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Original Article

Internal Medicine Section

Non-Alcoholic Fatty Liver Disease (NAFLD) in Obesity

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ABSTRACT

Background and Objectives: Limited studies have been undertaken to characterize Non-Alcoholic Fatty Liver Disease (NAFLD) in the Indian population. The main objective of our study was to document the prevalence of NAFLD amongst a cohort of obese Indian patients and demonstrate its relationship with other components of the metabolic syndrome.

Methods: A total of 60 adult obese patients were subjected to a detailed history, clinical exam, anthropometric study and laboratory workup. Focus was on liver function and components of the metabolic syndrome like blood pressure, glycemic status and lipid profile. Subjects enrolled were divided into two groups Group A (n=48), with NAFLD and Group B (n=12) without NAFLD. The two groups were then compared amongst themselves as well as with data from previous similar studies.

Results: A comparison of the anthropometric measurements revealed a statistically significant difference between the Body mass index (BMI) and Waist Hip Ratio of the two groups and in the mean triglyceride values between the two groups. Although the mean bilirubin levels measured in the serum were not statistically different the mean levels of SGOT and SGPT in the two groups was found to be statistically significant. On the contrary no significant difference in the values of alkaline phosphatase and synthetic liver functions could be discerned. A statistically highly significant difference in the mean liver span is seen.

Interpretation and Conclusions: NAFLD is common in Indian obese populations and is associated with significant differences in anthropometric, clinical, laboratory and ultrasonographic aspects as compared with obese individuals not affected with liver disease.

Keywords: Non-Alcoholic Fatty Liver Disease, Obesity, Metabolic Syndrome

INTRODUCTION

Obesity has reached epidemic proportions in India in the 21st century, with morbid obesity affecting 5% of the country's population [1]. This is only the tip of an iceberg and the incidence is growing. The metabolic syndrome (Syndrome X, insulin resistance syndrome) consists of a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease (CVD) and diabetes mellitus (DM). Central adiposity is a key feature of the syndrome, reflecting the fact that the syndrome's prevalence is driven by the strong relationship between waist circumference and increasing adiposity [2]. Increasing attention around the world is being drawn now to NAFLD. In fact NAFLD is now considered a manifestation of the metabolic syndrome.

The true prevalence of NAFLD and non alcoholic steatohepatitis (NASH) is unknown given that the disease definition and modalities used for diagnosis are not standardized. In the west NAFLD is now recognised as the most common cause of altered liver function tests. Methodology of epidemiology studies of NAFLD vary widely as well, with only limited data from large population-based studies. Based on imaging studies, the prevalence of NAFLD in the adult population ranges 14–31% [3]. Incidence of steatosis clearly increases with obesity. A large population-based study found that 91% of obese individuals (BMI>30kg/m2) had evidence of steatosis on ultrasound [4].

With the increased incidence of DM, obesity and insulin resistance in India in last two decades it is only logical to expect an increase in the incidence of NAFLD in India. However there is limited data on the prevalence of NAFLD from India. Whether the clinicopathological profile of NAFLD in Indian patients could in fact differ significantly from that in the West is a question still open to debate [5].

NAFLD spans a spectrum of hepatic pathology from hepatic steatosis at the most clinically benign end, through an intermediate lesion NASH, to cirrhosis at the opposite end of the disease spectrum. While the exact proportion of patients progressing to cirrhosis is perceived to be low (5%), the rapidly escalating prevalence riding on the wave of the obesity epidemic has made it among the most common causes of chronic liver disease [6]. Cirrhosis associated with NAFLD is associated with a list of complications considerably adding to morbidity, mortality of the patients and the burdens of cost to the health care system.

NAFLD is the hepatic manifestation of the insulin resistance (metabolic) syndrome. Risk factors underlying "primary" NAFLD include obesity, type 2 DM, dyslipidaemia, hypertriglyceridemia, history of cyclic weight gain and loss, and hypertension [7]. Each of these conditions also conveys a risk for CVD. Thus, treatment of patients who have NAFLD should aim to identify and treat associated metabolic factors such as obesity, glucose intolerance, dyslipidaemia, and hypertension. Although the frequent association of NAFLD with the metabolic syndrome is well-known, the metabolic syndrome is now recognized as a strong predictor of the presence of NAFLD [8].

To date, there is a growing body of evidence suggesting that NAFLD is associated with an increased risk of incident CVD that is independent of the risk conferred by traditional risk factors and components of the metabolic syndrome [9]. It is clear that NAFLD leads to liver-related morbidity and mortality in a subset of people; however, a better understanding of the natural history for NAFLD will permit better identification of those patients at risk for fibrosis

progression. Although diagnosis and evaluation are relatively straightforward [10], many issues remain unresolved. Large series of well-characterized patients will need to be followed to better establish the natural history and to clearly define the associated morbidity and mortality caused by this chronic condition. Further more, non-invasive means of discerning risk factors for fibrosis progression will allow clinicians and investigators to select out patients at high risk for disease progression for more comprehensive diagnostic evaluations, follow-up, and treatment interventions.

Hence the prime objective of our study was to document the prevalence of NAFLD amongst a cohort of obese Indian patients and demonstrate its relationship with other components of the metabolic syndrome. We hypothesized that the patients with NAFLD would differ with respect to their anthropometric and metabolic profiles from the obese population without liver affection. The ultimate aim being to identify the factors helpful in controlling liver disease in obesity and its outcomes.

MATERIALS AND METHODS

The study was conducted in medical wards and OPD of SSGH Hospital between the months of November 2010 and November 2011. A total of 60 adult obese patients were selected. BMI > 30kg/m2. Exclusion criteria included alcohol consumption above the safe limit (Asian standard: 14 units/week for men, 7 units/week for women), pregnancy, known cases of chronic infectious hepatitis (C or B), patients who were on medications known to induce fatty liver such as methotrexate, oestrogens, amiodarone and tamoxifen.

All candidates were explained about the purpose and nature of the study. Written and informed consent was obtained. A detailed clinical history and physical examination were undertaken to assess inclusion and exclusion criteria. Anthropometric measurements were taken as per the WHO guidelines in the WHO Monica Project [11]. Blood pressure was measured as per the recommendations of JNC VII [12]. Patients were also screened for skin changes like xanthoma, xanthelesmas, acantosis nigricans and strias.

A 10-mL sample of venous blood was obtained from each subject in the fasting state. This was used to determine fasting glucose, glycosylated hemoglobin A1c (HbA1c), serum lipids and liver profile including AST ALT, Alkaline Phosphatase, S Albumin and Prothrombin Time. Also all subjects who had an abnormal liver on ultrasound were screened for hepatitis B and C (hepatitis B surface antigen HbsAg) and anti-hepatitis C virus.

All subjects underwent ultrasonography of the liver with a 8-MHz probe (Toshiba Ultrasound Diagnostic Systems SSA-51 OA, Toshiba Medical Systems Corporation, Otawara-City, Tochigi-prefecture, Japan). Ultrasonographic examination was carried out by doctors with training in ultrasonography. Fatty liver was diagnosed in the presence of two of the three following criteria: increased hepatic echogenicity compared to the spleen or the kidney, blurring of liver vasculature and deep attenuation of the ultrasonographic signal. This has an adequate threshold for detection of steatosis when more than 33% of hepatocytes contain fat on liver histology [13].

NAFLD was diagnosed in subjects who fulfilled ultrasonographic criteria for fatty liver, and who did not report alcohol consumption above the safe limit and who were negative for hepatitis B and C markers. All obtained data was then analysed statistically.

RESULTS AND DATA ANALYSIS

On completion of study of the clinical and investigative profile of the obese patients the analysis of the investigational data was done to derive results. Based on clinical opinion and correlating the clinical evidence with sonography and liver function tests the 60 subjects enrolled were divided into two groups Group A, with NAFLD and Group B without NAFLD. The two groups were then compared amongst themselves as well as with data from previous similar studies. Results are displayed in [Table/Fig-1 and 2].

DISCUSSION

Prevalence of Obesity is on a global increase, rising in tow are a number of conditions including but not limited to diabetes, hypertension, atherosclerosis, dyslipidemia, osteoarthritis, sleep apnea and gallstones. The importance of liver disease in obesity is now being recognized. Indeed NAFLD is the commonest cause of altered liver enzymes in the western world [14]. In the last few decades' developing countries like India have had a maximal increase in the rates of obesity especially in its younger populations.

In our study sixty patients with BMI over 30, thus obese, underwent a detailed clinical, anthropometric, laboratory and radiologic evaluation. At the end of evaluation they were divided into two groups, Group A: who were diagnosed with NAFLD based on sonographic correlation with clinical and laboratory data; And Group B, the remaining patients. The proportion of patients in Group A thus estimated the prevalence of NAFLD in the obese population under study.

A total of 48 amongst the 60 studied received a diagnosis of NAFLD on the basis of clinical, biochemistry and abdominal sonographic evaluation and the prevalence of NAFLD in the obese cohort of the population studied was thus 80 %.

NAFLD affects 10 to 24 percent of the general population in various countries. The prevalence increases to 57.5 percent [15] to 74 percent [7,16] in obese persons. NAFLD is the cause of asymptomatic elevation of aminotransferase levels in up to 90 percent of cases once other causes of liver disease are excluded [17].

The insidious progression of the disease translates into a majority of patients relatively asymptomatic for NAFLD [6]. Thus although it is rapidly becoming one of the commonest causes of alterations in Liver Functions and a cause for at least a substantial proportion of patients who receive the diagnosis of 'cryptogenic' cirrhosis, the majority of patients with hepatic steatosis may never be symptomatic. In our study only three patients had systemic complaints attributable to an underlying liver dysfunction. Two patients presented with decompensated cirrhosis and one with acute hepatitis. Two of these three patients ultimately received a biopsy proven diagnosis of cirrhosis due to NASH. One could not be biopsied due to prolongation of prothrombin time.

As demonstrated in [Table/Fig-2], in most studies undertaken on obese populations screened for NASH lack of symptoms is characteristic rather than exceptional.

A comparison was then undertaken between the two groups both to demonstrate the severity and characteristics in the abnormalities recorded in the Liver Function tests and to see whether and how the other components of the Metabolic Syndrome correlated with the presence and severity of NAFLD.

The apparently larger proportion of females in the study population can be explained by a possible higher prevalence of obesity in the female population. But also the fact that alcohol intake was a crucial exclusion criteria for the study may have led to a confounding bias of more male subjects being rejected as the prevalence of alcohol intake is higher in males, especially in the socioeconomic strata under trial.

The proportion of females in our study population with patients of NAFLD, i.e., Group A was 66.6%. Most studies in a meta analysis [16] also showed a female preponderance with the mean proportion of females 73 % (n=32). This was also reflected in our study.

Acanthosis Nigricans has long been recognized as a cutaneous marker of insulin resistance, it is widely prevalent in obesity [18]. This darkish velvety discoloration seen characteristically in body folds is believed to be because of the high levels of hyperinsulinemia

in circulation. Close to 90% (n=43) of the patients with NAFLD had clinically identifiable acanthosis. In the other group the prevalence of acanthosis was less than half of that at 41.6 % (n=5). Six of the 48 patients in Group A (12.5%) had palpable liver on per abdomen examination. This is in keeping with prior observations that suggest that a palpable liver is often the only clinical sign pointing to NAFLD [6].

The mean BMI was significantly higher in the two groups compared. BMI has been used to correlate risk amongst obese patients. A higher BMI can be interpreted as more body fat and has been directly correlated to a higher risk as well as more severe complications of Obesity including DM, hypertension and dyslipidemia [19]. Morbid obesity has significant implications on the complications of obesity as well as on the therapeutic measures like surgery [20]. The presence of obesity as a risk factor for NAFLD is well established and confirmed in our study.

Increasing central adiposity is associated with an increased risk of morbidity and mortality [21]. Therefore, in addition to measuring BMI, waist circumference was measured to assess abdominal obesity. The presence of intra abdominal fat has been proposed as the major determinant of insulin resistance. Insulin resistance is also the key mechanism in the pathogenesis of NASH/NAFLD [22]. In our study all our subjects with only a single exception fulfilled sex specific criteria for abdominal obesity. As the mean BMI of the study was 36.02±4.28 kg/m2, and the predisposition of the South Asian to abdominal obesity well established this is not surprising [23,24].

It follows that the significant difference in the Waist hip ratios of the two groups further strengthen the theories linking insulin resistance with NAFLD. A correlation between fatty liver and waist ratios has been published in literature [25]. It has been hypothesized that visceral fat releases free fatty acids and adipokines and thereby exposes the liver to fat accumulation. Studies using waist circumference to estimate abdominal fat mass suggested a direct association between abdominal fat and liver fat content.

Hypertension is amongst the important criterion in the diagnosis of Metabolic Syndrome. It is a very prominent feature of the metabolic syndrome, present in up to 85% of patients [26]. In a study published in Hepatology in 2005 the mean Blood pressure in the patients with NAFLD was 135/85 mm Hg [27]. In our cohort of patients diagnosed with NAFLD the mean blood pressure was 145.62/93.54 mm Hg [Table/Fig-2]. Again almost all our patients, with one exception of a single subject in Group B were hypertensive.

The risk of NAFLD is increased in individuals who have type 2 diabetes [28] with abdominal sonography demonstrating that at least half have hepatic steatosis [29]. 52% (n=25) of the patients diagnosed with NAFLD in our study fulfilled the criteria [30] for DM. 31.25% (n=15) patients fulfilled criteria for Impaired Fasting Glucose (prediabetes). Thus there was a difference in these proportions amongst the two groups. HbA1C levels were also checked in the subjects the mean HbA1C in Group A was 7.41±2.01 % as opposed to 6.65±1.26 % this can be compared to the patients in an Indian study [17].

Of all the patients diagnosed with NAFLD (Group A) 85% (n=41) fulfilled criteria set NCEP ATP III [31] for dyslipidemia. Dyslipidemia is an important potential target for therapeutic manoeuvres as well as important risk factors for atherosclerosis and vascular disease. The difference observed in the mean triglyceride levels in Group A and Group B tested to be statistically significant [Table/Fig-2].

A comparison was made between the complete liver function profiles of the two groups. Bilirubin levels and hepatic enzymes were compared.

Mildly to moderately elevated serum levels of aspartate aminotransferase, alanine aminotransferase, or both are the most common and often the only laboratory abnormality found in patients with NAFLD. The ratio of aspartate aminotransferase to alanine aminotransferase is usually less than 1, but this ratio increases as fibrosis advances, leading to a loss of its diagnostic accuracy in patients with cirrhotic NAFLD [32]. Hypoalbuminemia and alterations in prothrombin time are also features seen with late stage NASH or cirrhotic liver disease. The SGPT, SGOT values as well as the SGOT/SGPT ratio are compared to prior studies [Table/Fig-3].

Both Agrawal et al., [17] and Bedogni et al., [27] show a ratio of AST/ALT <1. Although the values are close if not below the normal upper limit of 40U/l, it has been suggested that the current reference ranges for ALT level probably underestimate the frequency of chronic liver disease. The normal level of 40 U/L was set based on population studies over the last 2 decades. These studies however probably overlooked patients with hepatitis C and low levels of viremia as well as the large number of patients with NAFLD in the reference population. A proposal to revise the upper limits to lower levels has been long on haul [33].

There was a statistically significant difference in the SGPT, SGOT values (shown in [Table/Fig-2]) is a reasonable observation considering the fact that elevation of enzymes as well as sonographic qualities of the liver was the most important considerations while separating the two groups in the first place. As barring 3 patients most of the patients in Group A were not in the cirrhotic stage of NAFLD it would explain the fact that there was no significant difference in the albumin levels or the Prothrombin ratio.

Some limitations of our study were identified. A study on a larger scale needs to be done to get a more accurate picture

	Group A/NAFLD (n=48)	Group B /No NAFLD (n=12)	p-value
Age: (Years)	45.3	54.9	0.024
Sex: (F:M)	2:1	3:1	0.99
Weight (kg)	83.6±9.74	74±6.70	0.002
Height (m)	1.52 ±0.0815	1.49±.127	0.332
BMI (kg/m2)	36.15 ±4.20	33.54±4.19	0.05
Waist circumference (cm)	95.66±6.23	94.08±6.20	0.43
Hip Circumference (cm)	103.60±-10.73	106.41±8.88	0.49
Waist: Hip Ratio	.92±060	.86±.05	0.03
Weight (kg)	83.6±9.74	74±6.70	0.002
Systolic (mm Hg)	145.62±11.4	141.16±12.4	0.24
Diastolic (mm Hg)	93.54±7.85	89.33±9.88	0.12
FBG (mg/dl)	129.72±60.51	119.08±21.3	0.553
HBA1c (%)	7.41±2.01	6.65±1.26	0.223
Total Cholesterol (mg/dl)	165.9±38.16	153.91±37.13	0.332
LDL (mg/dl)	91.50±42.58	87.08±28.89	0.735
HDL (mg/dl)	40.27±7.67	40.25±5.72	0.993
VLDL (mg/dl)	31.0±14.9	23.16±11.96	0.098
Triglyceride (mg/dl)	181.31±101.69	116.00±59.42	0.038
S. Bilirubin (mg/dl)	o.91±.46	0.84±.22	0.575
SGPT (U/L)	51.77±25.62	32.33±20.32	0.018
SGOT (U/L)	55.18±21.28	32.00±11.00	0.001
Alkaline Phosphatase (U/L)	139.45±73.27	110.18±39.94	0.207
PT INR	1.18±.22	1.19±.13	0.87
S. Albumin (mg/dl)	3.32±.59	3.68±.65	0.07
Liver Span	153.60±16.4	121.08±12.65	<.001
Altered Echo pattern	100% (n=48)	(0%) n=0)	

[Table/Fig-1]: Charecteristics of the two groups of obese patients with and without NAFLD in our study population

Source	n	Mean Age (years)	Female (%)	Obesity (%)	Diabetes/Raised Glucose (%)	Hyperlipidemia (%)	Asymptomatic (%)	Increased Fibrosis (%)
Ludwig et al., [34] (1980)	20	54	65	90	50	67	NA	15
Adler[35] (1979)	29	46	76	100	2	48	NA	47
Itoh et al., [36] (1987)	16	52	75	100	5	63	NA	19
Lee [37] (1989)	49	53	78	69	51	NA	100	34
Pinto et al., [38] (1996)	32	49	75	47	34	28	94	55
Bacon et al., [39] (1994	33	47	42	39	21	21	64	39
George et al., [40] (1998)	51	47	49	49	NA	54	28	NA
Teli et al., [41] (1995)	40	57	45	30	10	23	100	2.5

[Table/Fig-2]: Clinical, laboratory and pathological features of NASH in previously published case series

	Our Study Group A (n=48)	Agrawal et al., [17] (n=71)	Marchesini [8] (n=135)	Bedogni et al., [27] (n=30)
SGPT/ALT (U/L)	51.77±25.62	35.2	90	28
SGOT/AST(U/L)	55.18±21.28	28.4	42	22
AST/ALT	0.926	0.806	0.46	0.78

[Table/Fig-3]: A comparison of laboratory values in our study with previously published data

of the etiological factors and possible underlying pathogenetic mechanism of the study. The study being a crossectional study, a follow-up study preferably of at least two to three decades to help unravel the natural history of the disease including its progression and correlating the emerging evidence that NAFLD acts as an independent risk factor for coronary and CVD was not possible.

Liver biopsy was done in only 2 of the 48 patients. Although this seems to be a serious issue; as the vast majority of patients receiving the diagnosis of NAFLD in clinical practice are in fact asymptomatic to their liver disease, biopsies are rarely possible to confirm clinical diagnosis. Ultrasonographic changes are the commonest tool used to correlate the laboratory and clinical findings. This apparent deficit in the study is also the fact that enhances its relevance in clinical day to day practice.

CONCLUSION

With the rising prevalence of obesity especially in developing countries in India, the 'deadly quartet' or Syndrome X is threatening even larger segments of the productive population. Although Insulin resistance and central obesity are now firmly established as indisputable cogwheels in the understanding of its pathogenesis, for the most part the underlying mechanisms remain a mystery. Our study of obese individuals with a focus on liver functions adds to the growing understanding of the anthropometric, clinical, laboratory and radiologic aspects of NAFLD, a disease of growing importance.

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