DOI: https://doi.org/10.53350/pjmhs020231711656

ORIGINAL ARTICLE

Physiology and Biochemistry of Liver Dysfunction in Non-Alcoholic Fatty Liver Disease

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ABSTRACT
Background: Non-alcoholic fatty liver disease (NAFLD) is a liver condition that is one of the most common chronic liver diseases and has strong associations with obesity, insulin resistance, dyslipidaemia and metabolic syndrome. It is caused by abnormal accumulation of fat in the liver and can lead to steatohepatitis, fibrosis, cirrhosis and liver-related complications. Physiological changes like high BMI and central obesity, and biochemical changes like liver enzymes and lipid metabolism abnormalities, have significant impact in the progression of NAFLD.
Objective: To assess the physiological and biochemical patterns of liver dysfunction among patients with non-alcoholic fatty liver disease.
Methods: The study was descriptive cross sectional study which was carried out from January 2022 to January 2023 at Mohammad College of Medicine, Peshawar. The number of patients who were diagnosed with NAFLD was 72 patients, which was obtained by non-probability consecutive sampling. Age, gender, BMI, waist circumference, DM, HTN, dyslipidemia, liver function tests, FBS, HbA1c, lipid profile and the grading of fatty liver using ultrasound were documented. Analysis of data was carried out using SPSS version 25. The data obtained were presented using descriptive statistics of quantitative variables mean and standard deviation while qualitative variables were presented using frequency and percentage. Association and correlation were evaluated by suitable statistical tests and a p-value of <0.05 was considered significant.
Results: The mean age of patients was 42.8 ± 10.6 years. Out of 72 patients, 41 (56.9%) were females and 31 (43.1%) were males. The mean BMI was 29.4 ± 4.1 kg/m², and obesity was present in 34 (47.2%) patients. Diabetes mellitus was found in 27 (37.5%), hypertension in 25 (34.7%), and dyslipidemia in 46 (63.9%) patients. Ultrasound grading showed Grade I fatty liver in 31 (43.1%), Grade II in 28 (38.9%), and Grade III in 13 (18.0%) patients. Mean ALT, AST, ALP, and GGT levels increased progressively with higher fatty liver grade. ALT increased from 49.2 ± 18.5 U/L in Grade I to 82.6 ± 25.7 U/L in Grade III, while GGT increased from 44.6 ± 19.8 U/L to 87.2 ± 28.6 U/L. BMI, waist circumference, triglycerides, and fasting blood glucose showed positive correlations with liver enzyme levels.
Conclusion: NAFLD was commonly associated with obesity, central adiposity, dyslipidemia, impaired glucose metabolism, and elevated liver enzymes. Higher ultrasound grades of fatty liver were linked with greater biochemical liver dysfunction. Early detection of metabolic risk factors, regular biochemical monitoring, weight control, and lifestyle modification are important to prevent disease progression.
Keywords: Non-alcoholic fatty liver disease, liver dysfunction, liver enzymes, obesity, dyslipidemia, insulin resistance, ultrasound grading.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a public health problem and is one of the common causes of chronic liver disease in the world. It is defined as an excessive amount of fat in the liver of people who consume less alcohol. Sometimes the disease can be latent for several years, and then slowly develop from the early stages of hepatic steatosis to non-alcoholic steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma[1, 2]. According to a global systematic review in 2022, the global prevalence of NAFLD was about 32.4%, indicating its growing prevalence among the different populations[3].

Non-alcoholic fatty liver disease (NAFLD) is a public health problem and is one of the common causes of chronic liver disease in the world[4]. An excessive amount of fat in the liver of individuals who drink less alcohol is defined. In some cases, the disease can proceed for several years without symptoms and then progress from its early phases (hepatic steatosis) to later stages (non-alcoholic steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma). According to a global systematic review in 2022, the global prevalence of NAFLD was about 32.4%, indicating its growing prevalence among the different populations[5].

In NAFLD, biochemical liver dysfunction is often associated with an elevation of the liver enzymes, such as ALT and AST. Some patients also have elevated gamma-glutamyl transferase and alkaline phosphatase, suggesting "oxidative stress" or "cholestasis" or more advanced metabolic damage. Aminotransferase levels, however, do not necessarily reflect the severity of liver damage as patients with moderate or severe steatosis or fibrosis also may have normal aminotransferase levels. Hence biochemical parameters should be taken together with clinical, metabolic and radiological parameters[6-8].

There is a strong association between metabolic abnormalities and NAFLD. Patients with higher BMI, central obesity, diabetes mellitus, hypertension, high triglycerides, elevated LDL and low HDL are more likely to develop fatty liver disease. There is also evidence in studies that the correlation between metabolic dysfunction and fatty liver is present, such that increased liver enzyme levels correlate with greater grades of fatty liver[9]. This confirms the NAFLD as being not only a liver disease but also a metabolic disease characterized by possible systemic physiologic and biochemical changes[10, 11].

Ultrasonography is a conventional method that is often performed to identify fatty infiltration of liver. It is widely available, inexpensive, and convenient to grade hepatic steatosis into mild, moderate and severe categories. Liver biopsy is the standard test for diagnosis of steatohepatitis and fibrosis and is invasive, but impractical for all patients. Thus, ultrasonography in combination with liver function tests, glucose profile, lipid profile, and anthropometric parameters, is a practical solution for the assessment of NAFLD in clinical as well as research settings[12].

In Pakistan, lifestyle changes, increasing obesity, sedentary habits, diabetes mellitus, and dyslipidemia are contributing to the

Received on 11-09-2023
Accepted on 06-11-2023

rising burden of fatty liver disease. Despite this, local data regarding the physiological and biochemical pattern of liver dysfunction in NAFLD remain limited. Understanding these patterns is important for early diagnosis, risk stratification, and prevention of disease progression. Therefore, the present study was conducted at Mohammad College of Medicine, Peshawar, to assess the physiological and biochemical profile of liver dysfunction among patients with non-alcoholic fatty liver disease.

METHODOLOGY

This study was conducted as a descriptive cross-sectional study to assess the physiological and biochemical patterns of liver dysfunction among patients with non-alcoholic fatty liver disease. The study was carried out at Mohammad College of Medicine, Peshawar. The study focused on evaluating liver enzyme abnormalities, metabolic disturbances, lipid profile changes, and ultrasound-based grading of fatty liver disease among diagnosed NAFLD patients.

The study was conducted for a period of one year (January, 2022 to January, 2023). Eligible patients at the appropriate clinical and diagnostic departments were recruited during this period, who met the selection criteria.

In total 72 patients with non-alcoholic fatty liver disease were included. The number of patients included was determined by the number of eligible patients that were available during the study period. A non-probability sampling method (consecutive sampling) was applied, in which all patients who fulfilled the inclusion criteria were included until the required sample size was reached.

Adults who were diagnosed with non-alcoholic fatty liver disease from clinical assessment, biochemical, and ultrasonographic testing were included in the study. Both male and female patients were included. The aim of the study was to compare association of the physiological factors, like obesity, central adiposity, blood pressure and metabolic status, with biochemical markers of liver dysfunction in NAFLD.

The study included patients 18 years or older with non-alcoholic fatty liver disease (NAFLD) confirmed by abdominal ultrasound. Liver function tests, fasting blood glucose, lipid profile, and anthropometric measurements were available for both men and women. Patients were enrolled only if there was sufficient clinical and laboratory information and they consented to participate in the study.

Alcohol abusers were not included in the study. Other exclusion criteria included patients with a history of chronic viral hepatitis, autoimmune liver disease, drug-induced liver injury, Wilson disease, hemochromatosis, chronic kidney disease, malignancy, pregnancy or hepatotoxic drugs. Patients for whom laboratory records or the ultrasound report were incomplete or the report was of poor quality were excluded from the final analysis.

A structured proforma specifically designed for the study was used for data collection. Demographic data, like age and gender, was collected. Clinical history included was taken of diabetes mellitus, hypertension, dyslipidaemia, fatigue, right upper abdominal discomfort, medication history and family history of liver disease. Standard anthropometric measurements were taken such as weight, height, body mass index, and waist circumference. BMI was computed as weight (kg) / height (m2). Patients were divided into three groups based on their BMI: normal weight, overweight, and obese.

Physiological parameters measured were BMI, waist circumference and blood pressure. Blood pressure was taken sitting after a period of rest. Central obesity was measured using waist circumference. These variables were incorporated due to the strong relationship between NAFLD and obesity, insulin resistance, hypertension and metabolic syndrome. Diabetes mellitus, hypertension, and dyslipidemia were obtained from clinical history, previous medical record, and laboratory results.

Blood samples were taken after 18-hours fasting (when necessary) under aseptic conditions. Serum ALT, AST, ALP, GGT, total bilirubin, direct bilirubin, serum albumin, total protein, and INR were measured as liver function tests. These parameters were used to evaluate hepatocellular injury, cholestatic changes, and synthetic function of the liver. Blood glucose level, HbA1c, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, and uric acid level in serum were considered as metabolic and lipid parameters. The tests were carried out in the institutional laboratory with conventional biochemical techniques.

Fatty liver disease was diagnosed and graded by abdominal ultrasonography. Fatty liver was defined as Grade I, Grade II, and Grade III based on liver echogenicity, visualization of intrahepatic vessels and posterior attenuation of the ultrasound beam. Grade I was considered mild fatty infiltration, Grade II was considered moderate fatty changes and Grade III was considered as severe fatty infiltration. The relationship between disease severity and biochemical dysfunction was then evaluated by the ultrasound grading and liver enzymes and metabolic variables.

The SPSS version 25 was used. Data on quantitative variables like age, BMI, liver enzymes, fasting blood glucose, HbA1c, and lipid profile were expressed as mean and standard deviation. Qualitative variables (gender, diabetes mellitus, hypertension, dyslipidaemia, body mass index category, fatty liver grade) were summarized as frequency and percentage. An association between categorical variables was made using the Chi-square test. The mean levels of liver enzymes were compared using one-way ANOVA among the grades of fatty liver. The relationship between BMI, waist circumference, lipid profile, blood glucose and liver enzymes were evaluated by Pearson or Spearman correlation. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Overall, 72 patients were enrolled in the study who had non-alcoholic fatty liver disease (NAFLD). The average age of the subjects was 42.8 ± 10.6 years, with a range of 24-65 years. Most patients were in the age group of 41–50 years. Out of 72 patients, 41 (56.9%) were females and 31 (43.1%) were males. The mean BMI was 29.4 ± 4.1 kg/m² indicating that the majority of patients were overweight or obese. Central obesity was found in 49 (68.1%) patients, suggesting central obesity was a common physiological feature of NAFLD patients.

As regards clinical and physiological features, diabetes mellitus was present in 27 (37.5%) patients while hypertension was present in 25 (34.7%) patients. Forty-six (63.9%) patients had dyslipidemia. Fatigue was the most frequent symptom and was reported by 39 (54.2%) patients followed by right upper abdominal discomfort in 24 (33.3%) patients.

Thirty-one patients (43.1%) were diagnosed as having Grade I fatty liver, 28 patients (38.9%) as having Grade II fatty liver, and 13 patients (18.0%) as having Grade III fatty liver according to ultrasonographic grading. This demonstrated a predominately mild to moderate degree of fatty infiltration of the liver in most patients.

Biochemical analysis showed raised liver enzymes in a considerable number of patients. The mean ALT level was 61.4 ± 24.8 U/L, while the mean AST level was 48.7 ± 20.3 U/L. The mean serum alkaline phosphatase (ALP) level was 132.6 ± 39.5 U/L and serum gamma-glutamyl transferase (GGT) level was 58.9 ± 26.4 U/L, mostly in the normal range. Serum bilirubin level was 0.91 ± 0.32 mg/dL (normal range 0.2–1.0 mg/dL). In most patients, serum albumin is preserved (4.01 ± 0.47 g/dL) which indicates preserved synthetic liver function.

Many of the patients had disturbed glucose and lipid parameters by metabolic biochemical assessment. The mean fasting blood glucose was 119.3 ± 31.6 mg/dL, while the mean HbA1c was 6.2 ± 1.1%. The mean triglyceride level was 198.5 ± 62.4 mg/dL, total cholesterol was 207.8 ± 43.7 mg/dL, LDL cholesterol was 128.6 ± 34.2 mg/dL, and HDL cholesterol was 39.7 ± 8.6 mg/dL. From these findings, it appeared that metabolic disturbance was common in patients with NAFLD.

The mean ALT, AST and GGT were significantly higher for each ultrasound grade of fatty liver. Patients with Grade III fatty liver had the highest mean ALT level 82.6 ± 25.7 U/L, compared with 49.2 ± 18.5 U/L in Grade I and 65.7 ± 21.4 U/L in Grade II. This difference was significantly different at $p < 0.001$. AST and GGT levels were also seen to be different significantly for each grade.

Table 1: Demographic and Anthropometric Characteristics of NAFLD Patients

Variable	Frequency / Mean ± SD
Total patients	72
Age, years	42.8 ± 10.6
Male	31 (43.1%)
Female	41 (56.9%)
BMI, kg/m²	29.4 ± 4.1
Normal BMI	9 (12.5%)
Overweight	29 (40.3%)
Obese	34 (47.2%)
Increased waist circumference	49 (68.1%)
Normal waist circumference	23 (31.9%)

Table 2: Clinical and Physiological Characteristics of Patients

Variable	Frequency (%)
Diabetes mellitus	27 (37.5%)
Hypertension	25 (34.7%)
Dyslipidemia	46 (63.9%)
Fatigue	39 (54.2%)
Right upper abdominal discomfort	24 (33.3%)
Asymptomatic patients	18 (25.0%)

Table 3: Distribution of NAFLD Severity on Ultrasound

Fatty Liver Grade	Frequency (%)
Grade I	31 (43.1%)
Grade II	28 (38.9%)
Grade III	13 (18.0%)
Total	72 (100%)

Table 4: Liver Function Test Profile of NAFLD Patients

Biochemical Parameter	Mean ± SD
ALT, U/L	61.4 ± 24.8
AST, U/L	48.7 ± 20.3
ALP, U/L	132.6 ± 39.5
GGT, U/L	58.9 ± 26.4
Total bilirubin, mg/dL	0.91 ± 0.32
Direct bilirubin, mg/dL	0.29 ± 0.14
Serum albumin, g/dL	4.01 ± 0.47
Total protein, g/dL	6.89 ± 0.62
INR	1.06 ± 0.12

Table 5: Metabolic and Lipid Profile of NAFLD Patients

Parameter	Mean ± SD
Fasting blood glucose, mg/dL	119.3 ± 31.6
HbA1c, %	6.2 ± 1.1
Total cholesterol, mg/dL	207.8 ± 43.7
Triglycerides, mg/dL	198.5 ± 62.4
LDL cholesterol, mg/dL	128.6 ± 34.2
HDL cholesterol, mg/dL	39.7 ± 8.6
Serum uric acid, mg/dL	6.4 ± 1.3

Table 6: Association of Fatty Liver Grade with Liver Enzymes

Liver Enzyme	Grade I Mean ± SD	Grade II Mean ± SD	Grade III Mean ± SD	p-value
ALT, U/L	49.2 ± 18.5	65.7 ± 21.4	82.6 ± 25.7	<0.001
AST, U/L	39.8 ± 14.6	51.3 ± 18.9	65.4 ± 22.1	<0.001
ALP, U/L	121.5 ± 31.7	136.8 ± 37.9	151.9 ± 45.2	0.021
GGT, U/L	44.6 ± 19.8	61.3 ± 23.5	87.2 ± 28.6	<0.001

Table 7: Association Between BMI Category and Fatty Liver Grade

BMI Category	Grade I n (%)	Grade II n (%)	Grade III n (%)	p-value
Normal BMI	7 (22.6%)	2 (7.1%)	0 (0.0%)	
Overweight	16 (51.6%)	9 (32.1%)	4 (30.8%)	
Obese	8 (25.8%)	17 (60.7%)	9 (69.2%)	0.004

Table 8: Correlation of Metabolic Variables with Liver Dysfunction

Variable	Correlation with ALT	p-value	Correlation with AST	p-value
BMI	r = 0.42	<0.001	r = 0.36	0.002
Waist circumference	r = 0.38	0.001	r = 0.33	0.005
Triglycerides	r = 0.39	0.001	r = 0.34	0.004
Fasting blood glucose	r = 0.29	0.014	r = 0.27	0.021
HDL cholesterol	r = -0.28	0.017	r = -0.25	0.033

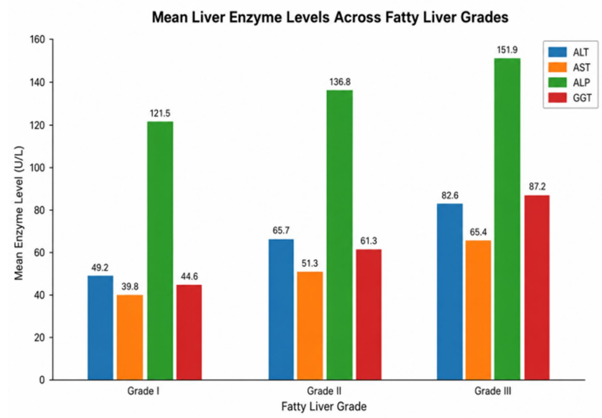

Figure 1. Mean liver enzyme levels across fatty liver grades in NAFLD patients.

BMI was also strongly correlated with the severity of fatty liver. 8 (25.8%) patients had Grade I fatty liver, 17 (60.7%) with Grade II fatty liver and 9 (69.2%) with Grade III fatty liver. The statistical significance of the association of BMI category with ultrasound grade was $p = 0.004$.

The correlation analysis revealed a positive correlation between BMI and ALT ($r = 0.42$, $p < 0.001$). Triglycerides also showed a significant positive correlation with ALT ($r = 0.39$, $p = 0.001$) and AST ($r = 0.34$, $p = 0.004$). There was an inverse relationship between HDL cholesterol and severity of fatty liver ($r = -0.31$, $p = 0.008$). These results indicate that biochemical liver dysfunction increased with deteriorating metabolic profile.

In general, NAFLD was found to be frequently associated with obesity, central adiposity, dyslipidaemia, abnormal glucose metabolism and increased liver enzymes. Higher BMI, triglycerides, lower HDL, and higher ALT, AST, and GGT were associated with more severe fatty liver. These findings suggest that, besides the physiological changes, biochemical changes are also involved in liver dysfunction in NAFLD.

DISCUSSION

The present study evaluated the physiological and biochemical pattern of liver dysfunction among 72 patients with non-alcoholic fatty liver disease (NAFLD). The findings showed that NAFLD was strongly associated with increased body mass index, central obesity, dyslipidemia, impaired glucose metabolism, and raised liver enzymes. Most patients were either overweight or obese, and a considerable proportion had diabetes mellitus, hypertension, and dyslipidemia. These findings support the concept that NAFLD is not only a liver disorder but also a metabolic disease closely related to insulin resistance, adiposity, and abnormal lipid metabolism. Recent literature also explains NAFLD as a multisystem metabolic condition in which hepatic fat accumulation is linked with obesity, insulin resistance, inflammation, and oxidative stress[13-15].

In this study, ultrasound grading revealed that the majority of patients had fatty liver Grade I or Grade II - fatty liver Grade III was less common. Biochemical derangements were, however, more severe in patients with higher ultrasound grades, particularly with higher mean ALT, AST, ALP and GGT. This suggests that the progressive fatty infiltration of liver is related to the rise of the hepatocellular injury and cholestatic enzyme disturbance. This has also been shown in more recent studies, which correlated the severity of fatty liver determined by ultrasound with biochemical and metabolic disturbances. Non-invasive assessment is also relevant in NAFLD as liver biopsy is not the first line of investigation or of follow-up, and ultrasound and biochemical markers are often used to diagnose and monitor the condition[16, 17].

The present study showed elevated ALT and AST levels, indicative of hepatocellular stress and damage. In most patients ALT was elevated more than AST, which is typical of early NAFLD. As fatty liver grade increased, ALT and AST also increased significantly, suggesting that the severity of hepatic steatosis could be a risk of liver cell damage. Further, GGT levels rose with the severity of the disease, indicative of oxidative stress and potential cholestasis. Studies have already established high levels of ALT, AST, triglycerides and fasting blood sugar as risk factors associated with NAFLD and the progression of the disease, as well as the low levels of HDL cholesterol[18, 19].

The metabolic profile of patients in this study for triglycerides was high, total cholesterol was raised, HDL cholesterol was raised, fasting blood glucose was increased and LDL cholesterol was raised. The changes indicate that lipid imbalance and glucose metabolism impairment are key biochemical abnormalities in the pathogenesis of NAFLD. Insulin resistance stimulates lipolysis in fat cells, leads to excess delivery of free fatty acids to the liver, promotes hepatic TG accumulation, and activates inflammation. This can result in oxidative stress, mitochondrial dysfunction and development of simple steatosis to steatohepatitis. In recent reviews, insulin resistance was highlighted as an important mechanism that underlies the connection between NAFLD and metabolic syndrome and liver injury[20].

In the present study, the correlation analysis revealed that BMI, waist circumference, triglycerides, and fasting blood glucose were positively correlated with the levels of ALT and AST, and HDL cholesterol was negatively correlated with them. This association translates to increased liver enzyme elevation and worsening obesity and metabolic disturbance. These results are in line with the data reported that NAFLD is highly correlated with obesity, metabolic syndrome, dyslipidemia and defective insulin signaling. Also, lifestyle and dietary interventions have been observed to improve anthropometric, biochemical and radiological parameters in NAFLD, further confirming the metabolic basis of this disease[16, 17].

The key points of the study are that it considered both physiological and biochemical parameters of NAFLD, such as BMI, waist circumference, liver enzymes, glucose profile, lipid profile and ultrasound grading. But there were some limitations in the study. This study was conducted in only one center and the patient population was small, and liver biopsy was not performed to diagnose steatohepatitis or fibrosis. Not included were advanced non-invasive fibrosis assessments like FibroScan, FIB-4 or NAFLD fibrosis score. In conclusion, larger, multicenter, and fibrosis assessment studies are recommended to better identify the predictive factors for progressive liver dysfunction in NAFLD.

CONCLUSION

This study concluded that non-alcoholic fatty liver disease is closely associated with physiological and biochemical disturbances, particularly obesity, central adiposity, dyslipidemia, impaired glucose metabolism, and raised liver enzymes. Higher grades of fatty liver on ultrasound were associated with significantly increased ALT, AST, ALP, and GGT levels, indicating greater biochemical liver dysfunction with increasing disease severity. BMI, waist circumference, triglycerides, and fasting blood glucose showed positive correlations with liver enzyme elevation, while HDL cholesterol showed a negative relationship. These findings suggest that early identification of metabolic risk factors, regular biochemical monitoring, weight reduction, and lifestyle modification are important for preventing progression of NAFLD and its related liver complications.

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This article may be cited as: Ali S., Zahid M., Zaidi A., Salman F., Haroon M., Khan A. M. K., Physiology and Biochemistry of Liver Dysfunction in Non-Alcoholic Fatty Liver Disease. Pak J Med Health Sci, 2023;17(11):656-659.