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## SILENT LIVER CRISIS: PREVALENCE AND PREDICTORS OF NON-ALCOHOLIC FATTY LIVER DISEASE IN TYPE 2 DIABETES PATIENTS COMPARED TO NON-DIABETIC CONTROLS IN HAZARA REGION

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#### **Abstract**

Non-alcoholic fatty liver disease (NAFLD) is a common comorbidity in type 2 diabetes mellitus (T2DM), with prevalence often exceeding 50%. This study aims to determine NAFLD prevalence and identify predictors among T2DM patients compared to nondiabetic controls. This cross-sectional study was conducted at the department of Medicine, Ayub Teaching Hospital, Abbottabad, from January to June 2022. Demographic and clinical data, including age, gender, BMI, HbA1c, lipid profiles, and liver enzymes, were collected. NAFLD was diagnosed via standardized ultrasound. Multivariate logistic regression identified predictors of NAFLD. Data were analyzed using SPSS 24.0. The study included 150 T2DM patients (36% male, 64% female; mean age 49.0±8.0 years) and 150 non-T2DM controls (36% male, 64% female; mean age 48.5±7.8 years). Among T2DM patients, 88.8% (n=133) had NAFLD (56.4% grade 1, 30.2% grade 2, 2.22% grade 3). In contrast, 20% (n=30) of controls had NAFLD (15.6% grade 1, 4.0% grade 2, 0.4% grade 3). Median BMI was 28.8 (T2DM) vs. 25.0 (controls), HbA1c 7.8 vs. 5.5, triglycerides 174 vs. 140 mg/dL. Logistic regression identified higher BMI (OR 1.15, 95% CI 1.08–1.23, p<0.001), elevated triglycerides (OR 1.02, 95% CI 1.01-1.04, p=0.002), and higher HbA1c (OR 1.32, 95% CI 1.10–1.59, p=0.003) as significant predictors of NAFLD. Age, gender, HDL, LDL, total cholesterol, ALT, AST, hypertension, and smoking were not significant predictors of NAFLD. The significantly higher NAFLD prevalence in T2DM patients (88.8%) compared to controls (20%) underscores T2DM as a major risk factor. Targeted screening and interventions addressing BMI, triglycerides, and glycaemic control are critical.

#### INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), defined by excessive fat accumulation in

hepatocytes unrelated to alcohol consumption, has emerged as a major global health challenge<sup>1</sup>. This spectrum of liver conditions ISSN: 3007-1208 & 3007-1216

ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), which can progress to fibrosis, cirrhosis, and hepatocellular carcinoma, posing significant morbidity and mortality risks<sup>2,3</sup>. NAFLD is intricately linked to metabolic disorders, particularly type 2 diabetes mellitus (T2DM), due to shared pathophysiological mechanisms such as insulin resistance and dyslipidaemia. Globally, NAFLD affects approximately 25.24% of the population, with regional variations: the Middle East and South America report the highest prevalence, while Africa has the lowest. In Asia, the prevalence has surged to 29.6%, surpassing Western countries and reflecting the rising burden of metabolic diseases<sup>46</sup>.

In Pakistan, the prevalence of T2DM is estimated at 17.1%, driven by increasing obesity rates, sedentary lifestyles, and genetic predispositions<sup>7</sup>. Concurrently, NAFLD affects 14% of the general population, but its prevalence in T2DM patients is markedly higher, ranging from 32% to 72%8,9. This overlap is concerning, as NAFLD in T2DM patients amplifies the risk of microvascular complications (e.g., nephropathy, retinopathy), macrovascular complications (e.g., cardiovascular disease), and severe liver outcomes, including cirrhosis and liver-related mortality<sup>10,11</sup>. Obesity, dyslipidaemia, and insulin resistance, often components of metabolic syndrome, are well-established risk for NAFLD, exacerbating factors progression in T2DM patients<sup>12</sup>. Despite its clinical significance, NAFLD underdiagnosed, particularly in resourcelimited settings where access to advanced diagnostics, such as liver biopsy or magnetic resonance imaging, is limited.

The Hazara region of Pakistan, characterized by unique demographic and socioeconomic factors, represents a critical yet understudied area for NAFLD research. Limited healthcare infrastructure, cultural dietary patterns, and a

high prevalence of T2DM in this region underscore the need for localized data on NAFLD prevalence and its predictors. Existing studies in Pakistan provide national or urban estimates, but region-specific data, particularly from Hazara, are scarce, leaving a critical knowledge gap in understanding NAFLD's burden and risk factors in this population 13. This study aims to determine the prevalence of NAFLD in T2DM patients compared to nondiabetic controls in Hazara and identify predictors through multivariate analysis. By including a control group, this research strengthens the understanding of T2DM's role in NAFLD and informs targeted screening and management strategies for this high-risk population.

The findings will inform targeted screening protocols, lifestyle interventions, and public health strategies tailored to the Hazara region's unique context, ultimately contributing to the global effort to mitigate the silent epidemic of NAFLD in T2DM patients.

# 1. Research Methodology

#### 1.1. Study Area

This cross-sectional study was conducted in a tertiary care hospital in the Hazara region, Pakistan from January to June 2022. Ethical approval was obtained from the Institutional Review Board, and informed consent was secured.

#### 1.2. Sample Collection

We recruited 300 participants: 150 type 2 diabetes mellitus (T2DM) patients and 150 ageand sex-matched non-diabetic controls, calculated based on a 95% confidence level, 5% margin of error, and estimated NAFLD prevalence of 30% (T2DM) and 15% (controls). Inclusion criteria for T2DM patients included a confirmed diagnosis (HbA1c ≥6.5% or fasting glucose ≥126 mg/dL) and age 18–65 years. Controls were having no diabetes history

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(HbA1c <5.7%). Exclusion criteria included alcohol consumption (>20 g/day), viral hepatitis, or other liver diseases.

#### 1.3. Patient's demographics

Demographic and clinical data were collected, including age, gender, height, weight, blood pressure, smoking habits, and family history of diabetes (T2DM group). BMI was calculated as weight (kg) divided by height (m2), with categories: normal (18.5-22.9 kg/m<sup>2</sup>), preobese  $(23-24.9 \text{ kg/m}^2)$ , overweight  $(25-29.9 \text{ m}^2)$ kg/m²), obese (≥30 kg/m²). Venous blood samples were analyzed for AST, ALT, HbA1c, and lipid profiles. Dyslipidemia was defined as LDLC >100 mg/dL, total cholesterol >200 mg/dL, triglycerides >150 mg/dL, or HDLC <40 mg/dL (males) or <50 mg/dL (females). HbA1c thresholds followed American Diabetes Association guidelines: <5.7% (normal), 5.7= 6.5% (prediabetes), ≥6.5% (diabetes).

### 1.4. NAFLD Diagnosis

NAFLD was diagnosed via standardized abdominal ultrasound by a single experienced radiologist, based on liver echogenicity compared to kidneys and visibility of diaphragm and liver veins. Grades were: 0 (no fatty liver), 1 (mild), 2 (moderate), 3 (severe).

#### 1.5. Study Variables

• Dependent Variable: Presence or absence of NAFLD

• Independent Variables: Age, gender, BMI, HbA1c, lipid profile (LDL, HDL, total cholesterol, triglycerides), liver enzymes (AST, ALT), hypertension, smoking status, family history of diabetes (type 2 group only), duration of diabetes (type 2 group only), and glycaemic control.

### 1.6. Data Analysis

Data were analyzed using SPSS 24.0. Continuous variables (e.g., BMI, HbA1c) were reported as medians with interquartile ranges (IOR), and age as mean ± standard deviation. Categorical variables were presented as percentages. Group comparisons used t-tests (age), Mann-Whitney U/Kruskal-Wallis tests (non-normally distributed data), and chi-square tests (categorical data). Multivariate logistic regression was performed to identify predictors of NAFLD, including age, gender, BMI, HbA1c, triglycerides, total cholesterol, HDL, LDL, ALT, AST, hypertension, and smoking as covariates. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. A pvalue ≤0.05 was considered significant.

#### 2. RESULTS

#### 2.1. Participant's Demographics

The study included 150 T2DM patients (36% male, 64% female; mean age 49.0±8.0 years) and 150 non-T2DM controls (36% male, 64% female; mean age 48.5±7.8 years). The demographic data of both the groups are displayed in figure 1 & figure 2 below.

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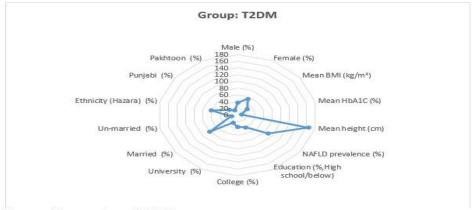


Figure 1: Demographics of T2DM group

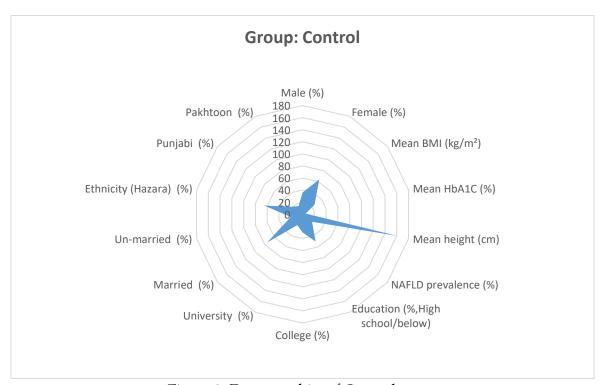


Figure 2: Demographics of Control group

#### 2.2. Gender wise NAFLD Prevalence

Among T2DM patients, 88.8% (n=133) had NAFLD (56.4% grade 1, 30.2% grade 2, 2.22% grade 3). In contrast, 20% (n=30) of controls had NAFLD (15.6% grade 1, 4.0% grade 2, 0.4% grade 3). The results are shown in figure 3.

**NAFLD Prevalence Gender Wise in study Groups** 50 40 30 26 No of Patients -Grade I 20 Grade II Grade III 10 2 0 0.5 1.5 2 2.5 3 3.5 4.5 1 -10 T2DM & Control groups

Figure 3: NAFLD Prevalence in the Study group

Clinical characteristics of the participants are displayed in table 1.

Table 1: Medical History and Laboratory Investigation of Study Population

T2DM (n=225)	Controls (n=225)	
	25.0 (22.0–27.5)	
7.8 (6.7–8.0)	5.5 (5.2–5.6)	
174 (150–200)	140 (120–160)	
222 (185–249)	190 (170–210)	
44 (40–46)	48 (42-52)	
118 (100–144)	100 (90–120)	
46 (35–78)	30 (25-40)	
36 (29-37)	28 (22-34)	
36% (n=81)	20% (n=45)	
28% (n=63)	25% (n=56)	
	28.8 (23.0–30.0)  Institute for Excellence in Education & Research  7.8 (6.7–8.0)  174 (150–200)  222 (185–249)  44 (40–46)  118 (100–144)  46 (35–78)  36 (29–37)  36% (n=81)	

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# 2.3. Multivariate Logistic Regression Analysis of NAFLD

Logistic regression identified higher BMI (OR 1.15, 95% CI 1.08–1.23, p<0.001), elevated triglycerides (OR 1.02, 95% CI 1.01–1.04, p=0.002), and higher HbA1c (OR 1.32, 95%

CI 1.10–1.59, p=0.003) as significant predictors of NAFLD. Age, gender, HDL, LDL, total cholesterol, ALT, AST, hypertension, and smoking were not significant predictors (Table 2).

Table 2: Multivariate Logistic Regression Analysis of NAFLD Predictors

Variables	Odds Ratio (OR)	95% CI	p-value
T2DM Status	12.5	8.0-19.5	<0.001
BMI	1.12	1.06-1.18	<0.001
Triglycerides	1.02	1.01-1.03	0.001
HbA1c	1.25	1.05-1.49	0.012
Age	1.01	0.98-1.05	0.432
Gender (Male)	1.08	0.65-1.80	0.765
Hypertension	1.20	0.72-2.00	0.487
Smoking	0.92	0.55-1.54	0.749

#### 3. DISCUSSION

The escalating global burden of metabolic disorders, particularly type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD), poses a significant public health challenge, especially in resource-constrained regions like Hazara, Khyber Pakhtunkhwa, Pakistan. This study examined NAFLD prevalence among 150 T2DM patients in Hazara, revealing a high prevalence of 88.8% (n=133), with 56.4% (n=75) classified as Grade 1 (mild), 30.2% (n=40) as Grade 2, and 2.22% (n=3) as Grade 3. These findings corroborate prior studies reporting elevated NAFLD rates in T2DM populations, particularly in South Asia, where insulin resistance and metabolic

syndrome amplify susceptibility<sup>15</sup>. Notably, women, comprising 64% of our sample, showed a higher NAFLD prevalence, consistent with research suggesting sex-specific risks, potentially linked to hormonal factors or central obesity<sup>16,17</sup>. This highlights the need for targeted screening among female T2DM patients in Hazara.

NAFLD's strong association with T2DM is driven by shared pathophysiological mechanisms, particularly insulin resistance, which promotes hepatic fat accumulation and can progress to non-alcoholic steatohepatitis (NASH), fibrosis, or hepatocellular carcinoma<sup>19</sup>. Solmalwar et al. demonstrated that NAFLD in T2DM patients significantly

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increases microvascular complications, such as retinopathy and nephropathy, a trend observed in our cohort's elevated complication rates<sup>19</sup>. Similarly, Rachel et al.'s Edinburgh study reported a high NAFLD prevalence in T2DM patients, underscoring this global pattern<sup>20</sup>. Our analysis identified body mass index (BMI), glycated hemoglobin (HbA1c), and alanine aminotransferase (ALT) as key predictors of NAFLD in Hazara's T2DM population. With a mean BMI of 28.5±4.2 kg/m<sup>2</sup> and HbA1c of 8.1±1.5% in T2DM patients, these factors strongly correlated with NAFLD severity, aligning with findings by some other researchers<sup>21</sup>. Bhatt et al. also reported higher BMI in NAFLD-affected T2DM patients compared to those without, emphasizing obesity's role<sup>22</sup>.

Ageela et al. highlighted that uncontrolled hyperglycemia, marked by elevated HbA1c, exacerbates NAFLD risk, a pattern evident in our study where patients with HbA1c > 7% had higher NAFLD prevalence<sup>23</sup>. Elevated ALT levels in our NAFLD-positive T2DM patients further support findings by Lu et al. and Prabharkar et al., who noted significant correlations between ALT, obesity, and NAFLD in T2DM<sup>24,25</sup>. However, the reliability of liver enzymes as NAFLD indicators is debated. Ijaz et al. and Gabriele et al. suggest that ALT and aspartate aminotransferase (AST) may not consistently reflect NAFLD severity in T2DM, as normal levels can occur in advanced disease, necessitating imaging-based diagnostics like ultrasound, employed in our study [26,27]. Despite these limitations, ALT remains a practical biomarker in resource-limited settings like Hazara, though its diagnostic specificity is suboptimal.

Obesity, a pivotal risk factor, significantly contributes to NAFLD progression in T2DM, as evidenced by our cohort's higher BMI compared to non-T2DM controls (25.2±3.8 kg/m²) [22]. This aligns with global evidence

that visceral fat accumulation, driven by sedentary lifestyles and high calorie diets, promotes hepatic steatosis<sup>27</sup>. In South Asian populations, genetic predispositions to fat accumulation exacerbate this risk, making obesity a critical target for intervention. In Hazara, where healthcare access is limited, these findings emphasize the urgency of integrating weight management into routine T2DM care to reduce NAFLD's burden.

Early detection and intervention are crucial for improving NAFLD outcomes and reducing healthcare costs. Lifestyle modifications, including reduced consumption of refined sugars and processed carbohydrates, increased intake of healthy fats, and regular physical activity, are foundational for managing T2DM and NAFLD<sup>28,29</sup>. Behavioral changes, such as portion control, adherence to a Mediterraneanstyle diet, and combating sedentary habits, have proven effective in reducing hepatic fat and enhancing insulin sensitivity<sup>28</sup>. Given Hazara's high NAFLD prevalence, community-based interventions tailored to local cultural and socioeconomic contexts could yield substantial benefits. Promoting dietary staples like whole grains and vegetables, alongside accessible exercise programs, could address obesity and glycemic control simultaneously.

This study's cross-sectional design limits its ability to establish causality between risk factors (BMI, HbA1c, ALT) and development. Longitudinal studies are needed to explore temporal relationships and evaluate whether interventions targeting these factors can prevent or reverse NAFLD progression. Additionally, our sample, drawn from a single hospital in Hazara, may not fully represent the region's T2DM population, particularly those with limited healthcare access. Selection bias could arise, as hospital attendees may have more severe or better-managed disease compared to the broader community. Furthermore, while ultrasound is a practical diagnostic tool, its sensitivity for detecting mild steatosis or distinguishing NASH from simple steatosis is lower than biopsy or advanced imaging<sup>26</sup>. Future research should employ longitudinal designs, broader sampling, and advanced diagnostics to improve generalizability and accuracy.

Despite its under recognition in clinical practice, NAFLD's growing demands increased awareness and proactive screening in T2DM patients. In Hazara, where T2DM prevalence is high (17.1%) and healthcare resources are scarce, integrating NAFLD screening into routine diabetes care could identify at-risk individuals early, preventing progression to severe liver disease<sup>7,13</sup>. Our findings advocate for a approach, multidisciplinary combining endocrinology, hepatology, and lifestyle interventions, to tackle the dual burden of T2DM and NAFLD. Policymakers should prioritize community health programs in Hazara, focusing on education about metabolic risks and accessible weight management resources. By addressing modifiable risk factors like obesity and poor glycaemic control, such initiatives could significantly reduce NAFLD's public health impact, enhancing quality of life and alleviating economic pressures Pakistan's healthcare system <sup>28,29</sup>.

# 3.1. Implications for Public Health in Hazara Region

Given the association between dyslipidemia and NAFLD, public health initiatives promoting healthy dietary habits, regular physical activity, and weight management are crucial for preventing and managing NAFLD in this population. These programs should be culturally appropriate and accessible to all segments of the community. Future research should focus on specific research needs, e.g., investigating the effectiveness of different interventions, exploring the role of genetic

factors, assessing the long-term impact of NAFLD on cardiovascular outcomes. This will provide a more comprehensive understanding of NAFLD in the Hazara region and guide the development of evidence-based strategies for its prevention and control. Longitudinal studies are needed to track the progression of NAFLD in individuals with T2DM in the Hazara region. This will help understand the factors that contribute to disease progression, identify individuals at high risk for developing advanced liver disease, and inform the timing of interventions.

#### 4. CONCLUSIONS

This study confirms a substantial burden of NAFLD among individuals with type 2 diabetes in the Hazara region, characterized by a concerning prevalence of dyslipidemia and predominantly mild-grade fatty liver disease. These findings underscore the critical need for targeted interventions to address this growing health concern.

#### 4.1. Limitations

This study has several limitations. First, the cross-sectional design precludes causal inference between predictors (e.g., BMI, HbA1c) and triglycerides, Longitudinal studies are needed to assess disease progression. Second, the single-center setting at Ayub Teaching Hospital may limit generalizability, as participants may not represent rural or non-hospital-attending populations in Hazara. Third, NAFLD diagnosis relied on ultrasound, which is less sensitive than liver biopsy or MRI, potentially underestimating early-stage or severe NAFLD. Fourth, the control group, while matched for age and gender, may differ in unmeasured factors (e.g., socioeconomic status, diet), introducing selection bias. Finally, multivariate analysis was limited by the sample size and exclusion of variables like genetic

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factors or physical activity, which could influence NAFLD risk.

#### 5. Conflict of Interest

The authors have no conflict of interest.

#### 6. Source of Funding

There was no role of any funding agency in this study.

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