Original Paper

Clinical Profile of Patients with Incidentally Detected Non-alcoholoic Fatty Liver Disease

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DOI:https://doi.org/10.3329/jafmc.v14i1.42712

Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) is the commonest liver problem worldwide with disease spectrum ranging from steatosis to steatohepatitis, advanced fibrosis and cirrhosis.

Objective: To delineate the clinical and biochemical profile of patients with incidentally detected NAFLD.

Materials and Methods: In this observational study, subjects without overt liver disease having sonological evidence of fatty liver underwent thorough physical examinations including anthropometric measurements and investigated for blood glucose level, lipid profile and liver function status. Aspartate aminotransferase (AST) /alanine aminotransferase (ALT) ratio and body mass index (BMI) and diabetes (BARD) score were computed to assess hepatic fibrosis status non-invasively.

Results: Out of 407 final participants, 213 were male and 194 were female. Mean age of the patients was 42.05±10.54 (range 21-71) years and BMI was 26.92±3.75 Kg/m². Visceral obesity as measured by abdominal circumference and waist-hip-ratio were found increased in 333(81.8%) and 336(82.5%) subjects respectively. Obesity (BMI > 25 Kg/m²), diabetes mellitus, hypertension, and metabolic syndrome (MS) were present in 68.8%, 48.2%, 36.4%, and 87.5% of patients respectively. Total cholesterol, low density lipoprotein (LDL) and triglyceride (TG) were found increased in 194 (47.7%), 174 (42.8%) and 328 (80.6%) patients respectively and high density lipoprotein (HDL) decreased in 338 (83.1%) patients. Elevated AST and ALT levels were found in 98 (24.1%) and 233 (57%) patients, respectively. AST/ALT ratio >1 and BARD score >2 were found in 112 (27.5%) and 119 (29.2%) patients respectively.

Conclusion: In Bangladesh, incidentally detected NAFLD patients are predominantly middle aged and obese. Metabolic Syndrome and hypertriglyceridaemia are highly prevalent among them. Around one fourth of them have evidence of advanced fibrosis non-invasively.

Key-words: Non-alcoholoic fatty liver, Nonalcoholoic steatohepatistis, Metabolic syndrome, Fibrosis score.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the commonest liver problem worldwide and up to one third of the general population is affected by it. By definition, this occurs in patients with little or no history of alcohol consumption[1]. Disease spectrum may range from simple steatosis to steatohepatistis (NASH), advanced fibrosis and cirrhosis[2]. Disease presentation also ranges from asymptomatic to cirrhosis with complications of liver failure and hepatocellular carcinoma[3]. Its prevalence varies between 15-46% in western countries[4-6] and 8-40% in Asian countries[6-11]. The growth of NAFLD as an epidemic is related to increasing prevalence of obesity, diabetes and metabolic syndrome (MS) in the general population. In fact, NAFLD is now considered as the hepatic manifestation of MS[12]. In parallel with industrialization, urbanization, changes of life style towards sedentary works and western type dietary habit, epidemic of obesity and metabolic syndrome, the prevalence of NAFLD is increasing rapidly in Asian countries[13-15]. Furthermore recently NASH / NAFLD is noticed in non-obese Asians, which is called Asian paradox. Bangladesh is a rapidly developing country with industrialization, urbanization, changes in life style, westernization in food habit and also experiencing detection of NAFLD in increasing numbers. But data on NAFLD is limited in Bangladesh. A few studies conducted on prevalence of NAFLD show a prevalence of 18.4-35.4%[16-18]. Male sex, middle age (40 years), obesity and overweight, higher family income, higher education, diabetes mellitus, hypertension and abdominal obesity were found to be associated with NAFLD in these studies[16,17].

Although NAFLD is a commonly encountered disorder, there is paucity of data on the clinical profile of general patients with NAFLD. So, this observational study was designed to delineate the clinical and biochemical profile of patients with incidentally detected NAFLD attending gastroenterology clinic.

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Materials and Methods

This is an observational study to delineate the clinical and biochemical profile of patients with incidentally detected NAFLD. Consecutive patients attending a gastroenterology clinic with sonographic evidence of hepatic steatosis were included provided that relevant data pertaining to clinical, anthropometric, metabolic and biochemical profile were available. Alcohol consumption of >20 ml/day (as evident from patients' confession or interview of close relatives), presence of hepatitis B or C virus infection or other liver diseases such as autoimmune hepatitis, Wilson's disease, α 1-antitrypsin deficiency, haemochromatosis, and patients on medications producing steatosis within the past 6 months were excluded from the study. Patients referred for increased transaminases or with overt chronic liver disease were also excluded.

The study period was 2014 to 2017 and a total of 429 patients incidentally detected to have sonographic evidence of NAFLD were included in the study 236 of them from gastro-enterology departments of North East Medical college, Sylhet and 193 from Enam medical college, Dhaka. Seventeen patients who denied to do relevant investigations and or unwilling to participate in the study were excluded from the study. Four patients were excluded due to HBsAg positivity and one for anti HCV positivity. The remaining 407 patients with complete anthropometric, biochemical and metabolic parameters constituted the study subjects. All study subjects underwent thorough clinical history and physical examination. In all the subjects, anthropometric measurements including height, weight, waist and hip circumferences were recorded. Biochemical and haematological tests including liver function test (LFT), lipid profile, fasting blood glucose (FBG) and oral glucose tolerance test (OGTT) were done in the laboratory of relevant institutions by standard methods. Socioeconomic status of the patients was arbitrarily decided according to the monthly income of the family. Monthly income less than 5000 taka, 5000-15000 taka and more than 15000 taka were taken as low, middle and high socioeconomic status. The study was approved by the Institutional Ethical Committee of the Enam Medical College Dhaka, Bangladesh.

Type II diabetes, impaired glucose tolerance (IGT), impaired fasting glycaemia (IFG) was diagnosed according to the American Diabetes Association (ADA) criteria[19]. For serum lipids, we followed National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) guidelines[20]. Hypertension (HTN) was defined by resting blood pressure >140/90 mmHg or treatment with antihypertensive drugs. BMI was classified according to the Asia-pacific criteria for BMI and abdominal obesity[21]. A BMI of 18.5 - 22.9 kg/m² was considered normal, 23 -24.9 kg/m² overweight and over 25 kg/m², obese. Diagnosis of MS in this study was made on the basis of Asian criteria. At least three of the five criteria mentioned below were considered: waist circumference ≥ 80 cm for women and ≥ 90 cm for men, serum triglyceride ≥ 150 mg/dL (1.7 mmol/L), serum high-density lipoproteins (HDL) cholesterol < 50 mg/dL (1.3 mmol/L) for women and < 40 mg/dL (1 mmol/L) for men, elevated blood pressure (systolic blood pressure ≥ 130 and or diastolic blood pressure ≥ 85 mm of Hg or drug treatment for hypertension) and fasting plasma glucose concentration ≥ 100 mg/dL (5.6 mmol/L) or drug treatment for diabetes[22].

Ultrasonographically fatty liver was graded according to Saadeh et al[23] AST/ALT ratio greater than 1 is a simple predictive model for advanced fibrotic form of the disease[24]. AST/ALT ratio was computed to detect status of fibrosis non–invasively. BMI, AST/ALT Ratio, and Diabetes score (BARD score) (BMI ≥28=1 point; AST/ALT ratio ≥0.8=2 points; and the presence of diabetes=1 point) equal to 2 or greater is another simple predictive model for advanced fibrosis[25]. It also computed BARD score to assess liver fibrosis non-invasively. Categorical variables presented as numbers and percentages, and the continuous variables presented as mean ± standard deviation (SD). The data were analyzed using SPSS version 21 package. Students' t–test was performed for continuous data where as Chi-square test was performed for categorical data and a p value <0.05 was considered as significant.

Results

Among the 407 final participants, 213 were male and 194 were female. Mean age of the patients was 42.05±10.54 (range 21-71) years. Subjects with NAFLD mostly (63.6%) belonged to 31-50 years age group. In this study, most patients (66.3%) with fatty liver disease were from high socioeconomic status (Table-I). About 180 (84.5%) male and 184 (94.8%) female were overweight or obese ($p < 0.001$). Visceral obesity as measured by abdominal circumference and waist-hip-ratio were found more in females than males ($p < 0.001$). Even 6 (18.2%) male and 5 (50%) female with normal BMI (<23kg/m²) had increased waist circumference (above 80cm and above 90 cm respectively) ($p < 0.001$) (Table-II).

Fifty-seven (26.9%) males and 91 (46.9%) females were found to have hypertension. A total of 93(43.7%) males and 103(53.1%) females had type II diabetes. Another 39 (18.3%) males and 17(8.8%) females had impaired fasting glucose (Table-III). The mean values of biochemical parameters (lipid profile and LFT) are presented in Table-IV. Hepatomegaly was found in only 20 (5.0 %) patients.

Hyperbilirubinaemia (>1.2 mg/dL) was present in 10 (2.45%) patients and elevated AST and ALT levels were found in 98 (24.1%) and 233 (57.0%) patients, respectively. When upper limit of normal (ULN) for ALT is reduced to 30 IU/ml 170(79.8%) males were found to have elevated ALT levels. When ULN for ALT is reduced to 19 IU/ml 173(89.2%) females were found to have elevated ALT levels[26]. AST/ALT ratio > 1 was found in 49(23.0%) male and 63(32.6%) female NAFLD patients ($p < 0.05$) indicating advanced fibrosis. Total cholesterol and LDL increased were found in 194 (47.7%) and 174 (42.8%) NAFLD patients respectively and HDL decreased 338 (83.1%) patients. More males had increased triglyceride (TG) level than females ($p < 0.001$) (Table-III). All together 181(85.0%) males and 175(90.2%, $p > 0.05$) females met the Asian criteria for metabolic syndrome. In this study 36(16.9%) male and 83(42.8%) female had BARD score equal to 2 or greater ($p < 0.001$), which is predictive of advanced fibrosis.

Table-I: Socio-demographic features of NAFLD patients (n=407)

Characteristics		Male (n=213)	Female (n=194)	p-value
Age (Mean±SD)		40.35±10.536	43.93±10.243	< 0.001
Education	Illeterate	27(12.7%)	48(24.7%)	< 0.001
	Primary	73(34.3%)	83(42.8%)	
	SSC	28(13.1%)	42(21.6%)	
	HSC	25(11.7%)	8(4.1%)	
	Graduate and above	60(28.2%)	13(6.7%)	
Occupation	House wife	0	176(90.7%)	< 0.001
	Service	53(24.9%)	13(6.7%)	
	Farmer	9(4.2%)	0	
	Business	92(43.2%)	3(1.5%)	
	Others	59(27.7%)	2(1.0%)	
Income (Taka/month)	Up to 5000	8(3.8%)	1(0.5%)	< 0.05
	5000-15000	71(33.3%)	57(29.4%)	
	>15000	134(62.9%)	136(70.1%)	
Residence	Urban	95(44.6%)	114(58.8%)	< 0.01
	Rural	118(55.4%)	80(41.2%)	
Habit	Tobacco (smoking/chewing)	100(46.9%)	31(16.0%)	< 0.01
	Alcohol	1(0.5%)	0	
	Both alcohol & tobacco	2(.9%)	0	

Table-II: Anthropometric measurements of NAFLD patients (n=407)

Characteristics		Male n (%)	Female n (%)	p-value
Body Mass Index (BMI)	Under weight(<18.5kg/m^2)	2(0.9%)	2(1.0%)	< 0.001
	Normal(18.5-23 kg/m^2)	31(14.6%)	8(4.1%)	
	Overweight(23-25 kg/m^2)	57(26.8%)	27(13.9%)	
	Obese(>25 kg/m^2)	123(57.7%)	157(80.9%)	
Waist circumference	Normal	63(29.6%)(≤ 90 cm)	11(5.7%)(≤ 80 cm)	< 0.001
	Increased	150(70.4%)(> 90 cm)	183(94.3%)(> 80cm)	
Waist-hip-ratio	Normal	51(23.9%)(≤.90)	20(10.3%)(≤.85)	< 0.001
	Increased	162(76.1%)(>.90)	174(89.7%)(>.85)	

Table-III: Distribution of NAFLD patients according to clinical profile (n=407)

Characteristics		Male n(%)	Female n(%)	p-value
Hypertension		57(26.9%)	91(46.9%)	< 0.001
Hyper glycaemia	Diabetes Mellitus	93(43.7%)	103(53.1%)	< 0.001
	IGT	4(1.9%)	14(7.2%)	
	IFG	39(18.3%)	17(8.8%)	
Fatty Liver(USG)	Mild fatty liver	184(86.4%)	163(84.0%)	> 0.05
	Moderate fatty liver	29(13.6%)	28(14.3%)	
	Severe fatty liver	0	3(1.7%)	
Hypothyroidism	Overt hypothyroid	2(0.9%)	2(1.0%)	> 0.05
	Sub-clinical hypothyroid	7(3.3%)	9(4.6%)	

IGT: Impaired glucose tolerance test, IFG: Impaired fasting glycaemia, USG: Ultrasonography

Table-IV: Distribution of NAFLD patients according to biochemical parameters, AST/ALT ratio and BARD score (n=407)

Characteristics	Male n (%)	Female n (%)	Total	p-value
ALT > 40IU/dl	149(69.95%)	83(42.8%)	233(57.0%)	< 0.001
AST >40 IU/dl	62(29.1%)	36(18.6%)	98(24.1%)	> 0.05
AST/ALT ratio >1	49(23.0%)	63(32.6%)	112(27.5%)	> 0.05
TG >150mg/dl	189(88.7%)	139(71.6%)	328(80.6%)	< 0.001
HDL: (Male <40mg/dl & Female <50mg/dl)	168(78.9%)	170(87.6%)	338(83.05%)	> 0.05
LDL >130mg/dl	84(39.4%)	90(46.4%)	174(42.8%)	> 0.05
Cholesterol >200mg/dl	100(46.9%)	94(48.5%)	194(47.7%)	> 0.05
BARD score ≥2	36(16.9%)	83(42.8%)	119(29.2%)	< 0 .001

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, BARD score: BMI, AST/ALT Ratio and Diabetes Score

Discussion

NAFLD is commonly encountered condition in clinical practice but data on various aspects of incidentally detected NAFLD are lacking in Bangladesh. NAFLD is a disease of middle age and mostly affects male[6, 7, 9, 10,27]. The mean age of the study population was 40.35 years which is consistent with previous data[28,29]. However, age did not influence the development of NASH. Male preponderance was not found in this study which is consistent with the findings of other studies in Bangladesh[16-18,28]. Around 68.8% this study population were obese (BMI>25 kg/m^2). In India[9,30], and Sri Lanka[27] 60-70% NAFLD patients are found to be obese. In Bangladesh, Madhu[17] showed that around 87% NAFLD patients had BMI over 33 Kg/m^2. In the study of Masud[16] around 70.34% had BMI over 25 Kg/m^2. Mean BMI of the patients was 26.92±3.75 Kg/m^2 which is lower than Western studies (30–38 kg/m^2)[31,32] but similar to Asian countries[9,29,30]. Despite having lower BMI, the patients had fatty liver, possibly due to greater propensity to insulin resistance (IR) and central obesity (South Asian phenotype)[33]. IR was not measured In this study. Previous studies showed high prevalence of IR among NAFLD patients[28,29]. Visceral obesity as measured by abdominal circumference and waist-hip ratio were found increased in 81.81% and 82.5% subjects respectively in the present study. Masud reported that 66.9% of their NAFLD patients had abdominal obesity[16]. High prevalence of visceral obesity also reported from Sri Lanka (61%) among NAFLD patients[27].

NAFLD patients are mostly from high income group in the present study which supports the previous data[16,17,27]. Diabetes and HTN are two components of NAFLD and important risk factors for NAFLD. In this study, 48.2% patients had DM and 36.4% had hypertension. In the population-based study of Rahman 39.3% patients with NAFLD had DM[16]. Other studies of Bangladesh reported a lower prevalence of diabetes among NAFLD patients (15-22%)[17,28]. A lower prevalence of diabetes (7%–22%) was also found in some Indian studies[9,29,30]. This is in contrast to western figures where 40-50% cases of diabetes in NAFLD is reported from UK[34] and USA[35]. Hypertension was present in 23.1% NAFLD patients in the study of Shaheen[28] whereas 27.5% patients with NAFLD had HTN in the study of Madhu[17]. In a Russian study hypertension was present in 69.9% patients[36]. In this study, the serum TG (>150mg/dl) and serum LDL levels (>130mg/dl) were above the normal upper limit in 80.6% and 42.8% patients respectively, while the serum HDL level was below the normal limit in approximately 83%, signifying that most patients had dyslipidaemia, a known risk factor for fatty liver. Dyslipidaema was found in 75.9% patients with NAFLD in Russia[36] and in 62% NAFLD patients in India[29].

It is not known to us how many patients had steatohepatis and advanced fibrosis as liver biopsy and fibroscan were not done due to lack of feasibility. However 57% patients had raised ALT. This finding is similar to the Indian study[29], but lower than western studies[31,32]. Masud reported a lower prevalence of raised ALT (25.5%) among NAFLD patients[16]. But raised ALT is not a good predictor of NASH or advanced fibrosis. In the study of Verma, there was no difference in the rate of advanced fibrosis between normal and elevated ALT (26.8% vs. 18.1%, $p > 0.05$). However, significantly lower percentage of normal ALT group had NASH compared to elevated ALT group (10.7% vs. 28.9%, $p < 0.01$)[37]. AST/ALT ratio >1 and BARD score ≥2 are two predictors of advanced fibrosis[24,25]. Around 24% and 29% of the NAFLD patients were found to have advanced fibrosis based on AST/ALT ratio and BARD score respectively. Whereas In the study of Shaheen only 8.3% patients had advanced fibrosis[28] and NASH was present in 42.4% NAFLD cases which is much higher compared to other published report[29,38].

The presence of MS is associated with NASH and advanced fibrosis in NAFLD patients. With addition of each component of MS the risk of hepatic steatosis increases exponentially[12]. In this study, 87.5% of NAFLD patients had MS which is higher than reports from Rahman et al.(68.3%)16 and Shaheen et al.(52.3%)[28]. Indian[29,30] and Russian[36] studies also reported a low prevalence of MS(20-40%) in NAFLD patients.

Limitations

1) It is not a population-based study. Therefore the findings of this study may not be representative and applicable to the general population.

2) NAFLD was detected on the basis of USG findings. Still today gold standard for diagnosis of NAFLD is histological evaluation. The sensitivity of USG for detecting >30% steatosis is 92.3% when compared with the histological evaluation and positive predictive value of ultrasound is only 34%[39]. Inter observer reliability designed to provide a major of correlation between the observers rating for ultra-sonographic evaluation was not done. Ultrasonography can not differentiate NAFLD and NASH[40].

3) Due to lack of feasibility liver biopsy and elastography were not done. Therefore, it could not validate ultrasound finding in the patients with histology and cannot be exactly said how many patients had NASH or advanced fibrosis reliably.

Conclusion

Despite limitations it is a valuable attempt to delineate the clinical profile of incidentally detected NAFLD patients. This

study clearly demonstrates that subjects with NAFLD are mostly middle aged, obese and from higher socioeconomic status. DM, MS, dyslipidaemia and hypertension are prevalent among the NAFLD patients. Around one fourth of NAFLD patients were detected to have advanced hepatic fibrosis non-invasively. NAFLD is a silent killer. So clinicians must be aware of clinical, biochemical and histological profile of this disease and should take appropriate steps for early detection and to halt the progression of this benign disease to advanced fibrosis through life style modification. Further well-designed studies with appropriate investigations involving large number of population at community level are required to find out the true clinical profile of NAFLD patients.

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