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PREVALENCE OF INSULIN RESISTANCE IN NON-DIABETIC NAFLD

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Abstract

Purpose: *To determine the prevalence of insulin resistance (IR) in non-diabetic patients with non-alcoholic fatty liver disease (NAFLD) and identify associated risk factors in a Pakistani population.*

Materials & Methods: *A cross-sectional study was conducted at Sir Ganga Ram Hospital, Lahore, enrolling 112 non-diabetic NAFLD patients. Data on demographics, BMI, waist circumference, blood pressure, lipid profile, fasting plasma glucose, and fasting insulin levels were collected. Insulin resistance was defined using the HOMA-IR index (HOMA-IR >2.0). Logistic regression analysis was performed to assess predictors of insulin resistance.*

Results: *The prevalence of insulin resistance among non-diabetic NAFLD patients was 72.3%. Key predictors of IR included age, BMI, and hypertension. Patients aged ≥40 years had a 47% increased likelihood of IR per additional year (p=0.026). Overweight/obese individuals had 2.39 times higher odds of IR (p=0.017). Hypertension was the strongest predictor, with hypertensive patients having nearly 12 times higher odds of IR (p=0.012). Dyslipidemia and gender were not significant predictors.*

Conclusion: *Insulin resistance is highly prevalent in non-diabetic NAFLD patients, with age, obesity, and hypertension as major risk factors. Early identification of IR in NAFLD patients is crucial for metabolic risk assessment and preventive interventions. Given Pakistan's rising burden of metabolic disorders, routine screening for IR in NAFLD patients and targeted lifestyle modifications should be prioritized to mitigate diabetes and cardiovascular risks.*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver disorders characterized by excessive fat accumulation in hepatocytes without significant alcohol use. Closely linked to metabolic dysfunction, it often coexists with obesity, dyslipidemia, hypertension, and insulin resistance-hallmarks of metabolic syndrome. Also termed metabolic dysfunction-associated fatty liver disease (MAFLD), NAFLD is the most common chronic liver disease globally, affecting nearly 25% of adults [1,2]. It progresses from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and in severe cases, cirrhosis or hepatocellular carcinoma. NAFLD's strong association with metabolic risk factors reinforces its classification as a metabolic liver disease rather than an isolated hepatic disorder.

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Insulin resistance occurs when muscle, liver, and adipose tissues fail to respond effectively to insulin, leading to compensatory hyperinsulinemia and metabolic disturbances. IR manifests as elevated blood glucose, hypertriglyceridemia, low HDL cholesterol, and hypertension. It is central to NAFLD, promoting fat accumulation in the liver. Impaired insulin action in adipose tissue increases lipolysis, flooding the liver with free fatty acids, while hyperinsulinemia stimulates de novo lipogenesis. This combination drives hepatic steatosis and metabolic dysfunction. Even in non-diabetic individuals, NAFLD is strongly linked to insulin resistance, suggesting it precedes type 2 diabetes.

NAFLD prevalence ranges from 25% to 30% globally, making it the leading cause of chronic liver disease [3]. It exceeds 30% in parts of the Middle East and South America, particularly in urban populations with sedentary lifestyles and high-calorie diets, while lower rates are observed in some African populations due to genetic and lifestyle factors [1,4].

Insulin resistance follows a similar pattern, with higher obesity rates driving its prevalence. In South Asia, urbanization and dietary shifts have increased IR-related conditions, with NAFLD prevalence ranging from 24% to 33%, reaching 53% in some cities [5,6]. Although exact global prevalence is difficult to determine, metabolic syndrome, a proxy for insulin resistance, affects about a quarter of adults [7,8]. Studies show most NAFLD patients, including non-diabetics, exhibit insulin resistance, emphasizing their strong metabolic connection.

In Pakistan, NAFLD is rising alongside increasing obesity and metabolic syndrome rates. Estimated to affect 15–20% of adults [1], its prevalence is higher among overweight individuals and diabetics, where it ranges from 32% to 72% [9]. Insulin resistance is a key driver, even before diabetes develops. Small studies show NAFLD patients often exhibit elevated fasting glucose, triglycerides, and low HDL, consistent with insulin-resistant dysmetabolism.

Rapid urbanization and dietary changes have led to obesity in 58% of adults and central obesity in over 70% [9]. Pakistan ranks third globally in diabetes prevalence, with 26–27% of adults affected and another 10% pre-diabetic [10]. Metabolic syndrome prevalence ranges from 18% to 46%, suggesting nearly half of adults have insulin resistance-related issues [11]. Common NAFLD risk factors, obesity, high triglycerides, low HDL, and hypertension, are widespread, creating conditions for increasing NAFLD prevalence.

Focusing on insulin resistance in non-diabetic NAFLD is critical for early intervention. These individuals have not yet developed diabetes but are on a concerning metabolic trajectory. NAFLD patients with insulin resistance are at a significantly higher risk of progressing to type 2 diabetes, with studies showing a twofold increase in risk. Up to 78% of non-diabetic NAFLD patients may develop abnormal glucose tolerance or diabetes within a decade if untreated [12].

Insulin resistance not only accelerates diabetes onset but also drives liver disease progression, contributing to NASH and fibrosis. Addressing insulin resistance in NAFLD patients can prevent diabetes and reduce liver-related morbidity. In Pakistan, where healthcare resources are limited, recognizing insulin-resistant NAFLD patients early allows for timely interventions, including lifestyle modifications, to improve insulin sensitivity.

The primary objective of this study is to determine the prevalence of insulin resistance in non-diabetic NAFLD patients.

METHODS

Study Design and Setting

This cross-sectional study was conducted at the Medicine OPD and wards of Sir Ganga Ram Hospital, Lahore, over a period of three months following the approval of the research protocol.

Study Population

A total of 112 non-diabetic patients diagnosed with NAFLD were enrolled in the study using non-probability consecutive sampling. The inclusion and exclusion criteria ensured the selection of appropriate candidates for the study.

Inclusion Criteria

- Patients aged 20 to 60 years diagnosed with NAFLD (Grade 1 and 2 on ultrasound).
- Non-diabetic individuals (fasting plasma glucose <126 mg/dL and postprandial glucose <200 mg/dL).
- Both male and female participants.

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Exclusion Criteria

- Patients with secondary causes of hepatic steatosis (alcohol abuse, viral hepatitis, or other etiologies).
- Patients diagnosed with cirrhosis, liver failure, ischemic heart disease (IHD), or chronic kidney disease (CKD).
- Grade III fatty liver on ultrasound.
- LDL cholesterol levels >160 mg/dL.

Data Collection and Procedures

Participants were identified from the hospital OPD and wards. After screening for diabetes, IHD, CKD, and other exclusion criteria, eligible individuals were invited for further evaluation.

The following clinical and biochemical parameters were recorded:

- Demographic information (age, gender, weight, height, BMI, waist circumference)
- Blood pressure measurement (hypertension defined as BP >160/90 mmHg)
- Fasting blood tests including:
    - Lipid profile (Total cholesterol, LDL, HDL, triglycerides)
    - Fasting plasma glucose (mg/dL)
    - Fasting insulin (uIU/mL)

Insulin Resistance Calculation

HOMA-IR was calculated using the following formula: HOMA – IR = Fasting Insulin (uIU/mL) x Fasting Glucose (mg/dL)/405. A HOMA-IR >2.0 was used to define insulin resistance.

Statistical Analysis

Data analysis was conducted using SPSS (Statistical Package for Social Sciences) version 25.0. Continuous variables (age, BMI, fasting glucose, fasting insulin, HOMA-IR) were presented as mean ± standard deviation (SD). Categorical variables (gender, hypertension, dyslipidemia, fatty liver grade, insulin resistance status) were presented as frequencies and percentages. Associations between insulin resistance and demographic/clinical parameters were analyzed using Chi-square tests for categorical data and independent t-tests for continuous data. Logistic regression analysis was performed to determine predictors of insulin resistance, with a p-value <0.05 considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

A total of 112 non-diabetic patients diagnosed with NAFLD were included in the study. The mean age of the patients was 39.6 ± 11.7 years. The gender distribution was 54.5% male and 45.5% female. The mean BMI was 27.6 ± 4.6 kg/m^2. Among the patients, 44.6% had hypertension, while 45.5% had dyslipidemia. Based on ultrasound findings, 62.5% had Grade 1 NAFLD, while 37.5% had Grade 2 NAFLD. Table 1 presents the detailed demographic and clinical characteristics of the study population.

Table 1: Demographic and Clinical Characteristics.

Variable	Mean/Percentage
Age (years)	39.6 ± 11.7
Male (%)	54.5%
Female (%)	45.5%
BMI (kg/m^2)	27.6 ± 4.6
Hypertension (%)	44.6%
Dyslipidemia (%)	45.5%
NAFLD Grade 1 (%)	62.5%
NAFLD Grade 2 (%)	37.5%

Prevalence of Insulin Resistance

The overall prevalence of insulin resistance (HOMA-IR >2.0) was 72.3%, indicating a high burden of metabolic dysfunction in non-diabetic NAFLD patients.

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Predictors of Insulin Resistance

Logistic Regression Analysis

A multivariate logistic regression analysis was conducted to assess the independent predictors of insulin resistance. The results indicated that age was significantly associated with insulin resistance (p = 0.026, OR = 1.47, 95% CI: 1.05-2.02), meaning each additional year increased the odds of insulin resistance by 47%. BMI was a significant predictor (p = 0.017, OR = 2.39, 95% CI: 1.20-4.78), showing that overweight/obese patients had 2.39 times higher odds of developing insulin resistance. Hypertension showed the strongest association (p = 0.012, OR = 11.78, 95% CI: 2.58-20.97), indicating that hypertensive individuals had nearly 12 times higher risk of insulin resistance. Table 2 presents the detailed logistic regression analysis results.

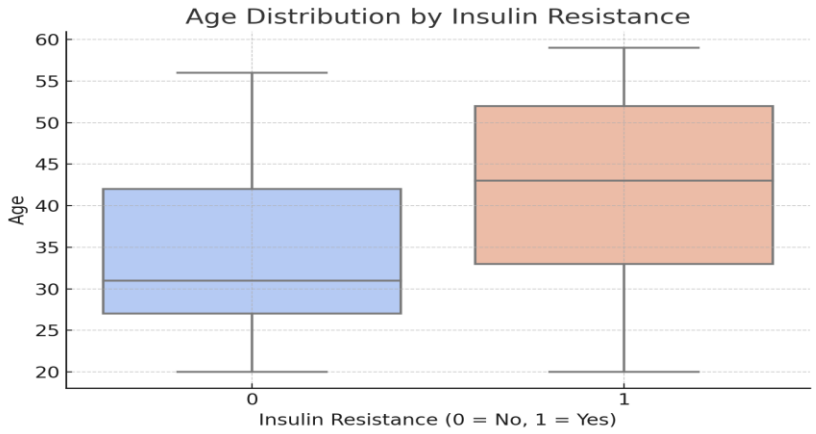
Table 2: Logistic Regression Analysis Results

Coef.	Std.Err.	z	P>|z|	[0.025	0.975]
62.558679527715171	24.883807129124744	2.5140316834595073	0.011935971025247766	111.33004529900407	13.787313756389636
0.3842614679654095	0.1729377064497529	2.2219646360179803	0.026285695615733382	0.045309791754933604	0.7232131441758853
0.9733460634168526	1.4296942001231747	0.6808071707453205	0.4959935121326855	1.8288030777303703	3.7754952045640753
1.1319107575283796	0.4756419488093486	2.3797538471151185	0.017324206186775368	0.19966966832561217	2.0641518467311147
11.781316016604412	4.691430037938784	2.511241971281879	0.012030720108126808	2.586282106255016	20.976349926995381
32.153783363400164	4139.322169150682	0.00776788615368855	0.9938021858973678	8080.768588580149	8145.076155306953
10.556262784767416	4.152706089346765	2.5420202050533156	0.011021380211539186	2.4171084112675842	18.695417158267247

Age and Insulin Resistance

Patients aged ≥40 years had a significantly higher likelihood of insulin resistance compared to younger patients. This finding aligns with previous research indicating that aging leads to metabolic dysfunction, including increased insulin resistance due to decreased insulin sensitivity, higher fat accumulation, and hormonal changes. Figure 1 presents the distribution of age and insulin resistance.

Figure 1: Age Distribution by Insulin Resistance.



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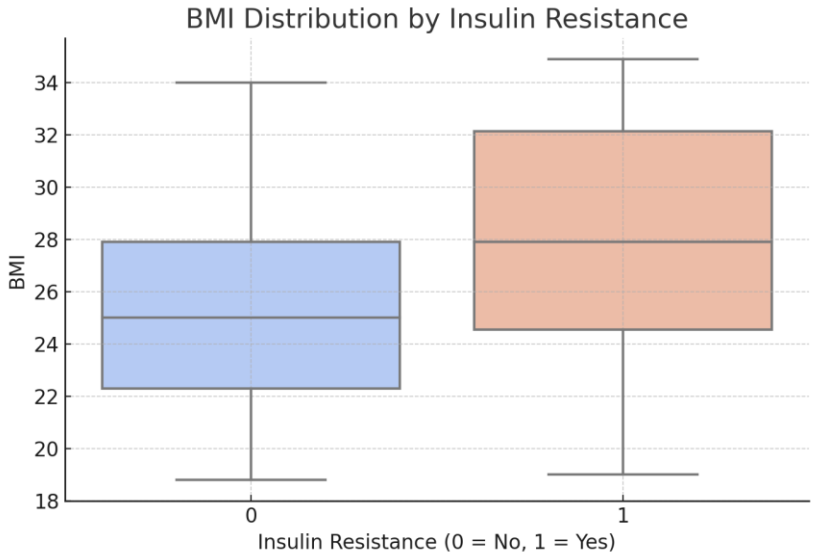
BMI and Insulin Resistance

Patients with higher BMI were at significantly increased risk of insulin resistance. The 2.39 times increased odds indicate a strong relationship between obesity and insulin resistance. Excess adiposity, particularly visceral fat, has been shown to contribute to insulin resistance through increased inflammation and altered adipokine secretion. Figure 2 illustrates the BMI distribution among insulin-resistant and non-insulin-resistant patients.

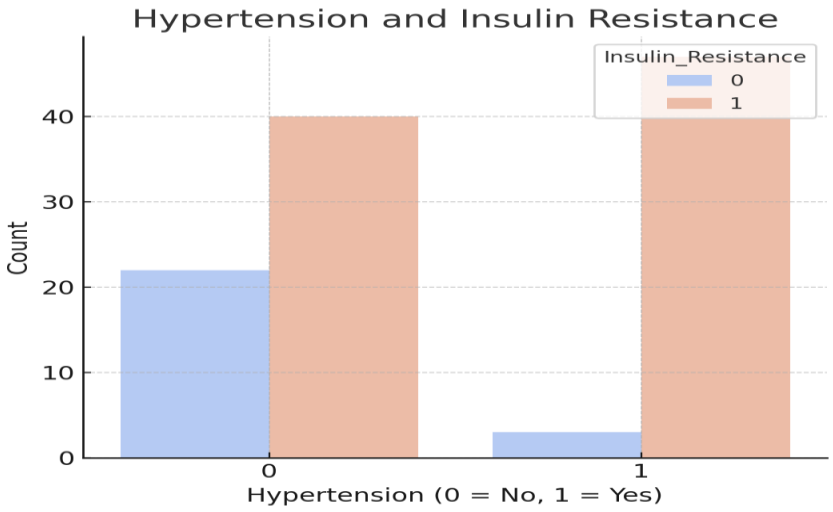
Figure 2: BMI Distribution by Insulin Resistance.



Hypertension and Insulin Resistance

Hypertension emerged as the strongest predictor, with nearly 12-fold increased odds of insulin resistance. This highlights the metabolic interplay between blood pressure dysregulation and insulin resistance, possibly mediated through endothelial dysfunction, inflammation, and renin-angiotensin system activation. Figure 3 shows the relationship between hypertension and insulin resistance.

Figure 3: Hypertension and Insulin Resistance.



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Non-Significant Factors

Gender did not show a statistically significant association with insulin resistance (p = 0.49), although a slightly higher proportion of males had insulin resistance. Dyslipidemia was also not a significant predictor (p = 1.00), suggesting that other metabolic pathways might mediate insulin resistance more strongly in NAFLD. Figure 4 illustrates the distribution of dyslipidemia and insulin resistance, while Figure 5 presents the distribution of NAFLD grade and insulin resistance.

Figure 4: Dyslipidemia and Insulin Resistance

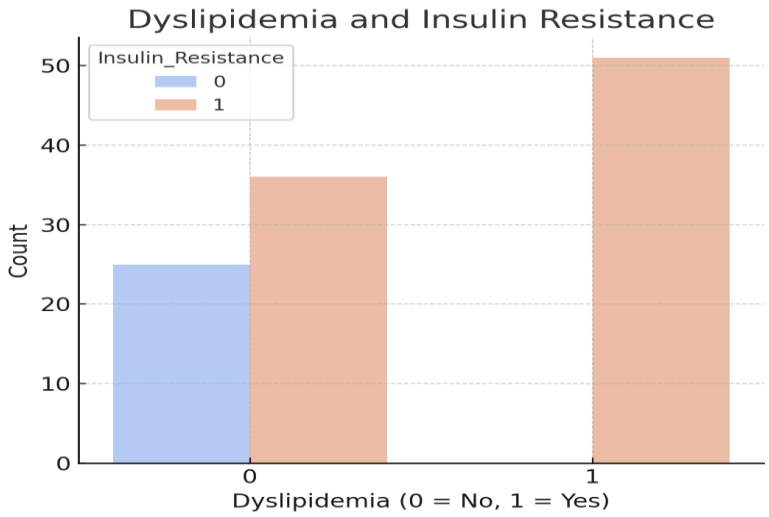
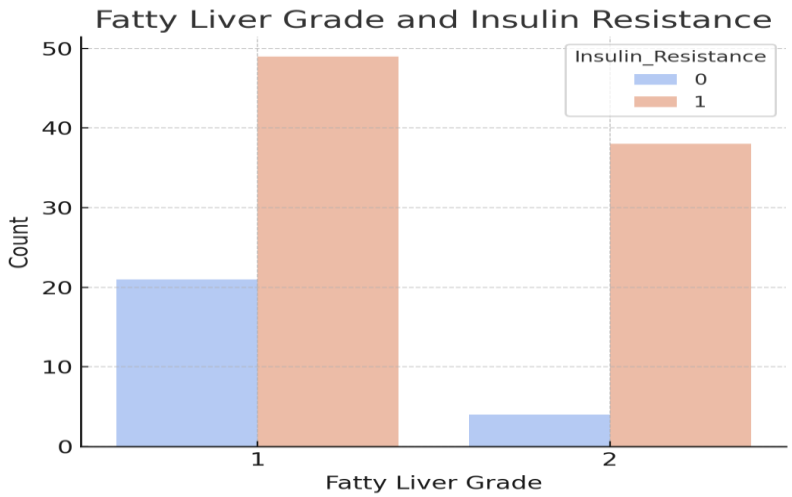


Figure 5: Fatty Liver Grade and Insulin Resistance



DISCUSSION

Our study confirms that insulin resistance is highly prevalent among non-diabetic NAFLD patients in Pakistan, aligning with global data. Among the 112 non-diabetic NAFLD patients studied, 72.3% exhibited insulin resistance (HOMA-IR >2.0), reinforcing the concept that NAFLD is closely tied to metabolic dysfunction, even in the absence of diabetes. This figure is comparable to international studies, which report insulin resistance prevalence between 60–80% in non-diabetic NAFLD patients [13]. Previous studies have described NAFLD as the "hepatic manifestation" of insulin resistance, and our findings further support this association. A South Asian meta-analysis found that NAFLD patients had significantly higher HOMA-IR levels

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than healthy controls, with a pooled difference of 1.3 units, consistent with our data [3]. Similarly, an Asian cohort study found that 60% of non-diabetic NAFLD patients had insulin resistance, aligning with our 72.3% prevalence estimate [14]. In practical terms, our study suggests that many non-diabetic NAFLD patients are in a prediabetic state, with insulin resistance present even if blood glucose levels remain within normal limits. This reinforces the need for early metabolic screening in NAFLD patients, particularly in regions with a rising burden of obesity and metabolic syndrome, such as Pakistan.

When compared to global trends, our findings highlight both similarities and unique characteristics of NAFLD and insulin resistance in Pakistan. Internationally, NAFLD affects 25–30% of adults, while in Pakistan, the estimated prevalence is 15–20% [1,2]. Although slightly lower, this may be due to demographic factors such as a younger population and historically lower obesity rates in rural areas. However, urbanization and lifestyle changes are rapidly increasing NAFLD prevalence, making it an emerging public health concern.

The mean age of our study population was 39.6 years, with 54.5% male and 45.5% female. A gender distribution consistent with global data, where males tend to have a higher NAFLD burden. Nearly 45.5% had dyslipidemia, and 44.6% had hypertension, reinforcing the strong association between NAFLD, hypertension, and lipid abnormalities observed worldwide. Our study found that BMI was a significant predictor of insulin resistance, with overweight/obese patients having 2.39 times higher odds of developing IR (p=0.017). This supports previous findings that higher BMI and visceral adiposity are key drivers of insulin resistance in NAFLD [10]. An analysis of South Asian NAFLD patients showed that obese individuals had significantly higher HOMA-IR levels than non-obese NAFLD patients [3], a trend that is evident in our results.

Additionally, our data confirm that age is a strong predictor of insulin resistance. Patients aged ≥40 years had a significantly higher likelihood of insulin resistance, with each additional year increasing the odds of IR by 47% (p=0.026). This aligns with global observations that aging is associated with declining insulin sensitivity, increased visceral fat accumulation, and hormonal changes that promote metabolic dysfunction [15]. A key finding in our study was that hypertension had the strongest association with IR, with hypertensive patients being nearly 12 times more likely to develop IR (p=0.012). This emphasizes the well-established metabolic interplay between hypertension and insulin resistance, likely mediated by endothelial dysfunction, inflammation, and the renin-angiotensin system [16].

Our logistic regression analysis identified age, BMI, and hypertension as significant predictors of insulin resistance. These findings highlight key intervention points. Older NAFLD patients (≥40 years) should be closely monitored for insulin resistance. Overweight/obese individuals need targeted weight management strategies to reduce insulin resistance. Hypertension is a critical red flag. blood pressure control should be an integral part of NAFLD management. Gender and dyslipidemia were not significant predictors of insulin resistance in our study, suggesting that other metabolic pathways may have a stronger influence in Pakistani NAFLD patients.

Recommendations

Physicians should routinely assess insulin resistance in non-diabetic NAFLD patients, particularly in those with hypertension, high BMI, and advancing age. Simple tests like fasting insulin, HOMA-IR, and HbA1c should be incorporated into NAFLD management protocols.

Our findings reinforce that obesity is a major driver of IR in NAFLD. Public health initiatives in Pakistan should promote weight loss programs focusing on dietary changes, increased physical activity, and behavioral modifications. Even a 7–10% weight reduction has been shown to significantly improve insulin sensitivity and liver health [17].

Given the multi-fold increased risk of insulin resistance in hypertensive patients, blood pressure management should be prioritized [18]. Lifestyle interventions (low-sodium diet, exercise) and antihypertensive therapy may help mitigate metabolic complications in NAFLD patients. While lifestyle modification remains the primary approach, insulin-sensitizing medications like pioglitazone and GLP-1 receptor agonists may be beneficial in select NAFLD patients with severe insulin resistance.

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Further research is needed to explore pharmacological strategies tailored to South Asian populations.

CONCLUSION

The primary objective of this study was to determine the prevalence of insulin resistance in non-diabetic NAFLD patients. Our findings highlight that insulin resistance is highly prevalent (72.3%) in this population, with age, BMI, and hypertension as key risk factors. These results reinforce the need for early detection and intervention strategies to prevent NAFLD progression and associated metabolic diseases. Given the increasing burden of obesity, hypertension, and type 2 diabetes in Pakistan, targeted lifestyle modifications and public health policies are essential to curb the rising trend of metabolic dysfunction. By identifying insulin resistance early in NAFLD patients, we can implement timely preventive strategies to reduce diabetes risk, improve liver health, and mitigate cardiovascular complications.

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