Frequency, Clinical Characteristics, and Risk Factors of Nonalcoholic Fatty Liver Disease in Lean Individuals attending Qena University Hospital

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) involves liver fat accumulation without alcohol, including NAFL and Non alcoholic steatohepatitis (NASH). Rising globally due to obesity, and diabetes, affecting even lean individuals (lean-NAFLD), demanding focused management and prevention.

Objectives: To assess the frequency, clinical characteristics, and risk factors of NAFLD in lean individuals.

Patients and methods: The cross-sectional study at South Valley University Hospital involved 200 lean participants with BMI within ethnic-specific cutoffs. Comprehensive assessments included history, examinations, laboratory tests, and abdominal ultrasonography. Fibroscan, Fibrosis-4 (FIB-4), and Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) scores were used to determine liver fibrosis stages and predict fibrosis and cirrhosis.

Results: The study involved 200 lean participants with an average age of 40.72 ± 6.71 years, 166 (83%) non-NAFLD patients and 34 (17%) NAFLD patients. Males made up 60.2% of the non-NAFLD group and 70.6% of the NAFLD group, while females made up 39.8% of the non-NAFLD group and 29.4% of the NAFLD. Lean NAFLD was associated with increased hip circumference, altered waist-to-height ratio and arm circumference, higher Systolic and diastolic blood pressure, also higher levels of HOMA-IR, TSH, and uric acid. 6% of the NAFLD group had ASMA, AMA positive with significant elevations in fibrosis and liver stiffness measurements.

Conclusion: Lean NAFLD associated to elevated lipid profile, liver enzymes, protein, HOMA-IR, blood sugar, uric acid, TSH.

Keywords: Liver; NAFLD; Obesity; Lean individuals.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is characterized by the presence of hepatic steatosis (accumulation of fat in the liver) without a history of heavy alcohol consumption or other secondary causes **(Wang et al., 2022a).** It encompasses two subtypes: nonalcoholic fatty liver (NAFL), where steatosis occurs without significant inflammation, and nonalcoholic steatohepatitis (NASH), where steatosis is accompanied by hepatic inflammation. NASH can be histologically similar to alcoholic steatohepatitis. The prevalence of NAFLD has been increasing globally, linked to rising rates of obesity and type 2 diabetes, forming part of the metabolic syndrome (MetS) along with cardiovascular disease **(Lindenmeyer et al., 2018)**. However, NAFLD can also affect lean individuals, referred to as "lean-NAFLD," highlighting the role of other factors like diet, ethnicity, gut-liver axis derangement, and gut microbiota **(Ahadi et al., 2021)**.

Recognizing NAFLD in lean individuals is vital for various reasons. Firstly, it allows for early detection and management in those who may not present traditional risk factors like obesity or metabolic abnormalities **(Marjot et al., 2020)**. Secondly, the clinical course and prognosis of NAFLD in lean individuals may differ, necessitating tailored diagnostic and therapeutic approaches. The understanding of underlying pathophysiology has evolved beyond solely excess body fat and obesity, with factors like diet, gut-liver axis, and gut microbiota gaining prominence **(Vallianou et al., 2021)**. While initially observed in the Asian population, lean NAFLD is now recognized as a global health issue. As NAFLD can progress to cirrhosis, addressing the condition in lean individuals is critical for preventive measures and improved patient outcomes **(El-Kassas et al., 2022)**.

This study aims to evaluate the frequency, clinical characteristics, and risk factors of nonalcoholic fatty liver disease (NAFLD) in lean individuals.

Patients and methods

This is a cross-sectional study conducted at the Tropical Medicine and Gastroenterology Department of South Valley University Hospital from April 2022 to April 2023.

The inclusion criteria lean individuals with a body mass index (BMI) within the ethnic-specific cutoff of 25 kg/m^2 for Caucasians and nonalcoholic consumption (less than 20 gm ethanol/day). The exclusion criteria obese patients (BMI >25 kg/m^2), underbody-built patients (BMI < 18 Kg/m^2), individuals who have taken medications causing fatty liver in the past year, and those with other causes of chronic liver disease, including excessive alcohol consumption (>20 gm ethanol/day), hepatitis B or C virus infection, and other relevant liver diseases based on detailed medical history and questionnaires (e.g., Wilson's disease, hemochromatosis, autoimmune hepatitis, primary biliary cirrhosis). The study sample size includes 200 lean individuals, drawn from medical staff members and patients attending the gastroenterology and hepatology outpatient clinic at SVU Hospital.

The study involved a comprehensive assessment of all included cases, covering history taking, clinical examinations, laboratory investigations, and abdominal ultrasonography. History taking included therapeutic history, alcohol intake, and past medical history. Clinical examinations involved measuring body weight, calculating Body Mass Index (BMI), assessing waist circumference and Waist/Hip ratio (W/H ratio), and recording blood pressure. An abdominal examination was performed, and electrocardiography and chest X-ray were conducted to rule out heart and lung diseases. Laboratory investigations

included complete blood picture, liver function tests, lipid profile, fasting blood glucose, insulin resistance (HOMA), viral markers (HBsAg, anti-HCV), thyroid-stimulating hormone (TSH), autoantibodies (Anti-Smooth Muscle Antibody (ASMA) and Anti-Mitochondrial Antibody (AMA), and serum uric acid levels. Abdominal ultrasonography was carried out on all participants using standardized criteria using a convex probe with a 3.5–5 MHz frequency (SonoAce X6 Ultrasound System; Medison Electronics, Seoul, Korea).

Liver fibrosis stages were determined using the fibroscan score, with Stage F0-F1 indicating no or mild fibrosis (<7 kPa), Stage F2 representing moderate fibrosis (7-8.99 kPa), Stage F3 indicating severe fibrosis (9-12.49 kPa), and Stage F4 denoting cirrhosis (≥12.5 kPa) (**Castéra et al., 2005)**. During the hepatology clinic visit, liver stiffness measurement (LSM) and Cont)rolled Attenuation Parameter (CAP) were obtained using fibroscan 502 after an 8-hour fasting period. Steatosis grades were determined based on the CAP score, with Grade 0 indicating less than 5% of the liver affected by the fatty change, Grade 1 representing 5–33% involvement, Grade 2 indicating >33–66% involvement, and Grade 3 denoting >66% of the liver affected by the fatty change **(Chan et al., 2014).** The median of 10 LSM and CAP measurements were considered reliable and included in the final analysis if 10 successful acquisitions were obtained **(Liu et al., 2017).** Additionally, liver fibrosis was quantified using FIB-4 **(Sterling et al., 2006)** and APRI scores (**Wai et al., 2003)**, with specific cutoff values used to predict significant fibrosis and cirrhosis. The study found lower and upper cutoff values of 1.45 and 3.25 for FIB-4, respectively, and 0.5 and 1.5 for APRI to predict significant fibrosis, while APRI values of 1.0 and 2.0 were used to detect cirrhosis, as no satisfactory cutoff value for FIB-4 to detect cirrhosis was identified in the literature.

APRI AND FIB-4 formula: The scores were calculated by the following formulas: FIB-4 score = Age (years) × AST (IU/L)/Platelet count (10^9/L) × ALT (IU/L) 1/2

APRI = (AST level / Upper Limit of Normal AST) / Platelet count (10^9/L) × 100 **(Kim et al., 2016)**

Study ethical approval code: SVU-MED-GIT023-1-22-2-321.

Statistical analysis

Utilizing version 26 of the Statistical Package for the Social Sciences (SPSS) software, data was managed and analyzed. Continuous variables were illustrated as Mean ± SD or median and range. The median and range were utilized for assessing ordinal variables. When the P value was ≤0.05, the values were deemed significant. Test of data normality was Shapiro wilk test.

Results

NAFLD population ~~in our study~~ represented 17% (34) of total cases. The sex distribution of non-NAFLD and NAFLD groups was not significantly different (p = 0.257). Males made up 60.2% of the non-NAFLD group and 70.6% of the NAFLD group, while females made up 39.8% of the non-NAFLD group and 29.4% of the NAFLD. NAFLD patients were nonsignificantly older than non-NAFLD patients (p = 0.067). Waist Circumference (p = 0.916) and BMI (p = 0.142) did not vary. NAFLD was associated with a substantial increase in hip circumference (p < 0.001). The NAFLD group had significantly decreased the Waist-to-Height Ratio (p = 0.038~~)~~ and increased Arm Circumference (p = 0.006~~)~~ However, Waist-to-Hip Ratio was insignificant (p = 0.506), **(Table .1).**

Table 1. Demographic data and anthropometric measurements in the studied groups

Demographic data	Total (n = 200)		Non-NAFLD (n = 166)		NAFLD (n = 34)		Test of Sig.	p. value
	No.	%	No.	%	No.	%		
Sex								
• **Male**	124	62.0	100	60.2	24	70.6	χ^2= 1.282	0.257
• **Female**	76	38.0	66	39.8	10	29.4		
Age (years)	40.72 ± 6.71		40.43 ± 7.09		42.12 ± 4.23		t= 1.857	0.067
Anthropometric measurement								
Waist Circumference (cm)	83.65 ± 4.20		83.63 ± 4.34		83.71 ± 3.51		t=0.106	0.916
BMI (kg/m2)	22.55 ± 1.09		22.59 ± 1.12		22.32 ± 0.91		t=1.49	0.142
Hip circumference (cm)	88.32 ± 1.87		87.65 ± 1.24		91.55 ± 0.66		t=26.255*	<0.001*
Waist-to-height ratio	0.46 ± 0.05		0.48 ± 0.02		0.46 ± 0.05		t=2.087*	0.038*
Waist-to-hip ratio	0.84 ± 0.04		0.84 ± 0.04		0.83 ± 0.04		t=0.666	0.506
Arm circumference\cm	13.91 ± 0.79		13.84 ± 0.80		14.25 ± 0.66		t=2.792*	0.006*

*: Statistically significant at $p \leq 0.05$, SD: Standard deviation t: Student t-test; χ^2: Chi square test; p: p value for comparison between Non-NAFLD and NAFLD, BMI: body mass index

The mean systolic blood pressure was 121.5 ± 7.51 mmHg in the non-NAFLD group and 144.8 ± 4.86 in the NAFLD group ($p < 0.001$). The non-NAFLD group had 76.37 ± 5.07 mmHg mean diastolic blood pressure, whereas the NAFLD group had 91.09 ± 5.57 ($p < 0.001$), **(Table.2).**

Table 2. Comparison between the two studied groups according to blood pressure

Blood pressure	Total (n = 200)	Non-NAFLD (n = 166)	NAFLD (n = 34)	T	p. value
Systolic	125.5 ± 11.30	121.5 ± 7.51	144.8 ± 4.86	17.345*	<0.001*
Diastolic	78.87 ± 7.56	76.37 ± 5.07	91.09 ± 5.57	15.170*	<0.001*

SD: Standard deviation t: Student t-test, p: p value for comparison between Non-NAFLD and NAFLD *: Statistically significant at $p \leq 0.05$

Non-NAFLD and NAFLD groups had similar Hb, WBC, and platelet counts ($p > 0.05$). The NAFLD group had siginificantly higher Triglycerides (TGA), Low-Density Lipoprotein (LDL), and Total Cholesterol levels than the non-NAFLD group ($p < 0.001$), but siginificantly lower HDL levels. NAFLD patients had siginificantly increased ALT and AST levels ($p < 0.001$), suggesting liver damage. Glycemic markers including Fasting Blood Sugar and HOMA-IR were significantly higher in the NAFLD group ($p < 0.001$), indicating impaired glucose metabolism. NAFLD patients had siginificantly higher TSH levels ($p < 0.001$), **(Table .3).**

Table 3. Laboratory findings in the studied groups

Variables	Total (n = 200)	Non-NAFLD (n = 166)	NAFLD (n = 34)	t	p. value
CBC					
Hb (g/dl)	11.79 ± 0.90	11.80 ± 0.88	11.76 ± 1.03	0.189	0.851
WBCs (10^9/L)	6962.5 ± 1632.0	6975.2 ± 1550.91	6900.2 ± 2007.3	0.206	0.838
Platelet count ($x10^9$/L)	257.54 ± 20.54	257.60 ± 20.48	257.21 ± 21.16	0.102	0.919

Lipid profile					
TGA (mg/l)	126.95 ± 31.39	112.95 ± 5.03	195.29 ± 4.05	89.603*	<0.001*
HDL (mg/l)	51.73 ± 4.41	53.31 ± 2.59	44.03 ± 3.19	15.934*	<0.001*
LDL (mg/l)	93.77 ± 16.73	86.68 ± 6.16	128.4 ± 3.34	55.901*	<0.001*
Cholesterol	169.9 ± 11.88	168.3 ± 11.40	178.1 ± 10.83	6.648*	<0.001*
Liver enzymes					
ALT (ul/l)	29.10 ± 11.04	24.45 ± 3.40	51.76 ± 6.26	24.716*	<0.001*
AST (ul/l)	28.39 ± 10.34	23.95 ± 2.73	50.06 ± 4.96	29.790*	<0.001*
Total bilirubin (mg/dl)	0.79 ± 0.10	0.78 ± 0.10	0.81 ± 0.09	1.359	0.176
Albumin (g/dL)	4.50 ± 0.25	4.49 ± 0.25	4.54 ± 0.26	1.05	0.295
ALP (u/l)	75.25 ± 2.94	75.87 ± 2.65	72.21 ± 2.37	7.478*	<0.001*
Total protein (g/dl)	6.81 ± 0.43	6.71 ± 0.35	7.30 ± 0.46	7.023*	<0.001*
Glycemic profile					
Fasting serum insulin (mIU/L)	12.78 ± 0.68	12.82 ± 0.66	12.58 ± 0.74	1.913	0.057
Fasting blood sugar	86.77 ± 7.68	83.80 ± 3.87	101.26 ± 4.50	23.327*	<0.001*
HOMA-IR	1.84 ± 0.42	1.66 ± 0.03	2.75 ± 0.15	42.212*	<0.001*
Uric Acid (mg/dL)	4.82 ± 0.85	4.83 ± 0.84	4.78 ± 0.90	0.286	0.775
TSH (mIU/L)	1.63 ± 0.36	1.53 ± 0.24	2.11 ± 0.43	7.642*	<0.001*

SD: Standard deviation t: Student t-test p: p value for comparison between Non-NAFLD and NAFLD; *: Statistically significant at $p \leq 0.05$; CBC: Complete Blood Count, Hb: Hemoglobin, WBCs: White Blood Cells, TGA: Triglycerides, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, ALP: Alkaline Phosphatase, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, TSH: Thyroid-Stimulating Hormone.

6% of cases in the NAFLD group had ASMA, AMA positive, **(Table.4).** Significant differences were observed between the two groups in FiB4, fatty liver index (FLI), APRI, NAFLD fibrosis score, Liver stiffness measurement, and CAP. The FiB4 score was significantly higher in the non-NAFLD group ($p = 0.003$). Similarly, FLI and APRI scores were markedly higher in the NAFLD group ($p < 0.001$), The NAFLD fibrosis score, a composite marker of fibrosis, was also significantly higher in the NAFLD group ($p = 0.043$), Furthermore, Liver stiffness measurement and CAP, both indicators of liver stiffness and fat content, respectively, were significantly higher in the NAFLD group ($p < 0.001$), **(Table.5).**

Table 4. Positive ASMA and AMA in NAFLD group

Variables	No.	%	P. Value
ASMA	12	6.0	> 0.99
AMA	12	6.0	

ASMA: Anti smooth Muscle Antibody, AMA: Antimitochondrial Antibody

Table 5. Fibrosis scores and indices FiB4, FLI, and APRI in the studied groups

Variables	Total (n = 200)	Non-NAFLD (n = 166)	NAFLD (n = 34)	t	p. value
FiB4	1.49 ± 0.23	1.51 ± 0.24	1.39 ± 0.19	3.115*	0.003*
FLI	12.64 ± 6.79	9.68 ± 1.50	27.09 ± 2.72	36.169*	<0.001*
APRI	0.21 ± 0.11	0.17 ± 0.03	0.44 ± 0.02	67.736*	<0.001*
NAFLD fibrosis score	-1.41 ± 0.63	-1.37 ± 0.66	-1.61 ± 0.46	2.034*	0.043*
Liver stiffness measurement	5.03 ± 1.19	4.55 ± 0.57	7.37 ± 0.39	35.058*	<0.001*
CAP	202.2 ± 29.12	189.5 ± 8.50	263.8 ± 6.20	48.334*	<0.001*

SD: Standard deviation t: Student t-test, p: p value; FiB4: Fibrosis-4 Index, FLI: Fatty Liver Index, APRI: AST to Platelet Ratio Index, CAP: Controlled Attenuation Parameter.

Discussion

The global prevalence of obesity, type 2 diabetes, and NAFLD is on the rise, often coexisting with MetS and cardiovascular disease (CVD). Notably, a significant number of nonobese individuals are now presenting with lean NAFLD, suggesting that obesity alone may not be the sole driver of NAFLD **(Matsubayashi et al., 2022).**

Rather, factors such as diet, ethnicity, dysregulation of the gut-liver axis, and gut microbiota may play a role in inducing NAFLD in lean individuals. Lean NAFLD has become a pressing global health concern, necessitating a comprehensive understanding of its occurrence, clinical characteristics, and risk factors **(Safari et al., 2019).**

Ye et al. 2020 meta-analysis confirms 40% worldwide lean NAFLD prevalence. **Young et al. 2020** meta-analysis 11.2% of the population and 25.3% of NAFLD patients are lean. **Alam et al. 2021's** results of older lean NAFLD patients may be attributable to sample size, design, and demographic variations.

Hip, waist-to-height, and arm circumference changed considerably between NAFLD and non-NAFLD groups. The non-NAFLD group had a greater waist-to-height ratio and the NAFLD group had a larger hip circumference. NAFLD-enlarged arms. Both groups had similar waist, BMI, waist-to-hip ratio, and arm circumference.

Hip obesity increases NAFLD risk in slim people **(Bhowmik et al., 2019).** Lean persons with central obesity may have a decreased risk of NAFLD **(Zou et al., 2021).** Metabolic dysregulation and fat deposition increase arm circumference in NAFLD patients **(Wang et al., 2022b, Young et al., 2020).**

Zeng et al., 2020 discovered that lean NAFLD (LN) had a higher mean BMI (21.74 ± 1.01) than LNN (21.23 ± 1.33) ($p < 0.001$). Lean NAFLD (LN) had a higher mean waist circumference (76.27 ± 6.03) than LNN (73.49 ± 5.66) ($p < 0.001$).

We detected significant blood pressure differences between NAFLD and non-NAFLD individuals. NAFLD patients had significantly higher systolic and diastolic blood pressure. Non-NAFLD and NAFLD patients exhibited comparable hemoglobin, white blood cell, and platelet levels.

NAFLD is linked to high blood pressure due to MetS and chronic inflammation **(Aneni et al., 2020).** Lean NAFLD patients have MetS and higher hypertension risk **(Sookoian and Pirola 2017; Golabi et al., 2019).**

Our results confirmed **Golabi et al., 2019,** who showed significant hypertension prevalence differences between categories.

Hypertension was higher in NAFLD (31.29%) than in non-NAFLD (13.29%). Lean NAFLD patients have a higher risk of hypertension.

In our study, NAFLD patients had greater triglycerides, LDL, and total cholesterol than healthy people. NAFLD may cause dyslipidemia.

Lean NAFLD patients have low lipid profiles due to insulin resistance causing adipose tissue lipolysis and free fatty acid release, leading to elevated triglycerides. Hepatic steatosis and impaired HDL metabolism contribute to low HDL cholesterol. Dysregulated lipid metabolism elevates LDL cholesterol and increases hepatic LDL particle production, resulting in reduced LDL receptor activation. This imbalance, along with elevated triglycerides, leads to higher total cholesterol in lean NAFLD patients **(Pei et al., 2020; Ren and Fan, 2021; Liu et al., 2022).**

Our results corroborated **Yu et al., 2014,** who observed a strong link between non-obese, normotensive, and non-diabetic NAFLD patients and higher blood levels of total cholesterol, LDL-C, and TG.

Moreover, **Oral et al., 2019** discovered that Turkish non-obese NAFLD patients with BMIs below 30 kg/m2 had higher TG and TC levels than controls.

Our study found NAFLD patients had increased ALT and AST levels. This suggests the presence of NAFLD-related liver damage. NAFLD patients showed lower ALP and higher total protein. Groups had comparable total bilirubin and albumin levels. NAFLD seems to induce liver dysfunction and elevated liver enzymes.

Our results were comparable to **Zou et al., 2020,** who showed that nonobese NAFLD patients had significantly higher AST (27.3 U/L) and ALT (33.1 U/L) than non-NAFLD people (23.3 and 21.3 U/L)**.**

In our study, NAFLD patients had higher fasting blood sugar (101.26 mg/dL) than non-NAFLD patients (83.80). NAFLD patients exhibited a higher mean HOMA-IR (2.75) than non-NAFLD patients (1.66).

Our results were supported by the findings of **Younossi et al., 2012**, where NAFLD patients had higher mean HOMA-IR (2.77) compared to the non-NAFLD control group (1.67). Another study by **Kim et al., 2019,** showed that mean HOMA IR in the lean NAFLD group (3.81) was significantly higher compared to the lean non-NAFLD group (2.56). Contrary to our results, **Cho, 2016,** found that the mean HOMA-IR in the lean NAFLD group (1.34) was lower than the mean HOMA-IR in the lean non-NAFLD group (2.3).

NAFLD's metabolic imbalance raises fasting blood sugar due to insulin resistance and glucose absorption limitation **(Tilg et al., 2017; Pang et al., 2018).** In previous studies, Non-obese NAFLD patients have elevated HOMA-IR and higher fasting blood sugar compared to lean controls **(Wei et al., 2015; Alam et al., 2021).**

In our study, NAFLD patients had higher mean TSH levels, indicating thyroid dysfunction ($p<0.001$).

Our study was in line with a study of **Tao, et al., 2015**, in which patients with NAFLD had higher levels of TSH (1.96 mIU/L) compared to non-NAFLD patients (1.81 mIU/L). Another study by **Kaltenbach et al., 2017**, also concluded that TSH levels were higher among lean NAFLD patients (2.8 mIU/L) compared to non-NAFLD patients (2.5 mIU/L).

Our study agree of the finding that TSH levels may modify NAFLD development and progression regardless of thyroid hormones, supporting **Guo et al., 2018.**

High TSH levels were linked to NAFLD as **Martínez-Escudé et al., 2021** reported that when TSH ≥ 2.5 μIU/mL increases NAFLD risk independent of metabolic factors.

NAFLD patients had higher FIB-4 index values than non-NAFLD patients, indicating

a greater risk of liver fibrosis. They also had increased FLI readings, suggesting fatty liver disease. NAFLD patients showed elevated APRI, indicating liver damage.

FiB4 index predicts NAFLD liver fibrosis using age, AST, platelet count, and ALT. A high FiB-4 index suggests liver fibrosis. NAFLD group had higher FLI values, indicating fatty liver disease. FLI increases imply hepatic steatosis. NAFLD patients had increased APRI levels, indicating liver damage and advanced liver disease **(Vieira et al., 2022).**

Our study was in agreement with **Zeng et al., 2020** who discovered a strong connection between higher FLI values and NAFLD. **Eren et al., 2022,** imply that the FIB-4 score, developed and validated in populations with higher BMI and metabolic risk variables, may not accurately predict fibrosis risk in lean NAFLD patients.

Our NAFLD and non-NAFLD groups showed different fibrosis scores, liver stiffness, and CAP values. NAFLD enhance liver stiffness and inctaeses fibrosis. NAFLD causes liver fibrosis. Hepatic fat gain in NAFLD patients increased CAP. CAP assesses liver steatosis. **(Rigor et al., 2022). Wei et al. (2015)** found less fibrosis in lean NAFLD patients.

Conclusion

NAFLD is strongly associated with obesity and related comorbidities, a substantial proportion of lean subjects can also develop NAFLD. Lean NAFLD associated to elevated lipid profile, liver enzymes, protein, HOMA-IR, blood sugar, uric acid, TSH..

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