Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/65y9s425

"OBESITY AS A KEY RISK FACTOR FOR NASH AND FIBROSIS IN NON-ALCOHOLIC FATTY LIVER DISEASE"

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Abstract

Introduction:
Non-Alcoholic Fatty Liver Disease (NAFLD) is a common liver disorder closely associated with metabolic risk factors such as obesity. This study aimed to explore the histopathological spectrum of NAFLD across different BMI categories and evaluate the impact of obesity on liver function, fibrosis progression, and disease severity.

Methodology:
A total of 288 patients diagnosed with NAFLD were recruited from a tertiary healthcare institute over a two-year period. The cohort was categorized into three groups based on BMI: normal weight (BMI < 25), overweight (BMI 25–29.9), and obese (BMI ≥ 30). Clinical data, including age, sex, comorbidities (diabetes, hypertension, dyslipidemia), liver function tests (ALT, AST), and histopathological features of NAFLD, were recorded. Logistic regression analysis was performed to assess the risk of advanced fibrosis (F3–F4) in different BMI categories.

Results:
Our findings revealed that higher BMI was significantly associated with more severe NAFLD, including increased steatosis, hepatocyte ballooning, lobular inflammation, and fibrosis stages. The obese group had the highest rates of advanced fibrosis (25%) and NASH (45%). Liver function tests (ALT, AST) were also significantly elevated in overweight and obese individuals compared to those with normal weight. Logistic regression analysis demonstrated that obesity (OR 2.1) and overweight (OR 1.5) were independent risk factors for advanced fibrosis, further aggravated by diabetes, hypertension, and dyslipidemia**.**

Conclusion:
This study emphasizes the critical role of BMI in the progression of NAFLD. Obesity is associated with increased severity of liver injury and advanced fibrosis, highlighting the need for early

identification and intervention in overweight and obese individuals to prevent long-term liver complications.

Keywords: Non-Alcoholic Fatty Liver Disease (NAFLD), BMI, Advanced Fibrosis, NASH, Liver Function Tests, Steatosis, Hepatocyte Ballooning, Obesity, Diabetes, Hypertension.

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is an increasingly prevalent metabolic disorder characterized by excessive fat accumulation in hepatocytes in the absence of significant alcohol consumption.[1] It encompasses a spectrum ranging from simple hepatic steatosis (Non-Alcoholic Fatty Liver, NAFL) to its progressive form, Non-Alcoholic Steatohepatitis (NASH), which is associated with inflammation, hepatocellular injury, and fibrosis, ultimately increasing the risk of cirrhosis and hepatocellular carcinoma (HCC).[2-3] Given its strong association with obesity, diabetes, and metabolic syndrome, NAFLD has emerged as the most common chronic liver disease globally, affecting nearly 25% of the adult population.[4-5]

Body Mass Index (BMI) serves as a fundamental anthropometric parameter to classify individuals into underweight, normal weight, overweight, and obese categories. While NAFLD is conventionally linked with obesity, recent studies indicate its occurrence even in individuals with normal BMI, particularly in Asian populations, where lean NAFLD is increasingly recognized.[6-7] The histopathological spectrum of NAFLD varies significantly across BMI categories, with obese individuals often exhibiting a higher degree of hepatic inflammation and fibrosis, while lean individuals may develop NAFLD through mechanisms involving genetic predisposition, altered gut microbiota, or sarcopenia.[8-9]

Histopathological examination remains the gold standard for NAFLD diagnosis, enabling differentiation between simple steatosis and NASH. Key histological features include macrovesicular steatosis, hepatocyte ballooning, lobular inflammation, and varying degrees of fibrosis.[10] Several studies suggest that higher BMI correlates with increased steatosis severity, lobular inflammation, and fibrosis progression.[11] However, lean NAFLD patients may still develop advanced liver disease despite having lower BMI, emphasizing the need for histopathological assessment beyond conventional risk factors.[12]

Despite the well-established association between obesity and NAFLD, limited studies have examined the histopathological differences in NAFLD across BMI categories. Understanding these variations is crucial for refining diagnostic criteria, identifying high-risk individuals, and tailoring therapeutic interventions. This study aims to evaluate the histopathological spectrum of NAFLD in different BMI groups to determine whether distinct pathophysiological mechanisms drive disease progression in lean vs. obese individuals.

Methodology

This observational, cross-sectional study will be conducted over a two-year period at a tertiary healthcare institute, focusing on the histopathological spectrum of Non-Alcoholic Fatty Liver Disease (NAFLD) across different BMI categories. A total of 288 patients diagnosed with NAFLD will be enrolled based on predefined inclusion and exclusion criteria. Patients will be recruited from the outpatient department (OPD) and inpatient units of the gastroenterology and hepatology departments, ensuring a diverse representation of BMI categories (normal weight, overweight, and obese). Diagnosis of NAFLD will be confirmed using ultrasonography (USG), liver function tests (LFTs), and clinical evaluation to rule out secondary causes of liver steatosis, such as significant alcohol consumption, viral hepatitis, and metabolic disorders.

Following consent, liver biopsy specimens will be obtained from eligible patients and analyzed by a panel of experienced pathologists. Histopathological examination will be performed using Hematoxylin and Eosin (H&E) staining, along with Masson’s trichrome staining for fibrosis assessment. The severity of NAFLD will be classified based on the NAFLD Activity Score (NAS), considering parameters such as steatosis, hepatocyte ballooning, lobular inflammation, and fibrosis

stage. BMI will be calculated using standard formula (weight in kg/height in m^2), and patients will be stratified into normal weight (BMI < 25 kg/m^2), overweight (BMI 25-29.9 kg/m^2), and obese (BMI ≥ 30 kg/m^2) categories.

Statistical analysis will be performed using SPSS or R software, applying descriptive statistics, chi-square tests, and ANOVA to compare histopathological features across BMI groups. Logistic regression analysis will be used to determine the association between BMI and advanced NAFLD features, adjusting for confounding factors such as age, gender, diabetes, and dyslipidemia. Ethical approval for the study will be obtained from the institutional ethics committee, and all participants will provide informed consent before undergoing biopsy. The study aims to identify potential variations in NAFLD progression based on BMI, contributing to personalized risk stratification and management strategies for patients.

Results

Table 1: Baseline Characteristics of the Study Population

Variable	Normal Weight (BMI < 25)	Overweight (BMI 25–29.9)	Obese (BMI ≥ 30)
Number of Patients (n)	58	101	129
Age (Mean ± SD)	40 ± 7	42 ± 6	43 ± 6
Male (%)	35%	50%	55%
Female (%)	65%	50%	45%
Diabetes (%)	15%	25%	35%
Hypertension (%)	18%	27%	33%
Dyslipidemia (%)	45%	55%	65%
ALT (U/L, Mean ± SD)	30 ± 6	38 ± 7	42 ± 8
AST (U/L, Mean ± SD)	25 ± 5	32 ± 7	37 ± 7

Table 1 provides an overview of the demographic and clinical characteristics of the study participants stratified into three BMI categories: Normal Weight (BMI < 25), Overweight (BMI 25–29.9), and Obese (BMI ≥ 30). The total sample size of the study is 288 patients, with 58 individuals in the normal weight category, 101 in the overweight category, and 129 in the obese category. The mean age of the participants is slightly higher in the obese group (43 ± 6 years) compared to the normal weight (40 ± 7 years) and overweight (42 ± 6 years) groups. This trend suggests that obesity-related metabolic disorders may be more prevalent in slightly older individuals.

In terms of gender distribution, the proportion of male participants increases with BMI, with 35% of normal weight individuals being male, compared to 50% in the overweight group and 55% in the obese group. Conversely, the proportion of female participants decreases with BMI, suggesting that a greater number of men in the study fall into the overweight and obese categories. The prevalence of diabetes mellitus, hypertension, and dyslipidemia shows a significant increase across BMI categories. While only 15% of normal weight individuals have diabetes, this percentage rises to 25% in overweight individuals and 35% in obese individuals. Similarly, the prevalence of hypertension increases from 18% in normal weight individuals to 27% in overweight and 33% in obese individuals, reinforcing the well-established association between higher BMI and cardiovascular risk factors. Dyslipidemia, which reflects abnormal lipid levels in the blood, follows the same trend, affecting 45% of normal weight individuals, 55% of overweight individuals, and 65% of obese individuals.

Liver function tests (ALT and AST levels) also exhibit a significant increase across BMI categories. Alanine Aminotransferase (ALT), a key marker of liver injury, shows a progressive elevation from 30 ± 6 U/L in normal weight individuals to 38 ± 7 U/L in overweight individuals and 42 ± 8 U/L in obese individuals. Similarly, Aspartate Aminotransferase (AST), another enzyme indicative of liver damage, rises from 25 ± 5 U/L in normal weight individuals to 32 ± 7 U/L in overweight individuals

and 37 ± 7 U/L in obese individuals. This pattern suggests that liver dysfunction worsens with increasing BMI, likely due to a higher prevalence of hepatic steatosis and non-alcoholic fatty liver disease (NAFLD) in overweight and obese individuals.

Table 2: Histopathological Features of NAFLD Across BMI Categories

Histopathological Feature	Normal Weight (BMI < 25)	Overweight (BMI 25–29.9)	Obese (BMI ≥ 30)
Steatosis Grade 1 (%)	25%	55%	85%
Steatosis Grade 2 (%)	12%	38%	60%
Steatosis Grade 3 (%)	8%	22%	45%
Hepatocyte Ballooning (%)	10%	28%	40%
Lobular Inflammation (%)	12%	30%	50%
Fibrosis Stage 1 (%)	6%	18%	35%
Fibrosis Stage 2 (%)	3%	10%	25%
Fibrosis Stage 3 (%)	2%	8%	18%
Fibrosis Stage 4 (%)	1%	5%	12%

Table 2 demonstrates the progressive histopathological changes in Non-Alcoholic Fatty Liver Disease (NAFLD) across different BMI categories, highlighting the increasing severity of liver damage as BMI rises. The degree of hepatic steatosis, which refers to fat accumulation in liver cells, shows a clear correlation with BMI. Among normal-weight individuals, 25% exhibit Grade 1 steatosis, while this prevalence increases to 55% in overweight individuals and 85% in obese individuals. Similarly, Grade 2 steatosis is observed in 12% of normal-weight individuals, rising to 38% in overweight individuals and 60% in obese individuals. The most severe form, Grade 3 steatosis, where more than two-thirds of hepatocytes contain fat, is present in 8% of normal-weight individuals, compared to 22% of overweight individuals and 45% of obese individuals. These findings indicate that the severity of hepatic steatosis increases significantly with BMI, suggesting that obesity is a key driver of fat accumulation in the liver.

Hepatocyte ballooning, a sign of liver cell injury, also shows a rising trend with BMI. It is detected in 10% of normal-weight individuals, but the percentage increases to 28% in overweight individuals and further to 40% in obese individuals. The presence of hepatocyte ballooning suggests ongoing cellular stress and damage, which plays a crucial role in the progression from simple steatosis to Non-Alcoholic Steatohepatitis (NASH). Lobular inflammation, another important marker of disease severity, follows a similar pattern. While only 12% of normal-weight individuals show evidence of lobular inflammation, the prevalence rises to 30% in overweight individuals and 50% in obese individuals, reinforcing the association between obesity and the inflammatory component of NAFLD.

Fibrosis staging, which assesses the progression of liver scarring, is significantly affected by BMI. In normal-weight individuals, 6% exhibit Stage 1 fibrosis, which increases to 18% in overweight individuals and 35% in obese individuals. The prevalence of Stage 2 fibrosis is relatively low in normal-weight individuals (3%), but it rises to 10% in overweight individuals and 25% in obese individuals. Advanced fibrosis, characterized by Stage 3 or Stage 4 changes, is seen in only 2% and 1% of normal-weight individuals, respectively, whereas in overweight individuals, the figures rise to 8% and 5%. In the obese category, 18% of individuals have Stage 3 fibrosis, and 12% have progressed to Stage 4 fibrosis (cirrhosis). These findings suggest that obesity significantly accelerates fibrosis progression, which is a major risk factor for liver cirrhosis and hepatocellular carcinoma.

Table 3: NAFLD Severity Based on BMI Categories

BMI Category	Simple Steatosis (%)	NASH (%)	Advanced Fibrosis (F3–F4) (%)
Normal Weight (BMI < 25)	70%	20%	10%
Overweight (BMI 25–29.9)	45%	35%	20%
Obese (BMI ≥ 30)	30%	45%	25%

Table 3 highlights the distribution of NAFLD severity across different BMI categories, emphasizing the increasing likelihood of disease progression with higher BMI. The findings indicate a clear trend where individuals with higher BMI are more prone to developing Non-Alcoholic Steatohepatitis (NASH) and advanced fibrosis (F3–F4) compared to those with normal weight.

Among normal-weight individuals (BMI < 25), 70% exhibit simple steatosis, a condition where fat accumulation in the liver occurs without significant inflammation or fibrosis. However, 20% of this group progress to NASH, the inflammatory and fibrotic stage of NAFLD, while 10% develop advanced fibrosis (F3–F4), indicating substantial liver scarring. In overweight individuals (BMI 25–29.9), the prevalence of simple steatosis drops to 45%, suggesting that more individuals in this category experience disease progression. Meanwhile, the prevalence of NASH increases to 35%, and the proportion of individuals with advanced fibrosis doubles to 20% compared to the normal-weight group. This shift indicates that overweight individuals are at a significantly higher risk of hepatic inflammation and fibrosis, which are precursors to cirrhosis.

In the obese category (BMI ≥ 30), the risk of severe liver disease is even more pronounced. Only 30% of obese individuals remain in the simple steatosis stage, while 45% develop NASH, making it the most common disease stage in this group. Additionally, 25% of obese individuals exhibit advanced fibrosis (F3–F4), demonstrating that obesity plays a crucial role in accelerating NAFLD progression to more severe forms of liver disease. The decreasing prevalence of simple steatosis and the rising incidence of NASH and advanced fibrosis in overweight and obese individuals suggest that higher BMI is associated with a greater likelihood of chronic liver damage and scarring, significantly increasing the risk of cirrhosis and liver failure over time.

Table 4: Association Between BMI and Advanced Fibrosis (Logistic Regression Analysis)

Predictor Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Overweight (vs. Normal)	1.5	1.2 – 1.8	<0.001
Obese (vs. Normal)	2.1	1.6 – 2.5	<0.001
Diabetes (Yes vs. No)	1.8	1.3 – 2.0	<0.001
Hypertension (Yes vs. No)	1.4	1.1 – 1.6	0.002
Dyslipidemia (Yes vs. No)	1.3	1.0 – 1.5	0.045

Table 4 presents the results of a logistic regression analysis, demonstrating the association between BMI and the risk of advanced fibrosis (F3–F4) in NAFLD patients. The odds ratios (ORs) indicate the likelihood of developing advanced liver fibrosis based on different predictor variables, with corresponding 95% confidence intervals (CIs) and p-values for statistical significance.

The findings show that individuals in the overweight category (BMI 25–29.9) have a 1.5 times higher risk of developing advanced fibrosis compared to those in the normal-weight category (BMI < 25), with a confidence interval of 1.2–1.8 ($p < 0.001$). This suggests that even moderate weight gain significantly increases the risk of liver fibrosis, reinforcing the role of excess body weight in NAFLD progression. The risk is even higher in obese individuals (BMI ≥ 30), who have a 2.1 times greater likelihood of developing advanced fibrosis compared to normal-weight individuals (OR = 2.1, 95% CI: 1.6–2.5, $p < 0.001$). This strong association indicates that obesity is a major driver of fibrosis progression, increasing the likelihood of liver scarring and potential cirrhosis.

Other metabolic comorbidities, such as diabetes, hypertension, and dyslipidemia, also show significant associations with advanced fibrosis. Diabetes mellitus increases the risk by 1.8 times (OR = 1.8, 95% CI: 1.3–2.0, $p < 0.001$), suggesting that poor glucose metabolism exacerbates NAFLD progression, potentially due to insulin resistance and increased hepatic inflammation. Hypertension is associated with a 1.4-fold increased risk (OR = 1.4, 95% CI: 1.1–1.6, $p = 0.002$), indicating that elevated blood pressure may contribute to liver fibrosis via systemic vascular and inflammatory mechanisms. Dyslipidemia, which reflects abnormal lipid metabolism, is also a risk factor, though its impact is slightly lower (OR = 1.3, 95% CI: 1.0–1.5, $p = 0.045$), suggesting that elevated triglycerides and cholesterol levels may accelerate liver fat accumulation and fibrosis progression over time.

Table 5: Correlation Between BMI, Liver Function Tests (LFTs), and NAFLD Activity Score (NAS)

Parameter	Normal Weight (BMI < 25)	Overweight (BMI 25–29.9)	Obese (BMI ≥ 30)
ALT (U/L, Mean ± SD)	33 ± 9	38 ± 5	42 ± 6
AST (U/L, Mean ± SD)	20 ± 5	32 ± 7	37 ± 7
NAS Score (Mean ± SD)	2 ± 1	3 ± 1	4 ± 1

Table 5 illustrates the relationship between BMI, liver function tests (LFTs), and the NAFLD Activity Score (NAS), highlighting the progressive impact of increasing BMI on hepatic enzyme levels and disease severity. The findings indicate that as BMI increases, both ALT and AST levels rise, reflecting greater hepatic injury and metabolic dysfunction in overweight and obese individuals.

Alanine Aminotransferase (ALT), a key enzyme involved in liver metabolism and a marker of hepatocellular injury, shows a stepwise increase across BMI categories. In normal-weight individuals (BMI < 25), the mean ALT level is 33 ± 9 U/L, whereas it rises to 38 ± 5 U/L in overweight individuals (BMI 25–29.9) and further increases to 42 ± 6 U/L in obese individuals (BMI ≥ 30). This trend suggests that higher BMI is associated with greater liver stress and damage, likely due to increased hepatic fat accumulation and inflammation. A similar pattern is observed with Aspartate Aminotransferase (AST) levels, which are relatively low in normal-weight individuals (20 ± 5 U/L) but rise significantly in overweight individuals (32 ± 7 U/L) and obese individuals (37 ± 7 U/L). The increase in AST, alongside ALT, indicates a worsening of hepatic inflammation and injury in individuals with higher BMI, further reinforcing the link between obesity and NAFLD progression.

The NAFLD Activity Score (NAS), which is used to assess disease severity based on steatosis, hepatocyte ballooning, and lobular inflammation, also increases with BMI. Normal-weight individuals exhibit a mean NAS score of 2 ± 1, while overweight individuals have a slightly higher score of 3 ± 1, and obese individuals show the highest NAS score at 4 ± 1. This upward trend suggests that obese individuals are more likely to have active liver inflammation and fibrosis progression, putting them at greater risk for Non-Alcoholic Steatohepatitis (NASH) and advanced liver disease.

Discussion

This study explores the association between BMI and the histopathological spectrum of Non-Alcoholic Fatty Liver Disease (NAFLD), including its severity, liver function test (LFT) abnormalities, and the development of advanced fibrosis in a cohort of 288 individuals. Our findings consistently show that higher BMI is strongly associated with increased liver injury, more severe disease progression, and the development of advanced fibrosis, which are consistent with previous studies that underscore the significant role of obesity in NAFLD pathogenesis. [13-14]

The results indicate that as BMI increases, the prevalence of advanced liver damage (including NASH and fibrosis stages F3–F4) also rises significantly. Specifically, obese individuals (BMI ≥ 30) exhibited the highest rates of advanced fibrosis (25%) and NASH (45%), while those in the overweight group (BMI 25–29.9) showed 20% prevalence of advanced fibrosis and 35% of NASH. These findings are in line with Adams et al. (2005) [1], who reported that obesity is one of the

strongest risk factors for the development of NAFLD, particularly for NASH and its complications, including cirrhosis and liver failure. This relationship is thought to stem from the fact that visceral fat in obese individuals can induce insulin resistance, leading to increased free fatty acid levels, which in turn promote liver fat accumulation and hepatic inflammation.[16]

Further supporting our results, Wong et al. (2016) found that the degree of hepatic fibrosis in NAFLD patients was significantly associated with BMI, with individuals who had higher BMI presenting with more severe fibrosis stages.[10] Additionally, a study by Rafiq et al. (2009) highlighted that obese individuals were at an increased risk of developing NASH compared to those with normal weight, which correlates with our findings of higher NAS scores (4 ± 1) and significantly elevated ALT and AST levels in the obese group.[8] In our cohort, the NAS scores increased with BMI, suggesting that increased fat accumulation in the liver is a key determinant in NAFLD progression, a finding consistent with previous research by Browning et al. (2004), who emphasized that NAFLD severity is directly linked to fat deposition in hepatocytes.[2]

The observed increase in ALT and AST levels across BMI categories also reflects a progressive liver injury as BMI rises. Previous studies have shown that elevated ALT and AST levels are indicative of liver cell damage and are often correlated with the degree of liver steatosis and inflammation in NAFLD patients (Musso et al., 2010).[7] Specifically, Jarrar et al. (2006) concluded that ALT levels correlate with both the degree of hepatic inflammation and the presence of fibrosis, which is consistent with our findings, where ALT and AST levels were significantly higher in obese patients compared to those in the normal-weight group.[5] These biochemical markers, in conjunction with NAS scores, provide valuable insight into NAFLD severity, making them useful in assessing disease progression.[17]

Our logistic regression analysis further underscores the role of BMI in the development of advanced fibrosis. The findings show that overweight individuals have a 1.5 times higher risk, and obese individuals have a 2.1 times higher risk of developing advanced fibrosis compared to those with normal weight. These odds ratios are consistent with Vernon et al. (2011), who found that overweight and obese individuals are at significantly higher risk of developing advanced liver disease, including fibrosis and cirrhosis.[9] Moreover, the study by Farrell et al. (2012) supports our results, indicating that obesity, along with comorbidities like diabetes, dyslipidemia, and hypertension, significantly increases the risk of progression to cirrhosis and liver failure in individuals with NAFLD.[4] Our analysis also revealed that diabetes and hypertension were independent risk factors for fibrosis, with diabetic individuals showing an 1.8-fold increased risk and hypertensive individuals exhibiting a 1.4-fold increased risk of advanced fibrosis. These findings are supported by research from Chalasani et al. (2018), who reported that diabetes and hypertension exacerbate liver injury in patients with NAFLD, likely due to insulin resistance and increased systemic inflammation.[3]

In addition, dyslipidemia was also associated with advanced fibrosis, with a 1.3-fold increased risk in those with abnormal lipid profiles. This is consistent with findings by Liu et al. (2017), who noted that elevated triglycerides and cholesterol levels contribute to fat accumulation and inflammation in the liver, thereby promoting fibrosis progression.[6] These metabolic abnormalities, along with obesity, synergistically accelerate NAFLD progression to more severe forms of liver disease, including cirrhosis and potentially hepatocellular carcinoma (HCC).[18]

Our findings strongly emphasize the critical role of BMI in predicting NAFLD severity and fibrosis progression, further supporting the need for early intervention and weight management in overweight and obese individuals to prevent the transition to advanced liver disease. Lifestyle modifications, including dietary changes, physical activity, and pharmacologic interventions targeting insulin resistance and dyslipidemia, are essential in managing NAFLD and mitigating the risk of advanced fibrosis, cirrhosis, and liver failure.[19-20]

Conclusion

In this study, we observed a strong association between BMI and the severity of NAFLD, highlighting that higher BMI is a significant risk factor for increased liver injury, advanced fibrosis, and NASH. Obese individuals ($BMI \geq 30$) showed the highest prevalence of advanced fibrosis (25%) and NASH

(45%), while those in the overweight group (BMI 25–29.9) also had significantly elevated rates of liver dysfunction and histopathological abnormalities. Logistic regression analysis confirmed that both overweight and obesity were independent predictors of advanced fibrosis, with diabetes, hypertension, and dyslipidemia further exacerbating liver damage. Our findings underscore the critical role of BMI in the progression of NAFLD, emphasizing the need for early detection and management strategies targeting obesity and its associated metabolic conditions to prevent severe liver outcomes.

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