip circumference, blood pressure and ultrasound of liver were performed .Serum triglyceride, total cholesterol, high density lipoprotein cholesterol and fasting plasma glucose level were measured. **Results:** A total of 39 patients of which 25 men and 14 women were included.36 (92.3%) were obese, hypertension in 23(65.2%), dyslipidemia in 32(82.1%). Mean value of CRP and TNF-α in hypertensive patients was 2.3±0.71mg/l and 84.1±17.8 pg/ml whereas it was 2.3±0.7mg/l and 87.6±7.4pg/ml respectively. A significant increase was found in the mean values of TNF-α and CRP with increasing grades of NAFLD (p-value<0.01).Both TNF-α and CRP were higher in patients of MS .Using Pearson´s correlation significant correlation of TNF-α and CRP was found with MS (r=0.8 and 0.7 respectively). **Conclusion:** There is a close association between MS and NAFLD. NAFLD was strongly associated with the MS, although it remains unknown whether NAFLD is a cause or effect of MS.

Key words: dyslipidemia; insulin resistance; metabolic syndrome; non alcoholic fatty liver disease; obesity; steatohepatitis.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathologic entity which includes a spectrum of liver damage ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), advanced fibrosis, and rarely, progression to cirrhosis. Recent studies point towards the role of insulin resistance, oxidative stress and subsequent lipid peroxidation, proinflammatory cytokines, adipokines and mitochondrial dysfunction in the development and progression of NAFLD. Furthermore, accumulating evidence supports an association between NAFLD and metabolic syndrome. NAFLD may be categorized as primary or secondary depending on the underlying pathogenesis. Primary NAFLD is associated with insulin resistance and metabolic

syndrome The pathogenesis of NAFLD and metabolic syndrome seems to have common pathophysiological mechanisms, with main focus on insulin resistance. Our present study is designed to see the association between non-alcoholic fatty liver disease, and various cardiovascular risk factors & plasma biomarkers of inflammation TNF-α & CRP in non-alcoholic subjects (taking alcohol less than 20 gramme per day). This article strongly support the association of nonalcoholic fatty liver disease as a possible component in the cluster of metabolic syndrome.

Materials and Methods:

Aims and Objectives:

To evaluate cardiovascular profile in patients having NAFLD,and to establish correlation, if any, between cardiovascular risk factors and inflammatory markers in patients with NAFLD.

The present study was undertaken on patients having non-alcoholic fatty liver disease diagnosed by ultrasound, attending medicine OPD, and admitted in medicine indoors, at UPRIMS & R, Etawah. Patients were evaluated as per predesigned proforma which included a detailed history, clinical examination including anthropometric measurements and necessary investigations which included TNF-α and CRP.

Inclusion Criteria

Patients included in the study are those having NAFLD, diagnosed by ultrasound on the basis of following criteria: Echo contrast, liver brightness, deep attenuation, vascular blurring.

Exclusion Criteria:

Known case of acute or chronic viral hepatitis, alcoholic hepatitis, cirrhotic portal hypertension, sepsis, decompensated cardiac disease, severe renal dysfunction.

Ultrasonography of abdomen- done by Sonoline 500 model of Siemens company with 3.5 megahertz real time scanner.

Criteria used for ultrasonographic grading of NAFLD (Abdominal and retroperitoneal Cavities. Hegen-Ansert SL(ed). Diagnostic ultrasonography. 1996, pp 120–123):-

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

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

Grade III: a marked increase in fine echoes with poor or no visualization of intrahepatic vessel borders, diaphragm and posterior portion of the right lobe of the liver.

Statistical Analysis:

All statistical data were analyzed by using SPSS software version 16.0. Statistical package for windows (Chicago. Inc.). Continuous variables were expressed as mean ± standard deviation (Gaussian distribution) or range and qualitative data was expressed as percentage. Depending on normality distribution, unpaired t test for independent samples was used for comparing continuous variables between two groups.

Linear relationship between variables was analyzed using Pearson's correlation coefficient and significance of 'r' was tested. All p values were two tailed and values of $p<0.05$ was considered statistically significant. All confidence intervals were calculated at 95% level.

Results:

Figure 1: Age and sex distribution of study group

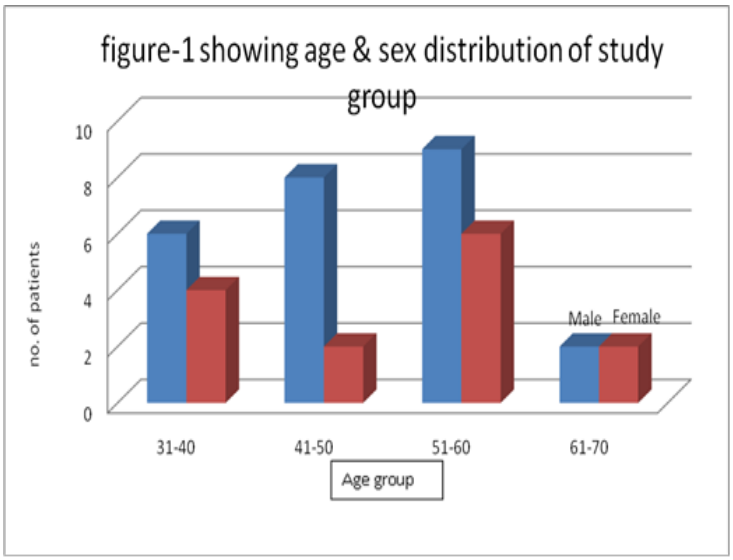


Figure 2: Age and sex distribution among smokers

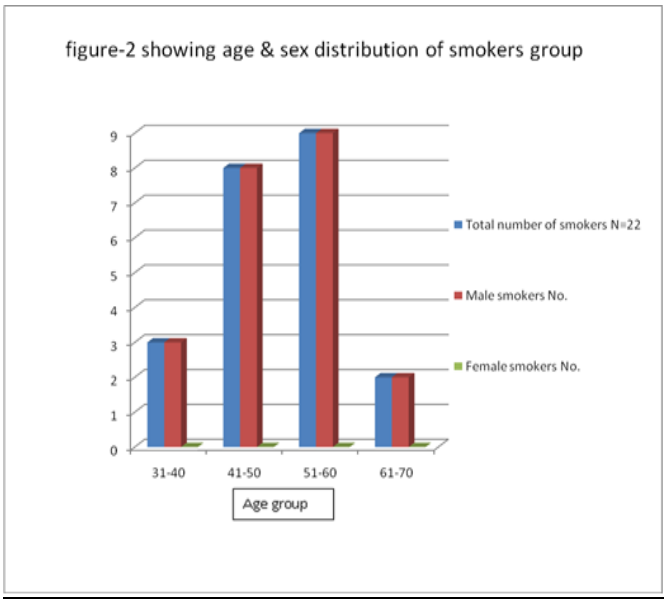


Figure 3: Age and sex distribution among hypertensive patients

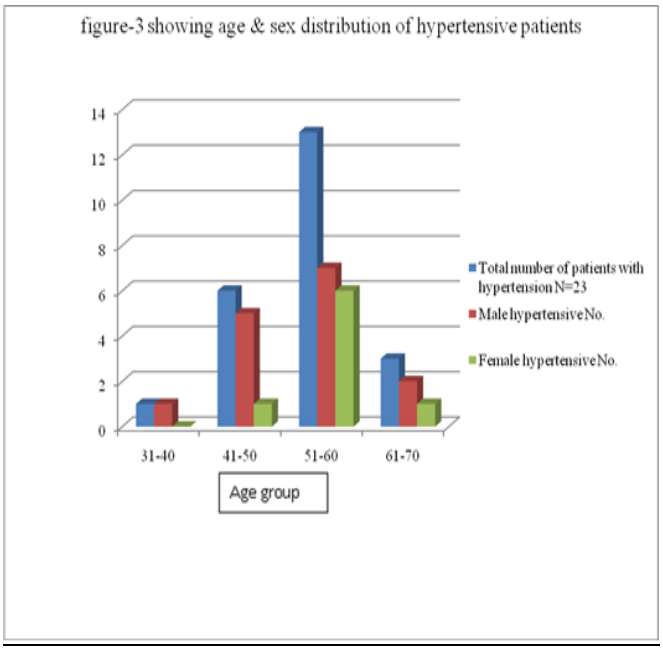


Figure 4: Age and sex distribution among Diabetes patients

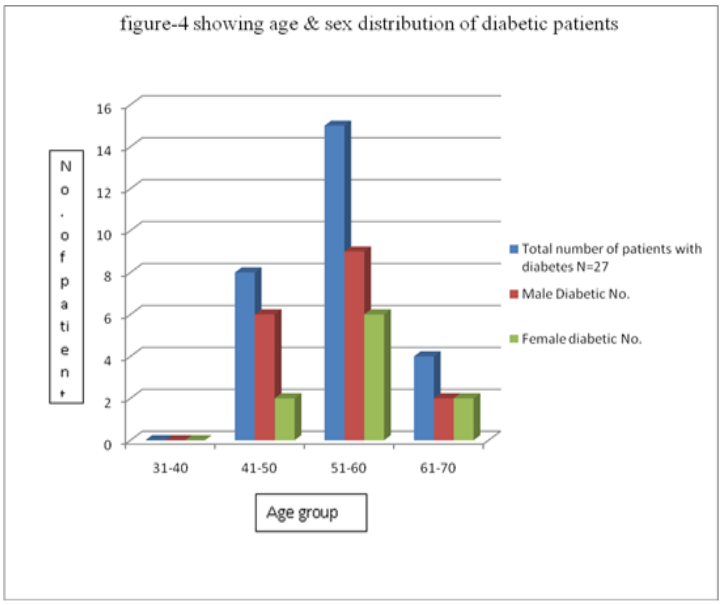


Figure 5: Age and sex distribution in obese patients

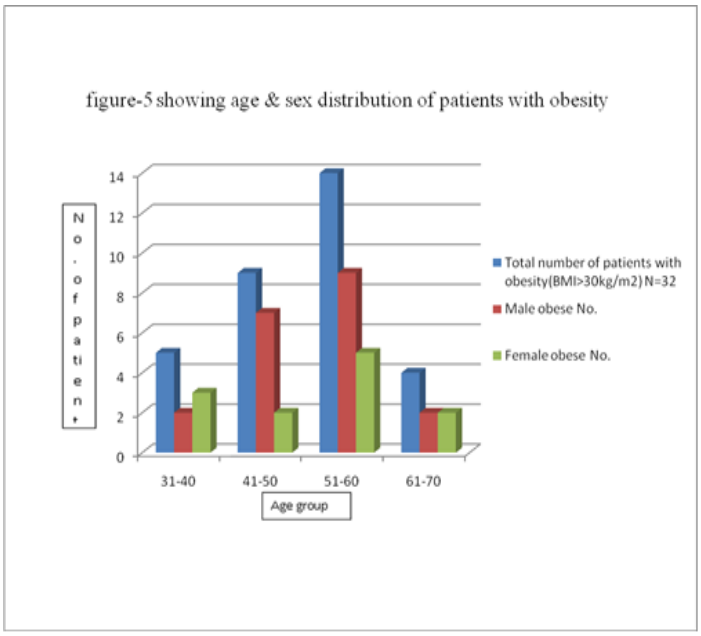


Figure 6: Age and sex distribution in patients with dyslipidemia

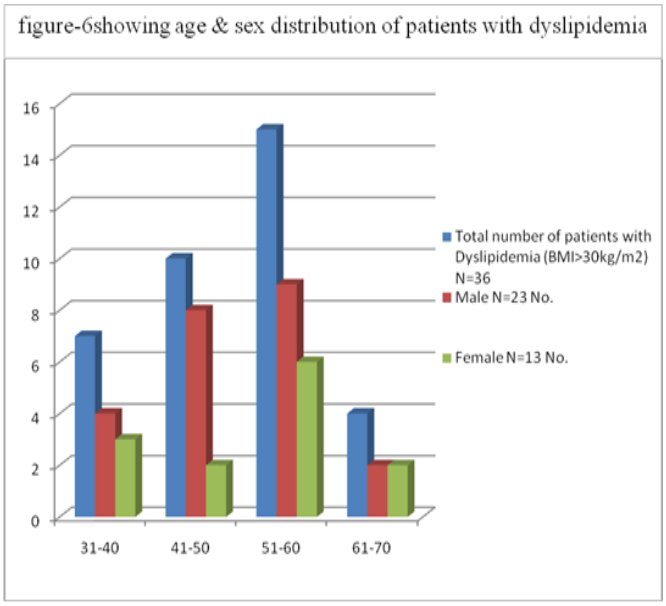
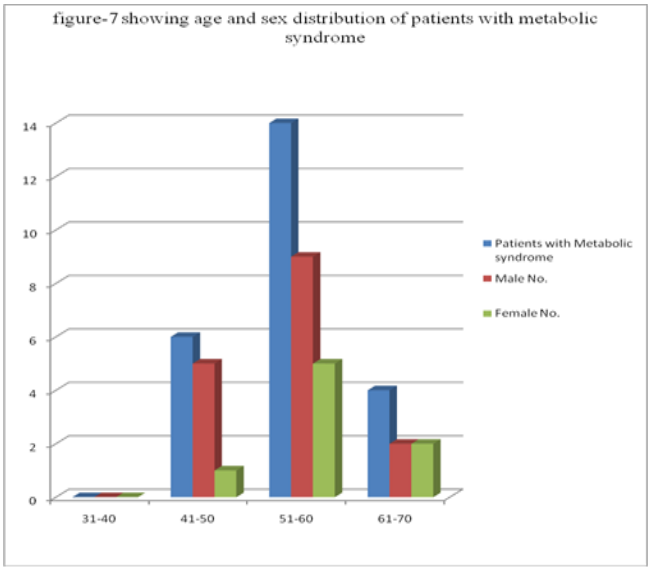


Figure 7: Age and sex distribution in patients with metabolic syndrome



Hepatic inflammatory markers in patients with metabolic syndrome and non-alcoholic fatty liver disease

In the present study, patients having metabolic syndrome were identified according to NCEP ATP-III criteria. There were 24 patients who were found to have metabolic syndrome (8 females and 16 males). Both TNF-α and CRP were significantly higher in patients with metabolic syndrome (both males and females) as compared to patients without metabolic syndrome. The mean value of TNF-α and CRP in these patients are shown in table 1 & table 2.

Table 1: Showing association of TNF-α and CRP with metabolic syndrome in females using t-test.

	Metabolic Syndrome	Mean±S.D	t-value	P-value
CRP (mg/l)	Absent N=6	0.4±0.4	-7.3	<0.01
	Present N=8	2.6±0.4		
TNF-α (pg/ml)	Absent N=6	38.3±40.9	-5.2	<0.01
	Present N=8	86.4±7.2		

Table 2: Showing association of TNF-α and CRP with metabolic syndrome in males using t-test analysis

	Metabolic Syndrome	MEAN±S.D	t-value	P-value
CRP (mg/l)	ABSENT	1.1±1.1	-3.5	<0.01
	PRESENT	2.4±0.5		
TNF-α (pg/ml)	ABSENT	39.4±34.7	-4.2	<0.01
	PRESENT	88.3±7.7		

Pearson Correlation of TNF-α and CRP with metabolic syndrome:

Using Pearsons correlation, a significant correlation of CRP and TNF-α was found with metabolic syndrome (r=0.8 and 0.7 respectively) as compared to those without metabolic syndrome (table-3).

Table 3: Correlations between metabolic syndrome and inflammatory markers (TNF-α & CRP) in patients of non-alcoholic fatty liver disease

Metabolic syndrome		CRP (mg/l)	TNF-α (pg/ml)
	Pearson Correlation	0.8	0.7
	p-value	<0.01	<0.01
	N	39	39

Association of inflammatory markers with various grades of non-alcoholic fatty liver:

The effect of various grades of fatty liver on TNF-α and CRP was studied, using one way anova analysis. A significant increase was found in the mean values of TNF-α and CRP with increasing grades of fatty liver in non-alcoholics [p-value<0.01]. On doing inter-group comparison (post-hoc analysis), the effects of increasing grades of fatty liver on TNF-α levels was significantly maintained in between Group 1 (grade 1-grade 2); Group 2 (grade 2-grade 3); Group 3 (grade 1-grade 3), but in case of CRP , the effect was not maintained on transition from grade-2 to grade-3.

Results:

This study was conducted on 39 patients having non-alcoholic fatty liver disease. Non-alcoholic fatty liver disease was graded as grade1, 2 & 3.

1. The study comprised of 25 males and 14 females. The age of patients in this study ranged from 31 to 70 years, mean age was 48.5±9.5 years. Among males, the age of patients ranged from 31 to 70 years (mean age 48.1±9.5years) while among females, the age ranged from 31 to 60 years (mean age 49.1±11.0 years).
2. Most of the patient found to have no symptoms or signs of liver disease at the time of diagnosis. The commonest sign detected in study was hepatomegaly in 62.5% patients.
3. There were 22(56.4%) smokers, all of them were males. Mean value of CRP in smoker patients was 2.2±0.8 mg/l and it was 1.4±1.2 mg/l in non-smokers. Mean value of TNF-α in smoker patients was 78.9±31.8 pg/ml and in non-smokers, it was 70.7±31.8 pg/ml. Both TNF-α and CRP are found to be significantly higher in smokers as compared to non-smoker group with p-value being less than 0.05.
4. The study comprised of 23 hypertensive patients. Mean value of CRP in hypertensive patients was 2.3±0.71mg/l and in normotensives it was 1.1±1.0 mg/l. Mean value of TNF-α in hypertensive patients was 84.1±17.8 pg/ml and it was 55.9±38.0 pg/ml in normotensive group. In our study CRP and TNF-α levels was found to be significantly higher in hypertensive group as compared to normotensive group with p-value being less than 0.05.
5. There were 27 (69.2%) diabetic patients, with sex distribution of being 17 (62.9%) males and 10 (37.1%) females. Mean value of CRP and TNF-α in diabetic group was 2.3±0.7 mg/l and 87.6±7.4 pg/ml respectively, and it was 0.6±0.8 mg/l and 26.6±34.3 pg/l in non-diabetic group respectively. Diabetes was found to be significantly affecting the levels of TNF-α and CRP with p-value being less than 0.01.
6. There were 32 (82.1%) obese patients, with sex distribution of being 20 (62.5%) males and 12 (37.5%) females. Mean value of CRP and TNF-α in patients with obesity was 2.1±0.9 mg/l and 77.5±25.9 pg/ml. Obesity was found to be significantly affecting the levels of CRP and TNF-α with p-value being less than 0.01.
7. The study comprised of 36 (92.3%) patients with dyslipidemia, with sex distribution of being 23 (63.9%) males and 13 (34.8%) females. Mean value of CRP and TNF-α in patients with dyslipidemia was 2.9±0.9 mg/l and 73.9±29.0 pg/ml respectively. Both CRP and TNF-α were found to be significantly higher in diabetic patients with p<0.01.
8. There were 24 patients who had metabolic syndrome (male=66.7% & female=33.3%). Mean value of CRP and TNF-α in female patients with metabolic syndrome was 2.6±0.4 mg/l and 86.4±7.2 pg/ml respectively and in males, mean values were 2.4±0.5 mg/l and 88.3±7.7 pg/ml respectively.
9. On studying the effect of various grades of fatty liver on TNF-α and CRP using one way anova analysis, significant increase was found in the mean values of TNF-α and CRP with increasing grades of fatty liver disease in non-alcoholics [p-value<0.01].

Discussion:

Recent studies have pointed that NAFLD, in its whole spectrum ranging from pure fatty liver to non-alcoholic steatohepatitis (NASH), might represent another feature of MS. Pathophysiologic considerations, clinical associations, and laboratory investigations support that insulin resistance and hyperinsulinaemia have a central role in pathogenesis of both MS and non-alcoholic fatty liver. It was concluded in recent studies that NAFLD, in the presence of normoglycaemia and normal or raised body weight, is characterized by clinical and laboratory features similar to those found in diabetes and obesity such as impaired insulin sensitivity and abnormalities in lipid metabolism[3]. Ninty percent of individuals with NAFLD have at least one risk factor of MS, and 33% have all the features of MS. Study concluded that liver fat content is significantly increased in subjects with the MS as compared with those without the syndrome, independently of age, gender, and body mass index [1]. In 304 NAFLD patients without diabetes mellitus the prevalence of metabolic syndrome increased from 18% in normal weight individuals to 67% in obese individuals. The presence of multiple metabolic disorders such as diabetes mellitus, obesity, dyslipidaemia and hypertension is associated with a potentially progressive, severe liver disease [2,3]. Obesity is found in 30-100% of subjects with NAFLD. In obese persons steatosis is 4.6 fold higher than in normal weight persons [4,5]. Prevalence of type 2 diabetes mellitus in NAFLD patients ranges from 10% to 75%. A study reported that type 2 diabetes mellitus was found in 33% of individuals with NAFLD [6]. Another study in Japanese population showed that prevalence of NAFLD increased to 43% in individuals with impaired fasting glucose and 62% in individuals with type 2 diabetes mellitus [7]. Hyperlipidaemia and specifically high levels of triglycerides and low levels of HDL-cholesterol are strongly associated with NAFLD. Hypertriglyceridemia and low HDL-cholesterol level are present in 64% and 30-42% of NAFLD patients respectively[2].In 55 nonobese, non-diabetic patients with primary hypertension the prevalence of fatty liver was more than twofold than in the control group [8]. Recent studies have pointed that NAFLD is strongly associated with increased risk of cardiovascular disease. There is an independent association among hepatic steatosis and carotid atherosclerotic plaques and endothelial dysfunction. This relationship remains statistically significant after adjustment for risk factors of MS [9,10]. Participants with the MS have a 4 to 11 times higher risk for future nonalcoholic fatty liver disease. In addition, if nonalcoholic fatty liver disease and the MS coexist, disease regression is less likely [11]. 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 [12]. NAFLD was strongly associated with the MS, although it remains unknown whether NAFLD is a cause or effect of MS [13]. In the present study,significant increase in values of CRP and TNF-α was noted with increasing grades of fatty liver(p value-<0.01).Also in our study significant correlation of CRP and TNF-α was noted with smoking, hypertension, diabetes, dyslipidemia, obesity and metabolic syndrome, with different grades of fatty liver.

Conclusion:

Non alcoholic fatty liver is the object of significant scientific and clinical interest which is going to increase in the following years. Epidemiological studies demonstrate that NAFLD and MS are emerging as major problems of public health. The targets of future investigations are to clarify the pathogenesis and to establish effective treatment in both NAFLD and MS. Several studies are in progress and a few of them have provided encouraging results.

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All authors declare that they have no competing financial interest or any source of conflict in relation to their work.

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