ORIGINAL ARTICLE

Frequency of Non-Alcoholic Fatty Liver Disease among the Non-Obese Population Presenting to the Gastrointestinal Outpatient Clinic

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Abstract

Background: It has been reported that Asian males with BMI ≤ 23 kg/m^2 have considerably higher content of fat and visceral adipose tissue as compared to their Western counterparts. Multiple studies have reported variable frequency of Non-alcoholic Fatty Liver Disease (NAFLD) in lean population. However, the data is scarce regarding the prevalence of NAFLD in the lean Asian population.

Objective: To determine the frequency of NAFLD among the non-obese population presenting to gastroenterology outpatient clinics.

Methods: This cross-sectional study included all the lean individuals with BMI≤ 23 kg/m^2 presenting to the gastroenterology outpatient clinic from November 2020 to March 2022. Ultrasound abdomen was performed for the presence or absence of fatty liver which was diagnosed based on hyperechoic liver texture. The analysis of continuous variables was performed using the student t-test while the Chi-square test was applied for the analysis of categorical variables. A p-value ≤ 0.05 was considered as statistically significant.

Results: Among the 283 individuals presenting to the gastrointestinal clinic with BMI < 23 kg/m^2 is superscript, the majority were females [150 (53%)]. Out of 283 patients, 118(41.7%) had hypertension, 114(40.3%) had hypertriglyceridemia while 86(29.7%) patients had diabetes. On ultrasound abdomen, fatty liver was observed in 92 (32.5%) patients including 59 (64.1%) females and 33 (35.9%) males. The statistical analysis documented a significant association of NAFLD with female gender (p=0.006), hypertension (p<0.001), hypertriglyceridemia (p=0.130), high total lipids (p<0.001), and serum cholesterol levels (p=0.005). However, no statistically significant association of fatty liver was observed with body mass index (p=0.823), age (p=0.169), and diabetes (p= 0.522).

Conclusion: The presence of hypertension, hypertriglyceridemia, raised total lipids and serum cholesterol levels and female gender were the factors significantly associated with the presence of fatty liver in the lean population. However, to validate our results, multicentered studies on a larger scale are required.

Keywords: *Fatty liver, Non-alcoholic fatty liver disease (NAFLD), Pakistan, non-obese, hypertriglyceridemia.*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a well-defined condition that is characterized by hepatic steatosis, established based on either radiological tests or tissue biopsy, after excluding the other etiologies associated with increased accumulation of fat in the liver such as alcohol consumption, intake of certain drugs causing fatty liver or genetic disorders [1]. NAFLD is divided into three stages; steatosis, steatohepatitis with and without fibrosis (NASH); and lastly, cirrhosis [2]. Approximately, 25% of the world's population is suffering from fatty liver disease, while its prevalence in Asian countries ranges from 15% to 45% [3, 4]. In Pakistan, the prevalence of NAFLD ranges between 14-47% [5-8]. It is a multifactorial disorder that is frequently linked with other conditions like diabetes mellitus (DM), obesity, dyslipidemia, and metabolic syndrome (MS) [9, 10]. The parameter for measuring obesity is body mass index (BMI). Hence, it is considered an important predictor of NAFLD [11]. Generally, the patients with high BMI are at increased risk of developing NAFLD due to increased visceral fat accumulation.

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The high risk of metabolic syndrome in the Asian population can be attributed to the increased body fat leading to increased visceral fat accumulation in this population as compared to the Western population [12, 13]. Previously, studies have revealed a proportionally increased percentage of body fat in the Asian population even with a low BMI [14, 15]. This can be explained by the lower height of Asians as compared to the Western population [16]. Hence, in the Asian population, BMI is an inaccurate tool for the quantification of adipose tissue.

In South Asia, large data is available regarding the obese NAFLD. However, the data is scarce regarding the incidence and frequency of fatty liver in non-obese individuals. Das and his colleagues reported a 5.1% incidence of NAFLD in the non-obese population in a community-based study; but, BMI<25 kg/ m^2 was set as a cutoff [17].

To the best of our knowledge, the exact frequency of non-alcoholic fatty liver disease in the non-obese population is unknown in a densely populated developing country like Pakistan. Abbas *et al*. [5], reported a prevalence of NAFLD in 15.3 % population (n=142) in a hepatitis awareness program in which 22.5% population had a BMI <25 kg/ m^2. Although this above-mentioned study was carried out in the Pakistani population, it

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utilized a high cut-off of BMI (< 25 kg /m^2) as opposed to the current Asian population standard.

Therefore, our main objective was to evaluate the estimated frequency of fatty liver among the non-obese population presenting to our outpatient department (OPD). This study will be helpful for the community to estimate the burden of the disease in this group of patients which can help us in planning timely treatment and prevention of the NFLD related complications.

MATERIALS AND METHODS

This cross-sectional study was carried out at the Department of Hepato-gastroenterology, Sindh Institute of Urology and Transplantation between November 2020 to March 2022. Patients of either gender or ages ranging from 18-70 years presenting with abdominal pain and having BMI <23kg/m^2 were included in the study. The sampling technique used was non-probability consecutive sampling. While, those patients with current or prior history of viral hepatitis including Hepatitis A, Hepatitis B, Hepatitis C, and Hepatitis D (positive anti-HDV antibody), those with a history of significant alcohol consumption (>20 g/day or 14 standard drinks per week in women and 21 standard drinks/week in men) or space-occupying lesion in the liver, those with presence of fluid in the abdomen (ascites) or any history of recent abdominal surgery within past 4 weeks were excluded from the study.

Based on the previous studies, the estimate of NAFLD among the non-obese (BMI < 23 kg/m^2) was 15% to 21%. Taking a margin of error of 8% and a 95% confidence interval, an estimated sample size of 94 patients was proposed for this study.

After the approval from the ethical review committee, consecutive lean patients (BMI ≤23 kg/m^2) visiting the gastroenterology outpatient clinic of Sindh Institute of Urology and Transplantation for upper abdominal pain, were enrolled in this study as per inclusion criteria. Informed consent was taken from all the patients before the enrolment in the study. Ultrasound abdomen was carried out by a consultant radiologist; with more than 3 years post-fellowship experience; using US (TOSHIBA-apleo 50 Model MCM17545TS. Ultrasound abdomen was performed after 8-10 hours of fasting. Nonalcoholic fatty liver was labeled on percutaneous ultrasound based on the presence or absence of hyperechoic liver. Depending upon sonographic findings patients were divided into:

1) Presence of fatty liver
2) Absence of fatty liver

All the demographic information including the age, gender, body mass index, presence or absence of diabetes (FBS >126mg/dl), hypertension (systolic BP >140 mmHg), hypertriglyceridemia (>150 mg/dl), and findings on ultrasound abdomen were entered in the predesigned proforma.

Statistical Package for the Social Sciences (SPSS) version 24.0 was utilized for the data analysis. Mean ± standard deviation was computed for the continuous variables including age, duration of abdominal pain, weight, height, and body mass index (BMI); while categorical variables including gender, diabetes, and hypertension were expressed in terms of frequencies and percentages. The outcome was observed in terms of the presence or absence of fatty liver on ultrasound abdomen. Effect modifiers like age, gender, diabetes mellitus, and hypertension were controlled through stratification. Student t-test was used for the analysis of continuous variables while comparative analysis of categorical variables was performed using the Chi-square test. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 283 patients presenting to the gastrointestinal clinic with BMI ≤ 23 kg/m^2 were included in the study. Among them, the majority were females [150 (53%)] (**Table 1**). The population had a mean age of 39.1 ± 9.8 years and the mean BMI was 21± 1.6 kg/m^2. Out of 283 patients, 118(41.7%) had hypertension, 114(40.3%) had hypertriglyceridemia while 86(29.7%) patients had diabetes.142 (50.2%) patients had regular eating habits while 109(38.5) and 32(11.3%) patients had irregular and binge eating habits respectively. On ultrasound abdomen, fatty liver was observed in 92 (32.5%) patients including 59 (64.1%) females and 33 (35.9%) males. Among the 118 patients with hypertension, 57 (50%) had fatty liver while 78(66.4%) patients with hypertriglyceridemia and 25(29.8%) patients with diabetes had NAFLD.

Stratification concerning age, gender, BMI, diabetes, hypertension, hypertriglyceridemia serum cholesterol, and total lipids was performed to assess the associated factors with nonalcoholic fatty liver disease.

The statistical analysis documented a significant association of NAFLD with female gender (p=0.006), hypertension (p≤0.001), hypertriglyceridemia (p=0.13), high total lipids (p≤0.001), and serum cholesterol levels (p=0.005) (**Table 2**). However, no statistically significant association of fatty liver was observed with age (p=0.169), eating habits, and diabetes (p= 0.522) in our study.

DISCUSSION

Non-alcoholic fatty liver disease (NAFLD) is stated as the deposition of fat within hepatocytes in the absence of significant alcohol consumption (> 21 g/day in males

Table 1: Demographics of the studied population (n-283).

Study population(n=235)		n (%)
Mean age(years±S.D)		39.1 ± 9.8
Gender	Male	133(47)
	Female	150(53)
Height(m^2)		1.63 ± 6.8
Weight(Kg)		56±6
Body Mass Index(BMI)(kg/m^2)		21± 1.6
Diabetes		86(29.7)
Hypertension		118(41.7)
Hypertriglyceridemia		114(40.3)
Eating Habits	Regular	142(50.2)
	Irregular	109(38.5)
	Binge Eating	32(11.3)
Fatty liver on ultrasound	Yes	92(32.5)
	No	191(67.5)
Total Bilirubin(mg/dl)		0.7±0.3
Alkaline Phosphatase(IU/L)		135±109
Aspartate Transaminase(AST)(IU/L)		37.8±55.5
Alanine Transaminase(ALT)(IU/L)		47.4±31.8
Serum Cholesterol		360±155
Serum LDL		105± 31
Serum HDL		42.6± 9.3
Total Lipids		672±150
Serum Triglycerides		158±74

Abbreviations: *LDL: low density lipoprotein; HDL: high density lipoprotein.*

Table 2: Stratification of Non-alcoholic fatty liver disease (NAFLD) concerning age, gender, diabetes, hypertension, and hypertriglyceridemia (n= 283).

Variables		NAFLD (n-92) N(%)	Without NAFLD (n-191) N(%)	p-value
Age(years)		38.4±8.4	40±10.6	0.169
Gender	Male	33(35.9)	102(53.4)	0.006
	Female	59 (64.1)	89(46.6)	
BMI(Kg/m^2)		21± 1.9	21± 1.4	0.823
Diabetes	Yes	25(27.2)	61(31.9)	0.522
	No	67(72.8)	130(68.1)	
Hypertension	Yes	56(60.8)	60(15.7)	≤0.001
	No	36(39.2)	161(84.3)	
Hypertriglyceridemia	Yes	78(84.8)	36(18.8)	0.013
	No	14(15.2)	155(81.2)	
Serum Cholesterol		737±267	173± 38	0.005
Serum Lipids		154±11	129 ± 14	≤0.001

Abbreviation: *BMI: Body Mass Index.*

and > 14g/day in females), viral serology, steatogenic drugs, and hereditary disorders. The diagnosis of NAFLD is established on the presence of hyper-echoic liver on ultrasound abdomen or > 5% steatosis on liver biopsy [1]. Many factors such as metabolic syndrome, cardiovascular disease, obesity, and dyslipidemia are risk factors for NAFLD [9, 10]. Globally, one of the emerging causes of chronic liver disease is NAFLD. The reported prevalence of NAFLD worldwide is 25% [3, 4]. However, in Pakistan, the estimated prevalence of NAFLD is 14.8%-20% [5-8]. It is more common among the obese population, but it has also been documented among the lean population in both the developing as well as the developed countries [3-9]. Das *et al*. [17] reported the prevalence of NAFLD in India as 8.7 %, with 5.1% of these including non-obese (BMI < 23 kg/m2). In the United States, NAFLD prevalence in lean subjects (BMI < 25 kg/m2) was found to be 9.67% [18]. Kwon *et al*. showed that among the Korean population, non-obese NAFLD was found to be 12.6% [19].

In the Asian population, the people have more visceral adiposity as compared to the overall body fat. Visceral obesity is not only an important predictor of NAFLD but also a risk factor for cardiovascular and metabolic disease [20]. Visceral obesity cannot be defined by BMI as the latter measures the amount of fat and has different cutoffs in different populations. Wang *et al.* [14] and Deurenberg *et al.* [15] found higher body fat content in the Asian population as compared to that in the Western population even with low BMI. Xu *et al*. [21] reported that NAFLD prevalence among the non-obese lean Chinese population was 7.27%, and raised BMI and waist circumference (WC) were significantly linked with the development of NAFLD during the follow-up period. In our study, 92 (32.5%) lean patients had NAFLD on abdominal ultrasound. This can be attributed to the paradigm shift in the lifestyle of our population in recent years *i.e*., from a healthy to a sedentary lifestyle and the intake of food products with high glycemic index and saturated fats along with low physical activity.

A cross-sectional survey of the United States reported that the frequency of fatty liver was higher in females as compared to males (30.7% *vs.* 15.3%, $P < 0.001$) [18]. Similar to Younossi *et al.* [4], NAFLD was observed mostly in females in our population. Zheng *et al.* [22] documented that the mean age of NAFLD patients was 37.32 ± 10.19 years and non-NAFLD was 36.60 ± 11.14 years (p=0.62). Younossi *et al.* [23] reported patients with NAFLD were younger and were more commonly females. Similarly, our patients diagnosed with lean NAFLD were also young and had a mean age of 39.1 ± 9.8 years. This increased prevalence of lean NAFLD in our young population can again be attributed to certain factors like a sedentary lifestyle and genetic predisposition. However, the pattern of genetic inheritance of NAFLD in the local population is yet to be defined.

WHO expert consultation report stated that Asians have more chances of developing insulin resistance, Type 2 diabetes (T2DM), and cardiovascular disease than Europeans at any given body index [24]. This is because intraabdominal fat and body fat in Asians are comparatively greater than in Europeans [14, 25]. Younossi *et al*. [23] documented that fatty liver in the non-obese population was associated with diabetes and hypertension. Similarly, in our study population, eighty-six participants (29.7%) were diabetic, out of which 25(27.2%) had fatty liver on ultrasound abdomen. This shows that lean NAFLD is more prevalent in diabetics, although this does not show a statistically significant association with lean NAFLD (p = 0.522).

Previously, studies have shown a statistically significant association of hypertension with NAFLD. A study done by Donate *et al*. [26] reported hypertension in 30.9% of patients diagnosed with NAFLD. Furthermore, he also stated that insulin resistance and plasma insulin levels were higher in hypertensive patients as compared to the normal population [26]. Similarly, a study done by Lankarani *et al.* showed approximately 34.1% prevalence of lean NAFLD in the Iranian population [27]. In our study, hypertension showed a statistically significant association with NAFLD with 56(48.2%) hypertensive patients diagnosed with NAFLD ($p \leq 0.001$) which can again be attributed to the recent change in the lifestyle of our population. The other reason for such a high percentage of NAFLD in hypertensive patients as compared to the other studies can be due to the high prevalence of hypertension in our population.

Limitations of this study include that liver biopsy was not performed in our study population, considering this as a gold standard. The ultrasound abdomen demonstrated a varied sensitivity ranging from 89-91% along with specificity between 82-93% in diagnosing NAFLD [28, 29]. However, in our study ultrasound abdomen was performed by an expert radiologist with high expertise and skills with a special interest in NAFLD. Furthermore; other limitations can be attributed to this study including a small sample size and a single-centered study. Therefore, our results might not be generalized to the larger populations. Thus, multi-centric studies are required not only to validate our results but also to establish the true frequency of fatty liver in the non-obese population.

Our study also has strengths, as non-obese (Lean) NAFLD is a major but neglected issue in our population. This is the pioneer study showing the frequency of NAFLD in the lean population. The early diagnosis of NAFLD can be done by ultrasound abdomen which is readily available, non-invasive, and easy to perform investigation for diagnosing NAFLD. By identifying NAFLD in our population in the early stage, we can estimate the burden of the disease in this group which will help us in planning timely treatment and prevention of the related complications. *i.e*., liver cirrhosis.

CONCLUSION

This study demonstrated that a significant proportion of the population with BMI≤ 23kg/m^2 had NAFLD. The lean NAFLD population has a statistically significant association with the female gender along with the presence of hypertension, hypertriglyceridemia, increased total lipids, and serum cholesterol levels. As risk factors and biological behavior of the disease are not determined hence this study opens the door for further exploring the disease in a large population.

ETHICAL APPROVAL

Ethical approval was obtained from the Ethical Review Committee of Sindh Institute Of Urology And Transplantation, Karachi (REF letter No. SIUT-ERC-2022/PA-221, ERC No.: 216). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/ or national research committee and with the Helsinki Declaration.

CONSENT FOR PUBLICATION

Written informed consent was taken from the participants.

AVAILABILITY OF DATA

The data set may be acquired from the corresponding author upon a reasonable request.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR'S CONTRIBUTION

All the authors contributed equally to the publication of this article.

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