Section: Medicine

Original Research Article

A PROSPECTIVE STUDY OF NAFLD IN DIABETES

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Received : 11/05/2025
Received in revised form : 04/07/2025
Accepted : 26/07/2025

Keywords:
Nafld, ald, sgot, sgpt, prothrombin time, fib4 score ?.

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DOI: 10.47009/jamp.2025.7.4.136

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2025; 7 (4); 727-734

ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) has emerged as a significant global health concern, with an estimated global prevalence of around 25% of the adult population, reflecting an alarming rise in metabolic disorders worldwide. This condition is particularly prevalent in individuals suffering from obesity and type 2 diabetes mellitus (T2DM), where the prevalence can surge up to 70%. hence our study focussed on the association of NAFLD and Diabetes. **Materials and Methods:** The present prospective observational study was done in tertiary care hospital from Feb 2023 to Feb 2024.A total of 40 patients were collected and all routine investigations done. patients having fatty liver incidental finding on ultrasound were subjected to further tests like liver function tests, lipid profile, questioned about history and duration of diabetes, FIB4 score calculated and risk of mortality assessed. **Result:** in our study out of 40 patients 23 were male and 17 were female. out of 40, 20 were diabetic and 20 were non diabetic.it was observed that patients with longer duration of diabetes were affected more 14 with dm duration>5yrs,4patients with dm duration <5yrs, denovo were 2. In non alcoholics we had 8 patients with fatty liver as incidental finding on ultrasound.in non alcoholics we had 10 patients with increased LDL,9 patients with increased TGL, and 8 patients with decreased HDL. out of these 15 were diabetic. we had 2 patients with FIB4 score greater than 1.45.rest of them had FIB4 score less than 1.45. **Conclusion:** we conclude that there is male preponderance. that duration of diabetes influenced the process of nafld.it was also observed that dyslipidemia played significant role in diabetics in progression for nafld.

INTRODUCTION

1. The Rising Prevalence of NAFLD

Non-alcoholic fatty liver disease (NAFLD) has emerged as a significant global health concern, with an estimated global prevalence of around 25% of the adult population, reflecting an alarming rise in metabolic disorders worldwide,[1,2]

This condition is particularly prevalent in individuals suffering from obesity and type 2 diabetes mellitus (T2DM), where the prevalence can surge up to 70%.[3,4]

As a consequence of the obesity epidemic, the number of individuals affected by NAFLD is rapidly increasing, mirroring the rising rates of metabolic syndrome, which encompasses key risk factors such as dyslipidemia, hypertension, and insulin resistance.[5,6]

The co-occurrence of these conditions not only exacerbates the burden of NAFLD but also complicates its management and treatment.[7]

2. Pathophysiology of NAFLD

NAFLD results from complex metabolic disturbances that lead to the excessive accumulation of lipids within hepatocytes. The disease is initially characterized by simple hepatic steatosis, but with the progression to non-alcoholic steatohepatitis (NASH), fibrosis, and potentially cirrhosis, the condition becomes more dangerous.[8]

The classic "two-hit hypothesis" originally proposed to explain the pathophysiology of NAFLD has since been expanded into a "multi-hit hypothesis" that incorporates a variety of cellular mechanisms contributing to liver injury.[9,10]

Central to this process are factors like insulin resistance, lipotoxicity, oxidative stress, and inflammation, which not only affect the liver but also have systemic implications.[11,12]

More recent studies have highlighted the contribution of mitochondrial dysfunction and altered gut microbiota, which may further drive the pathogenesis of NAFLD, linking it to broader metabolic disturbances.[13,14]

3. Clinical and Biochemical Indicators of NAFLD

The clinical manifestations of NAFLD often go unnoticed, as many patients are asymptomatic, especially in the early stages. Central obesity, particularly as assessed by waist circumference, remains one of the strongest clinical indicators of NAFLD.[15]

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Furthermore, obesity, defined by body mass index (BMI), is an important factor influencing the development of both NAFLD and its progression to more severe forms such as NASH and fibrosis.[16]

In addition to obesity, patients with NAFLD frequently exhibit dyslipidemia, characterized by elevated low-density lipoprotein (LDL) cholesterol and triglycerides, alongside reduced high-density lipoprotein (HDL) levels.[17]

Liver fibrosis, assessed through non-invasive markers like the Fib-4 index, has become a key predictor of disease progression and long-term outcomes.[18]

The severity of liver fibrosis is an important determinant of the risk of cirrhosis, liver failure, and hepatocellular carcinoma.[19,20]

4. NAFLD as a Multisystem Disease

NAFLD is increasingly recognized not only as a liver disease but as a multisystem disorder with far-reaching implications for cardiovascular and renal health.[21]

Studies have shown that individuals with NAFLD are at a significantly higher risk of cardiovascular diseases (CVD), including myocardial infarction, independent of traditional cardiovascular risk factors.[22,23]

The association between NAFLD and chronic kidney disease (CKD) is also well-established, with evidence suggesting that liver dysfunction contributes to renal damage through mechanisms like systemic inflammation and altered lipid metabolism.[24,25]

Additionally, NAFLD is tightly interlinked with insulin resistance, creating a feedback loop that exacerbates both liver and systemic metabolic dysfunction.[26] This interrelationship underscores the need for a holistic approach to managing NAFLD, one that addresses not only liver health but also broader metabolic risks.

5. The Importance of Lipid Profiles in NAFLD

Lipid metabolism plays a central role in the pathogenesis of NAFLD, particularly the accumulation of triglycerides in the liver.[27]

Elevated triglycerides and LDL cholesterol levels are closely linked to worse liver outcomes, including the progression from simple fatty liver to more severe stages like NASH and cirrhosis.[28,29]

On the other hand, HDL cholesterol, often referred to as "good cholesterol," has protective effects against both cardiovascular and liver diseases. In patients with NAFLD, reduced HDL levels are commonly observed and are associated with more advanced liver fibrosis.[30]

Understanding the interplay between lipid metabolism and liver health is crucial, as targeting lipid abnormalities through lifestyle changes or pharmacotherapy may offer a potential therapeutic strategy to slow the progression of NAFLD.[31,32]

6. Challenges in NAFLD Diagnosis and Risk Stratification

Despite the increasing recognition of NAFLD as a major health concern, its diagnosis and management remain challenging due to the disease's heterogeneity and the lack of specific symptoms in the early stages.[33] Non-invasive markers, such as the Fib-4 index and imaging techniques like transient elastography (FibroScan), have become valuable tools for assessing liver fibrosis and stratifying risk.[34]

However, their accuracy can vary, particularly in patients with conditions like obesity or diabetes, which may confound the results.[35]

Furthermore, distinguishing between alcoholic and non-alcoholic fatty liver disease can be difficult, as the clinical and biochemical overlap between these conditions is substantial.[36]

Given these complexities, a thorough clinical evaluation, including patient history and biomarker assessment, is essential for accurate diagnosis and appropriate management.

7. The Role of Genetics and Epigenetics in NAFLD

Recent research has emphasized the role of genetic and epigenetic factors in the susceptibility to NAFLD. Several genetic polymorphisms, particularly in genes related to lipid metabolism and insulin sensitivity, have been identified as key determinants of NAFLD risk. Notably, variants in the PNPLA3 (patatin-like phospholipase domain-containing protein 3) gene have been strongly associated with the development of NAFLD, with some studies indicating that individuals with certain PNPLA3 genotypes are more likely to develop steatosis and progression to more severe forms such as NASH.[37,38] In addition, genetic factors influencing inflammation and fibrosis, such as variations in the MMP-9 (matrix metalloproteinase 9) gene, are implicated in the progression of liver damage.[39] The emerging field of epigenetics also sheds light on how environmental factors, such as diet and physical activity, interact with genetic predisposition to influence the risk and progression of NAFLD. Epigenetic modifications, including DNA methylation and histone modifications, can affect gene expression and may contribute to the pathogenesis of liver diseases by regulating inflammatory pathways and lipid metabolism.[40]

8. Metabolic Alterations in NAFLD

NAFLD is closely associated with a range of metabolic alterations that drive its pathogenesis and progression. Insulin resistance (IR) is considered a primary contributor to the development of both hepatic steatosis and systemic metabolic dysfunction. In individuals with insulin resistance, there is an increased influx of free fatty acids (FFAs) to the liver, leading to excessive lipid accumulation. Insulin resistance also disrupts normal hepatic glucose metabolism, resulting in hyperglycemia and exacerbating the overall metabolic burden.[41]

The liver's inability to properly metabolize FFAs results in lipotoxicity, which contributes to cellular injury, inflammation, and oxidative stress.[42] Additionally, alterations in adipose tissue function, such as increased secretion of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and adipokines (e.g.,

ISSN (O): 2687-5365; ISSN (P): 2753-6556

leptin, adiponectin), play an essential role in the systemic inflammation observed in NAFLD.[43]

9. The Gut-Liver Axis and NAFLD

Increasing evidence suggests that the gut microbiota plays a significant role in the development and progression of NAFLD. The "gut-liver axis" refers to the bidirectional communication between the gastrointestinal tract and the liver, which is mediated by various pathways, including the portal circulation and the immune system. Alterations in the gut microbiota composition (dysbiosis) have been linked to insulin resistance, inflammation, and hepatic fat accumulation, all of which are central features of NAFLD. Studies have shown that individuals with NAFLD have distinct gut microbiota profiles compared to healthy controls, with an increase in gut permeability that allows microbial products such as lipopolysaccharides (LPS) to translocate to the liver and trigger inflammation.[44,45] This chronic low-grade inflammation, in turn, exacerbates liver injury and contributes to the progression from simple steatosis to NASH and fibrosis. Probiotic and prebiotic interventions are being explored as potential therapeutic strategies to modulate the gut microbiota and improve liver health.[46]

10. Advances in NAFLD Diagnosis and Monitoring

The diagnosis of NAFLD traditionally relies on imaging techniques, such as ultrasound, CT scans, and MRI, which can assess the presence of hepatic steatosis. However, these modalities have limited ability to assess liver fibrosis, which is critical for determining the prognosis and need for intervention. Non-invasive biomarkers, such as the Fib-4 index, the AST-to-Platelet Ratio Index (APRI), and the NAFLD fibrosis score, have been developed to help assess liver fibrosis and stratify risk.[47,48] In addition, elastography techniques like FibroScan have gained popularity for quantifying liver stiffness, which is closely associated with the degree of fibrosis.[49] Despite these advances, the diagnostic challenge remains, as non-invasive methods may not always accurately detect advanced fibrosis, particularly in patients with obesity or diabetes.[50] As a result, liver biopsy remains the gold standard for diagnosing advanced stages of NAFLD, though its invasive nature limits its use in routine clinical practice.[51]

11. Management of NAFLD

Currently, there is no FDA-approved medication for the treatment of NAFLD, and management primarily focuses on lifestyle interventions, particularly weight loss through diet and physical activity. Weight reduction of 5-10% has been shown to improve liver histology, including reductions in hepatic steatosis and inflammation, and may prevent the progression to advanced fibrosis.[52,53] Pharmacologic interventions targeting insulin resistance, such as pioglitazone, and lipid-lowering agents, such as statins, have shown some efficacy in improving liver function and metabolic parameters.[54,54] The role of vitamin E as an antioxidant has been explored in patients with NASH, demonstrating potential benefits in reducing liver inflammation and fibrosis, particularly in non-diabetic individuals.[55,56] However, the search for effective pharmacological treatments for NAFLD continues, with promising candidates, such as FXR agonists and GLP-1 receptor agonists, currently under investigation.[57]

12. The Global Burden of NAFLD and Public Health Implications

The increasing prevalence of NAFLD has significant public health implications, especially as it is a major risk factor for cirrhosis, hepatocellular carcinoma (HCC), and cardiovascular diseases, which collectively place a substantial economic burden on healthcare systems worldwide.[58] In addition, the rising incidence of NAFLD in children and adolescents, driven by the obesity epidemic, presents a challenge for long-term management and prevention efforts.[59] Public health strategies aimed at preventing and managing NAFLD must include initiatives to reduce obesity and improve diet and physical activity patterns at the population level. Early identification and management of individuals at risk for NAFLD through routine screening for metabolic risk factors and liver abnormalities could help reduce the burden of liver-related morbidity and mortality.[60] The global nature of NAFLD highlights the need for international collaborations to understand its epidemiology and develop effective prevention and treatment strategies.

13. Study Rationale

The growing prevalence of non-alcoholic fatty liver disease (NAFLD) and its progression to more severe conditions such as non-alcoholic steatohepatitis (NASH) and liver fibrosis underscore the need for deeper insights into the factors driving these processes. While NAFLD is strongly associated with metabolic syndrome, obesity, and dyslipidemia, the specific contributions of individual lipid abnormalities and body mass index (BMI) to liver fibrosis progression remain insufficiently understood.

1. Linking Dyslipidemia to Liver Fibrosis

Dyslipidemia, a hallmark of metabolic syndrome, is characterized by elevated levels of triglycerides and low-density lipoprotein (LDL) cholesterol and decreased high-density lipoprotein (HDL) cholesterol.[61,62] These lipid abnormalities not only serve as systemic risk factors for cardiovascular disease but also contribute to hepatic steatosis and inflammation:

Elevated triglycerides promote hepatic fat accumulation, triggering lipotoxicity and oxidative stress.[63]

LDL cholesterol exacerbates inflammation and fibrosis by activating Kupffer cells and other immune pathways.[64,65]

Reduced HDL cholesterol diminishes the liver's protective mechanisms against oxidative stress and inflammation.[66]

Prior studies have established the role of lipid abnormalities in the development of hepatic steatosis.[67]

ISSN (O): 2687-5365; ISSN (P): 2753-6556

However, less is known about how specific lipid parameters influence the progression from simple steatosis to advanced fibrosis, particularly in the presence of other risk factors such as obesity and insulin resistance.[68] Understanding these pathways is critical for identifying patients at higher risk of fibrosis and developing targeted interventions.

2. Obesity and BMI as Predictors of NAFLD Severity

Obesity, as measured by BMI and central adiposity, is a major risk factor for both NAFLD onset and progression.[69,70]

Excess adipose tissue leads to increased free fatty acid (FFA) release into the circulation, promoting hepatic lipid accumulation.[71]

In addition: Central obesity, indicated by increased waist circumference, is particularly predictive of severe liver disease, as visceral fat secretes pro-inflammatory cytokines such as TNF-α and IL-6.[72]

The relationship between BMI and liver fibrosis is non-linear; higher BMI is associated with increased risk of advanced fibrosis, but some individuals with normal BMI also develop severe NAFLD due to other metabolic dysfunctions.[73]

Further research is needed to clarify the interplay between BMI, body composition (e.g., visceral vs. subcutaneous fat), and lipid metabolism in driving fibrosis.[74,75]

3. Role of Liver Fibrosis in Disease Progression

Liver fibrosis is a critical determinant of long-term outcomes in NAFLD, including the risk of cirrhosis, liver failure, and hepatocellular carcinoma.[76,77]

Studies suggest that fibrosis severity is the strongest predictor of mortality in NAFLD patients.[78,79]

However, fibrosis develops at varying rates across individuals, influenced by genetic, metabolic, and environmental factors:

Genetic variants, such as those in the PNPLA3 and TM6SF2 genes, may predispose certain individuals to faster fibrosis progression.[80,81]

Dysregulated lipid metabolism, insulin resistance, and systemic inflammation act as amplifiers of hepatic fibrogenesis.[82,83]

Research into the drivers of fibrosis can help identify biomarkers for early detection and stratification of high-risk patients, enabling timely intervention.[84]

4. Research Gaps

While previous studies have explored the role of lipid metabolism and obesity in NAFLD, several critical gaps remain:

Limited understanding of how specific lipid parameters (e.g., HDL, LDL, and triglycerides) interact with other metabolic factors to influence fibrosis severity.[85,86]

Lack of clarity on the relative contribution of genetic vs. environmental factors in modulating lipid profiles and fibrosis risk.[87,88]

Insufficient longitudinal data linking changes in lipid profiles and BMI to fibrosis progression over time.[89,90]

Further study is needed for investigating the relationship between lipid profiles (triglycerides, LDL, and HDL cholesterol), BMI, and liver fibrosis severity.[91,92]

Identifying specific lipid abnormalities that are most predictive of fibrosis progression.[93]

Exploring potential therapeutic targets, such as lipid-lowering therapies, to mitigate the risk of advanced fibrosis.[94,95]

Understanding these relationships could guide more effective prevention and treatment strategies for NAFLD, with implications for reducing the global burden of liver-related morbidity and mortality.[96]

MATERIALS AND METHODS

The present prospective observational study was done in tertiary care hospital from Feb 2023 to Feb 2024.A total of 40 patients were collected and all routine investigations done. patients having fatty liver incidental finding on ultrasound were subjected to further tests like liver function tests, lipid profile, questioned about history and duration of diabetes, FIB4 score calculated and risk of mortality assessed.

Inclusion Criteria

1. All patients above 18yrs
2. All patients having fatty liver incidental finding on ultrasound

Exclusion Criteria

1. Pregnant women
2. Patients with previous lipid disorders
3. Alcoholics

RESULTS

In our study out of 40 patients 23 were male and 17 were female. out of 40 ,20 were diabetic and 20 were non diabetic.it was observed that patients with longer duration of diabetes were affected more 14 with dm duration>5yrs,4patients with dm duration <5yrs, denovo were 2.

In non alcoholics we had 8 patients with fatty liver as incidental finding on ultrasound.in non alcoholics we had 10 patients with increased LDL,9 patients with increased TGL, and 8 patients with decreased HDL. out of these 15 were diabetic. we had 2 patients with FIB4 score greater than 1.45.rest of them had FIB4 score less than 1.45.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

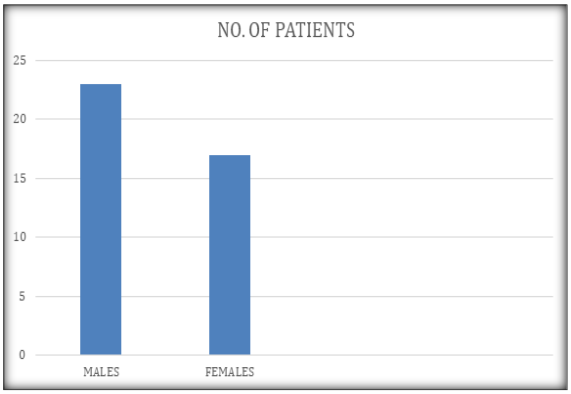

Figure 1

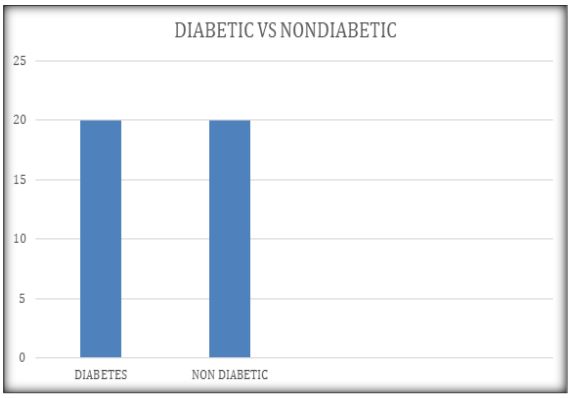

Figure 2

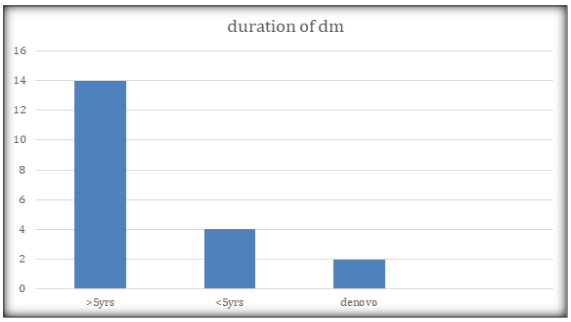

Figure 3

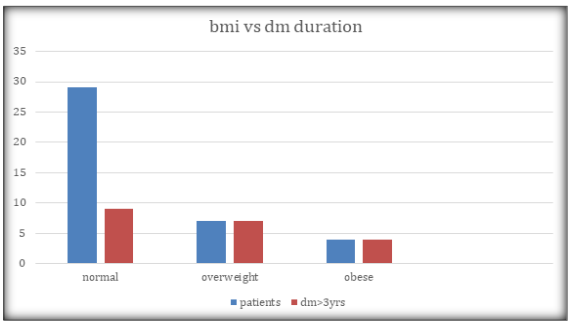

Figure 4

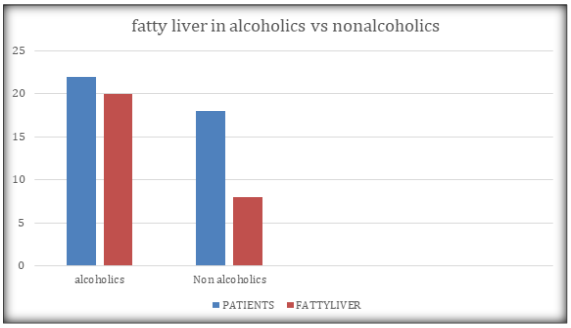

Figure 5

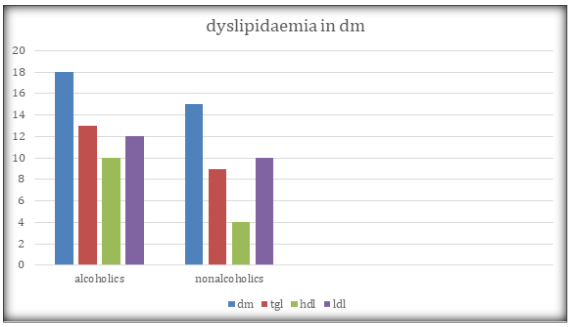

Figure 6

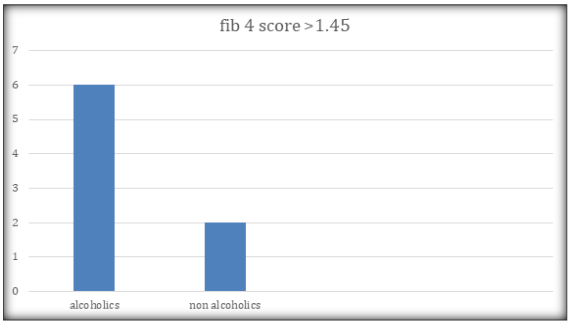

Figure 7

DISCUSSION

- In our study there was male preponderance males 23(57.5%) females 17(42.5)
- In our study fatty liver finding was found in 28[70%] patients out of 40 patients.
- In our study 18 diabetic patients were there in 22 alcoholics with dyslipidaemia,15(83.3%) diabetics in 18 non alcoholics with dyslipidaemia.
- There were 8(20%) patients with FIB 4 score >1.45.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Parameter	Our Study	Williamson et al.study	Ferrieir et al.study
Study population	40	939	100
Gender distribution	Males: 23 (57.5%). Females: 17 (42.5%).	Males: 511 (54.4%). Females: 428 (45.6%).	Males: 44(44%). Females: 56(56%).
Prevalence of fatty liver	70%	70.4%	70%
Dyslipidemia in diabetics	Non alcoholics 83.3% Alcoholics 81.8%	60%	70%
FIB 4 score>1.45	20%	15%	Not specified
Key observations	Male preponderance High prevalence of fatty liver and dyslipidemia in diabetics	Male preponderance High prevalence of fatty liver in diabetics	High prevalence of fatty liver in smaller cohort, dyslipidemia linked to NAFLD

CONCLUSION

we conclude that there is male preponderance. that duration of diabetes influenced the process of nafld. it was also observed that dyslipidemia played significant role in diabetics in progression for nafld.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556