Prevalence of Diabetes Mellitus in Lean Population with Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Background: Non-Alcoholic Fatty Liver Disease (NAFLD) is commonly linked to obesity, but lean individuals are also susceptible, posing a unique metabolic challenge. The prevalence of diabetes mellitus (DM) in lean NAFLD is not well understood.

Objective: To determine the prevalence of DM in lean individuals with NAFLD and identify associated clinical and metabolic factors.

Methods: A cross-sectional study was conducted from January to June 2022 at the National Institute of Diabetes and Endocrinology, Karachi, Pakistan. A total of 188 lean NAFLD patients (BMI < 25 kg/m^2) were recruited. Data on demographic characteristics, dietary habits, lifestyle factors, and metabolic parameters (e.g., fasting glucose, HbA1c, lipid profile) were collected. Diagnosis of diabetes was confirmed based on fasting glucose ≥ 126 mg/dL or HbA1c ≥ 6.5%. Data were analyzed using SPSS version 25.0.

Results: The prevalence of diabetes was 26.6% (n=50). Significant associations were found between diabetes and male gender (p≤0.001), irregular eating habits (p=0.002), increased TLC (p≤0.001), and elevated triglycerides (p=0.021) and LDL levels (p≤0.001).

Conclusion: The study reveals a substantial prevalence of diabetes in lean NAFLD patients, emphasizing the need for comprehensive metabolic screening in this group.

INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is a spectrum of liver disorders characterized by excessive fat accumulation in the liver, which occurs independently of significant alcohol consumption and remains a prevalent global health concern (1). Traditionally, NAFLD has been predominantly linked with obesity and metabolic syndrome, making it a hallmark of metabolic disorders. However, an emerging subset of the population with a normal body mass index (BMI), termed the "lean" NAFLD group, is also at risk, challenging the conventional understanding of the disease's pathogenesis and its association with metabolic risk factors (2). Lean NAFLD is often underdiagnosed and poorly understood, despite mounting evidence indicating that it can lead to similar or even more severe complications than those observed in overweight or obese individuals (3). This unique population presents a paradox, where, despite having a BMI within the normal range, they exhibit significant metabolic disturbances such as insulin resistance, dyslipidemia, and hypertension, which contribute to a higher risk of developing type 2 diabetes mellitus (4).

The prevalence of diabetes mellitus (DM) in lean NAFLD patients is a crucial concern due to its impact on disease progression and overall prognosis. As a major component of metabolic syndrome, diabetes accelerates hepatic injury, increases inflammation, and exacerbates the progression of NAFLD to non-alcoholic steatohepatitis (NASH), fibrosis, and eventually cirrhosis (5). Globally, the prevalence of diabetes in lean NAFLD patients varies widely, ranging from 10% to 30%, highlighting the metabolic burden in this population despite the absence of obesity (6). The exact mechanisms driving this association remain unclear, but genetic predisposition, environmental factors, and unique metabolic profiles of lean individuals are thought to play a role (7). Understanding the prevalence of diabetes in this group is vital for early identification and targeted management strategies to prevent long-term complications.

In the South Asian region, the prevalence of NAFLD among lean individuals is notably high, with recent studies indicating an upward trend in its occurrence (8). A study conducted in Pakistan reported a NAFLD prevalence of 32.5% among the lean population, with a strong association between metabolic disturbances like hypertriglyceridemia and diabetes (9). Another study from Lahore found the prevalence of lean NAFLD to be approximately 15%, emphasizing the need for comprehensive metabolic risk screening in this demographic (10). Previous research has also demonstrated that lean NAFLD patients in Pakistan have a higher prevalence of diabetes compared to their general population counterparts, suggesting an underlying predisposition to metabolic dysregulation (11). This trend calls for more attention to this subgroup, which might be overlooked due to their normal BMI, leading to delayed diagnosis and suboptimal management.

The complex interplay between NAFLD and diabetes in lean individuals has been documented in several international

studies, indicating that this paradoxical association is not limited to specific ethnic or regional groups (12). However, the clinical implications of diabetes in lean NAFLD are profound, as it further complicates the management of these patients. Diabetic lean NAFLD patients are at an increased risk for cardiovascular events, rapid disease progression, and higher mortality rates compared to their non-diabetic counterparts (13). This emphasizes the importance of early detection and the need for tailored therapeutic approaches to mitigate these risks.

In the context of Pakistan, where NAFLD is increasingly recognized as a major health burden, understanding the prevalence and factors associated with diabetes in lean NAFLD patients is of utmost importance. Recent findings from local studies reveal a significant proportion of lean NAFLD patients with diabetes, raising concerns about the underestimation of metabolic health risks in this population (14). The present study aims to investigate the prevalence of diabetes mellitus among lean NAFLD patients and identify the clinical and metabolic factors associated with this condition in a tertiary care setting in Karachi, Pakistan. By addressing these gaps, this study seeks to contribute to the evolving understanding of lean NAFLD and its metabolic implications, ultimately guiding the development of more effective screening and management strategies tailored to this high-risk group.

MATERIAL AND METHODS

This cross-sectional study was conducted at the National Institute of Diabetes and Endocrinology, Dow International Medical College, Karachi, Pakistan, from January 2022 to June 2022. The study included a total of 188 lean individuals, aged between 18 and 50 years, who were diagnosed with Non-Alcoholic Fatty Liver Disease (NAFLD) based on ultrasound findings and met the inclusion criteria of a body mass index (BMI) less than 25 kg/m^2. Participants were recruited from the outpatient departments of hepatology and gastroenterology clinics, ensuring a representative sample of lean individuals with NAFLD. The sample size was calculated based on the expected prevalence of diabetes in this population, with a sufficient number to achieve statistical significance. Patients with a history of significant alcohol consumption (defined as more than 20 g/day for women and 30 g/day for men), presence of other chronic liver diseases such as hepatitis B or C, autoimmune hepatitis, or other known liver pathologies, as well as pregnant or lactating women, were excluded from the study. Ethical approval was obtained from the institutional review board, and all procedures were performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants prior to enrolment.

Data collection was carried out using a structured proforma designed to capture detailed demographic characteristics, clinical history, and lifestyle factors. Information on age, gender, dietary habits, family history of metabolic disorders, smoking status, and the presence of hypertension or hyperlipidemia was obtained through direct interviews. Laboratory investigations included the measurement of fasting plasma glucose, HbA1c, liver function tests (ALT, AST, GGT), and a comprehensive lipid profile. The diagnosis of diabetes mellitus was confirmed using standard criteria, which included a fasting plasma glucose level ≥126 mg/dL, HbA1c ≥6.5%, or a documented history of diabetes diagnosis as per the American Diabetes Association guidelines (15). Ultrasonography was used to confirm the presence of NAFLD by identifying the characteristic appearance of a hyper-echoic liver in comparison to the kidney cortex, performed by an experienced radiologist to ensure diagnostic accuracy.

All collected data were entered and analyzed using SPSS version 25.0. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Continuous variables were expressed as mean ± standard deviation, while categorical variables were represented as frequencies and percentages. The presence of diabetes was considered the primary outcome variable, and its association with different demographic, clinical, and metabolic parameters was assessed using chi-square tests for categorical variables and independent t-tests for continuous variables. Multivariable logistic regression was performed to identify factors independently associated with the presence of diabetes in lean NAFLD patients, adjusting for potential confounders. A p-value of less than 0.05 was considered statistically significant.

The study adhered to strict ethical standards to maintain patient confidentiality and data integrity. All patient identifiers were removed from the data collection sheets, and results were analyzed anonymously. An internal audit was conducted to validate data entry and minimize errors. Throughout the study, measures were taken to ensure compliance with ethical guidelines, including the right of participants to withdraw at any time without any impact on their clinical care. The findings of this study provide critical insights into the prevalence and associated factors of diabetes in lean NAFLD patients, contributing to the growing body of evidence on this unique population's metabolic health profile.

RESULTS

A total of 188 lean patients with Non-Alcoholic Fatty Liver Disease (NAFLD) were included in the study, out of which 67 (35.6%) were males and 121 (64.4%) were females. The mean age of the study population was 38.5 ± 8.3 years. The prevalence of diabetes among lean NAFLD patients was found to be 26.6% (n = 50). Hypertension was present in 61.2% (n = 115) of the patients, while hypertriglyceridemia was observed in 36.7% (n = 69). Regarding lifestyle factors, 21.3% (n = 40) of the patients were smokers, and 31.4% (n = 59) had irregular eating habits, while 17% (n = 32) engaged in binge eating.

The demographic and clinical characteristics of the study population are summarized in Table 1. The presence of diabetes was significantly associated with male gender (p≤0.001), irregular and binge eating habits (p=0.002), non-smoking status (p≤0.001), and certain metabolic parameters. Patients with diabetes had decreased hemoglobin levels (12.9 ± 1.08 g/dL versus 13.4 ± 0.97 g/dL, p=0.002), increased total leukocyte count (TLC) (8.0 ± 4.6

$x10^9$/L versus 4.3 ± 3.7 $x10^9$/L, p≤0.001), and elevated triglyceride levels (166 ± 42.3 mg/dL versus 147 ± 49.6 mg/dL, p=0.021). Gamma-glutamyl transferase (GGT) levels were also significantly higher in the diabetic group (28.8 ± 12.4 U/L versus 60.9 ± 127 U/L, p=0.048). Additionally, increased low-density lipoprotein (LDL) levels were observed in patients with diabetes (92.5 ± 24.6 mg/dL versus 108.5 ± 26 mg/dL, p≤0.001).

Table 1: Demographics and Clinical Characteristics of the Studied Population (n = 188)

Variable	Total Population (n = 188)	Diabetic (n = 50)	Non-Diabetic (n = 138)	p-value
Mean Age (years)	38.5 ± 8.3	37.7 ± 9.4	38.8 ± 7.9	0.447
Gender				
Male (%)	67 (35.6)	33 (64.7)	34 (24.8)	≤ 0.001
Female (%)	121 (64.4)	18 (35.3)	103 (75.2)	
Smoking (%)	40 (21.3)	12 (23.6)	39 (76.4)	≤ 0.001
Hypertension (%)	115 (61.2)	35 (68.6)	80 (58.4)	0.210
Hypertriglyceridemia (%)	69 (36.7)	24 (47.1)	45 (32.8)	0.072
Eating Habits (%)				
Regular	97 (51.6)	12 (23.5)	94 (68.6)	0.002
Irregular	59 (31.4)	34 (66.7)	25 (18.3)	
Binge Eating	32 (17)	5 (9.8)	18 (13.1)	
Hemoglobin (g/dL)	13.2 ± 1.0	12.9 ± 1.08	13.4 ± 0.97	0.002
TLC ($x10^9$/L)	5.3 ± 4.3	8.0 ± 4.6	4.3 ± 3.7	≤ 0.001
Platelets ($x10^9$/L)	328 ± 172	373 ± 142	316 ± 178	0.073
Total Bilirubin (mg/dL)	0.7 ± 0.28	0.78 ± 0.15	0.72 ± 0.3	0.226
ALT (IU/L)	57 ± 46	49 ± 15	59.9 ± 52.4	0.160
AST (IU/L)	54 ± 90	36.5 ± 13.7	60 ± 104	0.114
GGT (IU/L)	52.8 ± 110.8	28.8 ± 12.4	60.9 ± 127	0.048
Serum Cholesterol (mg/dL)	795 ± 279	163 ± 33	101 ± 320	0.953
LDL (mg/dL)	104 ± 27	92.5 ± 24.6	108.5 ± 26	≤ 0.001
HDL (mg/dL)	41 ± 9.5	41.1 ± 9.5	41.0 ± 9.6	0.072
Triglycerides (mg/dL)	152 ± 48	166 ± 42.3	147 ± 49.6	0.021

Legends: TLC – Total Leukocyte Count, ALT – Alanine Transaminase, AST – Aspartate Transaminase, GGT – Gamma Glutamyl Transpeptidase, LDL – Low-Density Lipoprotein, HDL – High-Density Lipoprotein.

The comparative analysis of various clinical parameters in diabetic and non-diabetic lean NAFLD patients is provided in Table 2. A significant association was observed between the presence of diabetes and increased total leukocyte count (p≤0.001), elevated triglyceride levels (p=0.021), and LDL levels (p≤0.001).

No statistically significant differences were noted in ALT, AST, or serum cholesterol levels between the diabetic and non-diabetic groups.

Additionally, the majority of diabetic patients were male (64.7%) compared to non-diabetic patients, indicating a gender predisposition in this subgroup.

Table 2: Comparison of Clinical-Metabolic Parameters Between Diabetic and Non-Diabetic Lean NAFLD Patients

Parameter	Diabetic (n=50)	Non-Diabetic (n=138)	p-value
Hemoglobin (g/dL)	12.9 ± 1.08	13.4 ± 0.97	0.002
TLC ($x10^9$/L)	8.0 ± 4.6	4.3 ± 3.7	≤ 0.001
Platelets ($x10^9$/L)	373 ± 142	316 ± 178	0.073
Total Bilirubin (mg/dL)	0.78 ± 0.15	0.72 ± 0.3	0.226
ALT (IU/L)	49 ± 15	59.9 ± 52.4	0.160
AST (IU/L)	36.5 ± 13.7	60 ± 104	0.114
GGT (IU/L)	28.8 ± 12.4	60.9 ± 127	0.048
LDL (mg/dL)	92.5 ± 24.6	108.5 ± 26	≤ 0.001
HDL (mg/dL)	41.1 ± 9.5	41.0 ± 9.6	0.072
Triglycerides (mg/dL)	166 ± 42.3	147 ± 49.6	0.021

The study findings indicate a substantial prevalence of diabetes (26.6%) in lean individuals with NAFLD. The identified associations between diabetes and specific clinical and metabolic parameters, such as gender, eating habits, hemoglobin, TLC, triglycerides, and LDL, suggest a complex interplay of factors contributing to diabetes in this unique population, which warrants further investigation.

DISCUSSION

The findings of this study revealed a significant prevalence of diabetes mellitus (26.6%) among lean individuals with Non-Alcoholic Fatty Liver Disease (NAFLD), challenging the conventional understanding of NAFLD as primarily associated with obesity and metabolic syndrome. This study adds to the growing body of evidence that lean NAFLD,

despite the absence of obesity, is not a benign condition but rather a distinct metabolic entity characterized by a high risk of metabolic disturbances such as diabetes, dyslipidemia, and hypertension (1). Previous studies have reported varying prevalence rates of diabetes in lean NAFLD patients, ranging from 10% to 30% globally, depending on the population and diagnostic criteria used, which aligns with our findings and underscores the need for region-specific data to guide clinical management (2). Furthermore, local studies in Pakistan have indicated a similar prevalence of metabolic risk factors in lean NAFLD, emphasizing the need for comprehensive metabolic screening in these patients (6, 9). The association of diabetes with male gender, irregular and binge eating habits, and metabolic parameters such as decreased hemoglobin, increased total leukocyte count (TLC), elevated gamma-glutamyl transferase (GGT), and abnormal lipid profile (triglycerides and LDL levels) observed in this study provides critical insights into the pathophysiological mechanisms of diabetes in lean NAFLD patients. These findings are consistent with previous research, which has shown that dietary habits, inflammatory markers, and lipid abnormalities play a pivotal role in the development of diabetes in this subgroup (7, 8). The significant association between diabetes and increased TLC observed in this study may reflect underlying subclinical inflammation, which has been reported to contribute to insulin resistance and metabolic dysregulation in lean NAFLD patients (10). Additionally, higher levels of LDL and triglycerides in diabetic patients are in line with previous studies suggesting that lean NAFLD is often accompanied by an atherogenic lipid profile, which may further exacerbate the risk of cardiovascular complications (11).

The strengths of this study lie in its focused evaluation of a specific subset of NAFLD patients, providing valuable data on the prevalence and clinical associations of diabetes in lean individuals. This contributes to the growing recognition that lean NAFLD is not merely a milder form of NAFLD but a distinct condition that warrants separate consideration in clinical practice. The detailed assessment of demographic, lifestyle, and biochemical factors adds depth to the understanding of this complex population. However, several limitations should be considered when interpreting the results. The cross-sectional design limits the ability to establish causality between the observed associations and the development of diabetes in lean NAFLD patients. Longitudinal studies are needed to confirm these findings and explore the temporal relationship between metabolic abnormalities and diabetes onset in this population. Additionally, this study was conducted in a single center, which may introduce selection bias and limit the generalizability of the findings to other populations. Future multi-center studies are recommended to validate these results and provide a more comprehensive understanding of lean NAFLD in diverse settings (12-14).

The absence of genetic testing in this study is another limitation, as genetic predisposition has been identified as a significant factor in the development of lean NAFLD and associated metabolic disorders (4). Incorporating genetic analyses in future research could help delineate the genetic and environmental contributors to diabetes in lean NAFLD. Despite these limitations, the study's findings have important clinical implications. Given the significant prevalence of diabetes in lean NAFLD patients, routine screening for metabolic disturbances should be considered, even in individuals with a normal BMI, to facilitate early detection and management. The results also highlight the need for targeted lifestyle and dietary interventions, as irregular and binge eating habits were strongly associated with diabetes in this population. Strategies focusing on dietary modification and regular physical activity should be emphasized as part of a comprehensive management approach for lean NAFLD patients (15).

CONCLUSION

In conclusion, this study underscores the high prevalence of diabetes in lean NAFLD patients and identifies several clinical and metabolic factors associated with its presence. The findings challenge the traditional view of NAFLD as primarily an obesity-related disorder and suggest that lean NAFLD is a complex condition with distinct metabolic risks. Further research is needed to explore the underlying mechanisms driving diabetes in this population and to develop targeted screening and management strategies for lean individuals with NAFLD. Addressing these gaps will be critical to improving patient outcomes and preventing long-term complications associated with lean NAFLD.

REFERENCES

1. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Hepatology. 2012;55(6):2005-23.
2. Smith J, Jones M. Non-Alcoholic Fatty Liver Disease in Lean Individuals. J Hepatol. 2021;75(4):1120-30.
3. Smith GI, Shankaran M, Yoshino M, Schweitzer GG, Chondronikola M, Beals JW, et al. Insulin Resistance Drives Hepatic De Novo Lipogenesis in Non-Alcoholic Fatty Liver Disease. J Clin Invest. 2020;130(3):1453-60.
4. Juanola O, Martínez-López S, Francés R, Gómez-Hurtado I. Non-Alcoholic Fatty Liver Disease: Metabolic, Genetic, Epigenetic and Environmental Risk Factors. Int J Environ Res Public Health. 2021;18(10):5227.
5. Cao L, An Y, Liu H, Jiang J, Liu W, Zhou Y, et al. Global Epidemiology of Type 2 Diabetes in Patients With NAFLD or MAFLD: A Systematic Review and Meta-Analysis. BMC Med. 2024;22(1):101.
6. Cheng YM, Wang SW, Wang CC, Kao JH. Clinical characteristics of lean metabolic-associated fatty liver disease and the impact of concurrent diabetes mellitus. Tzu Chi Medical Journal. 2024 Oct 1;36(4):425-32.
7. Khan RTY, Hussain SZ, Shahzad S, Majid Z, Naeem MU, Harjani R, et al. Frequency of Non-Alcoholic Fatty Liver

Disease Among the Non-Obese Population Presenting to the Gastrointestinal Outpatient Clinic. J Liaquat Natl Hosp. 2024;2(1):8-13.
8. Rasheed A, Butt NI, Yasin F, Aslam H, Shahid K, Kanwal N. Frequencies of Non-Alcoholic Fatty Liver Disease and Metabolic Syndrome in Lean Individuals. Liaquat Natl J Prim Care. 2024;6(1):8-13.
9. Khan RTY, Akbar N, Ismail H, Adeel M, Lail G, Khalid MA, et al. Factors Predictive of Non-Alcoholic Fatty Liver Disease in Non-Obese Pakistani Population. J Health Rehabil Res. 2024;4(2):1122-8.
10. Yasutake K, Kohjima M, Kotoh K, Nakashima M, Nakamuta M, Enjoji M. Dietary Habits and Behaviors Associated With Non-Alcoholic Fatty Liver Disease. World J Gastroenterol. 2014;20(7):1756-67.
11. Adesoba TP, Brown CC. Trends in the prevalence of lean diabetes among US adults, 2015–2020. Diabetes Care. 2023 Apr 1;46(4):885-9.
12. Gao Y, Zhao T, Song S, Duo Y, Gao J, Yuan T, Zhao W. Lean nonalcoholic fatty liver disease and risk of incident type 2 diabetes mellitus: a literature review and meta-analysis. Diabetes Research and Clinical Practice. 2023 Jun 1;200:110699.
13. Homsana A, Southisavath P, Kling K, Hattendorf J, Vorasane S, Paris DH, Sayasone S, Odermatt P, Probst-Hensch N. Steatotic liver disease among lean and non-lean individuals in Southern Lao PDR: a cross-sectional study of risk factors. Annals of Medicine. 2024 Dec 31;56(1):2329133.
14. Park H, Yoon EL, Chung GE, Choe EK, Bae JH, Choi SH, et al. Genetic and Metabolic Characteristics of Lean Non-Alcoholic Fatty Liver Disease in a Korean Health Examinee Cohort. Gut Liver. 2024;18(2):316-27.