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Prevalence and Risk Factors of Non-Alcoholic Fatty Liver Disease (NAFLD) in Type 2 Diabetes Mellitus (T2DM): A Global and Regional Systematic Review.

Author information

Dr. Arshid Rafiq [1], Dr bilal ahmed baba [2], Dr Sandeep Jha [3], Summarah Mushtaq [4]

[1] GOLF course road DLF phase 5 sector 53 Gurugram haryana, Shelby Sanar International Hospital Delhi, Email ID: syedadiyaan.ar@gmail.com, Orchid id:- 0009-0003-8710-7475.

[2] GOLF course road DLF phase 5 sector 53 Gurugram haryana, Shelby Sanar International Hospital Email ID: sarmadhospital@gmail.com.

[3] GOLF course road DLF phase 5 sector 53 Gurugram haryana, Shelby Sanar International Hospital Email ID: sarmadhospital@gmail.com.

[4] Chenni Chowk Anantnag, Alaarash diabetic center, Email ID: summarah123@gmail.com

Abastract:

This systematic literature review aims to explore the prevalence and risk factors of non-alcoholic fatty liver disease (NAFLD) in individuals with type 2 diabetes mellitus (T2DM), focusing on global and regional trends. A comprehensive analysis of existing studies reveals that over 55% of individuals with T2DM have concurrent NAFLD, with a significant proportion progressing to non-alcoholic steatohepatitis (NASH). Common risk factors identified include insulin resistance, obesity, hypertension, dyslipidemia, and genetic predisposition. Additionally, regional variations in NAFLD prevalence and risk factors are highlighted, with studies from South Asia and Latin America suggesting that lifestyle factors and dietary habits play a key role. The review also examines emerging therapeutic targets, such as bile acid signaling and microRNAs, which may offer potential for managing both T2DM and NAFLD. Overall, the findings emphasize the need for early detection and integrated therapeutic strategies to address the dual burden of T2DM and NAFLD.

Keywords

Non-Alcoholic Fatty Liver, Type 2 Diabetes Mellitus, Severity Of Non-Alcoholic Fatty Liver Disease

1. Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) has emerged as one of the most prevalent liver conditions globally, with a growing number of cases associated with metabolic diseases, particularly type 2 diabetes mellitus (T2DM). Characterized by the accumulation of fat in the liver, NAFLD occurs in individuals with little or no alcohol consumption, encompassing a broad spectrum of hepatic abnormalities. These range from simple hepatic steatosis to more advanced stages, including non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and potentially hepatocellular carcinoma. NAFLD is strongly associated with obesity, dyslipidemia, and insulin resistance—key components of metabolic syndrome (Lee et al., 2022; Bryne & Targher, 2015; Rohm et al., 2022).

The incidence rates of NAFLD is rising rapidly, with approximately 38% of the global population being affected. While not all individuals progress to severe liver disease, the number at risk is growing, particularly as the condition now affects younger populations. Urbanization, dietary changes, and the increasing prevalence of obesity and T2DM are major factors contributing to the spread of NAFLD, especially in developing countries (Wong et al., 2023). While NAFLD is often observed in patients with obesity and T2DM, it is also found in individuals of normal weight, making it a more complex and widespread issue than previously understood. The condition spans a continuum of liver damage, from simple fat accumulation to NASH, fibrosis, cirrhosis, and potentially liver carcinoma. The pathophysiology of NAFLD involves a complex interplay of factors like lipotoxicity, insulin resistance, immune system dysregulation, as well as oxidative stress, all contributing to the disease's progression (Grander et al., 2023; Marusic et al., 2021; Dongiovanni et al., 2021).

The corelation between T2DM and NAFLD is well-established, with the prevalence of NAFLD in individuals with T2DM ranging from 70% to 95%, and even reaching 98% in those with morbid obesity. In contrast, the general population has a reported incidence rate of NAFLD from 16.1% to 25.2%, with variations depending on demographic factors such as age, sex, and ethnicity (Lee et al., 2020). The metabolic disturbances characteristic of T2DM, including chronic inflammation and oxidative stress, often assist in the manifestation and progression of NAFLD. Furthermore, recent investigations have implied that fatty acid metabolism is yet another crucial pathway which affects both T2DM and NAFLD. Key genes involved in lipid metabolism, like RP11, MSANTD1,

YTHDF3, and miR-29a, have been identified as potential contributors to the progression of T2DM and its association with NAFLD (Yang et al., 2024).

NAFLD is not only a significant concern due to its liver-related complications but also because of its association with other comorbidities, including cardiovascular disease and chronic kidney disease. As T2DM continues to rise globally, particularly in younger populations, the burden of NAFLD is anticipated to rise. Lifestyle modifications, particularly weight loss, remain the cornerstone of treatment for NAFLD, but new therapeutic options, including glucagon-like peptide-1 receptor antagonists and sodium-glucose transporter-2 inhibitors, are under investigation (Pafili & Roden, 2021; Amorim et al., 2024). Furthermore, the understanding of epigenetic mechanisms, including the role of diet-derived microbial metabolites and their influence on insulin resistance, inflammation, and metabolic dysfunction, is advancing, offering new insights into the connection between T2DM and NAFLD (Li et al., 2022).

Given the increasing incidence rates and significant health impacts of NAFLD, especially in T2DM patients, there is a pressing need for further research to understand its pathogenesis, risk factors, and global and regional variations. This study aims to systematically review the prevalence as well as predisposing factors associated with NAFLD in T2DM, shedding light on key molecular mechanisms and the role of fatty acid metabolism, with the goal of guiding future research, clinical practice, and public health initiatives to address these interrelated diseases.

Research Aim and Objectives

The primary aim of this study is to understand the prevalence and severity of non-alcoholic fatty liver disease (NAFLD) among patients with Type 2 Diabetes Mellitus (T2DM). Accordingly, the objectives that would be addressed through this study are:

- To analyze the risk factors and correlation of NAFLD among patients with T2DM.
- To analyze the prevalence of NAFLD among patients with T2DM among the Asian population as compared to the European, and the American population
- To examine the factors contributing to severity in the prevalence of NAFLD among patients with T2DM among the different groups of population

2. Methods

Study Selection

To comprehensively review the literature, two primary databases, PubMed and ScienceDirect, were searched using specific key terms to locate relevant studies on the relationship between NAFLD and T2DM. The initial search was designed to capture a broad range of studies that discuss NAFLD's risk factors, prevalence, and severity among T2DM patients.

Inclusion Criteria

To ensure relevant and high-quality sources, this review included studies published exclusively in English, as language uniformity allows for consistent interpretation and analysis. Only studies with complete and open access were selected, ensuring transparency and accessibility of data. Additionally, studies published from 2015 to 2024 were prioritized to reflect the most recent findings in this area. Studies specifically addressing NAFLD in T2DM patients, including those examining risk factors, prevalence, and severity, were the main focus.

Exclusion Criteria

Certain studies were excluded to maintain focus and relevance. Non-English studies, abstracts, books, and conference proceedings were omitted to avoid incomplete data and inconsistencies. Additionally, studies concentrating solely on the treatment or unrelated aspects of NAFLD and T2DM were excluded, as the primary aim was to explore associations, prevalence, and risk factors. Finally, studies published before 2015 were not considered, ensuring that the review encompassed only recent literature.

Search Strategy and Database Usage

The literature search was conducted using PubMed and ScienceDirect databases, chosen for their extensive coverage of medical and scientific research. Specific search terms were used to retrieve relevant studies: “non-alcoholic fatty liver and with Type 2 Diabetes Mellitus,” “non-alcoholic fatty liver with Type 2 Diabetes Mellitus prevalence,” “severity of non-alcoholic fatty liver disease with Type 2 Diabetes Mellitus,” and “contributing factors in non-alcoholic fatty liver with Type 2 Diabetes Mellitus.” This targeted approach facilitated the identification of studies directly relevant to the NAFLD and T2DM correlation.

PRISMA Findings

To conduct a systematic review on NAFLD in individuals with T2DM, an exhaustive literature search was conducted using PubMed and ScienceDirect. This initial search yielded a total of 37,666 references: 6,188 from PubMed and 31,478 from ScienceDirect. Given the large number of results, a multi-stage filtering process was applied to refine the dataset and select the most relevant studies.

Step 1: Elimination of Duplicate Studies

The first step focused on removing duplicate studies across the two databases, resulting in the exclusion of approximately 4,740 duplicate references. This step narrowed the collection to 32,926 unique studies.

Step 2: Filtering by Year of Publication

To ensure the inclusion of recent studies relevant to the current state of research, studies published outside the timeframe of 2015–2024 were excluded. This criterion led to the elimination of 6,945 references, reducing the dataset to 25,981 studies.

Step 3: Access Filtering

In the third step, a filter was applied to retain only studies with open-access availability, in line with the inclusion criteria. This step aimed to maximize accessibility and relevance to a broader audience. As a result, 16,414 studies with restricted access were excluded, leaving 9,567 studies eligible for further screening.

Step 4: Final Selection Based on Language, Scope, and Relevance

The final stage involved a thorough screening based on language, title, abstract relevance, and specific alignment with the study's focus on NAFLD in T2DM patients. Only research and review articles directly addressing this topic were considered for inclusion. After this detailed assessment, 4,978 references were retained for a closer review, from which 41 studies were ultimately selected for inclusion in the systematic review.

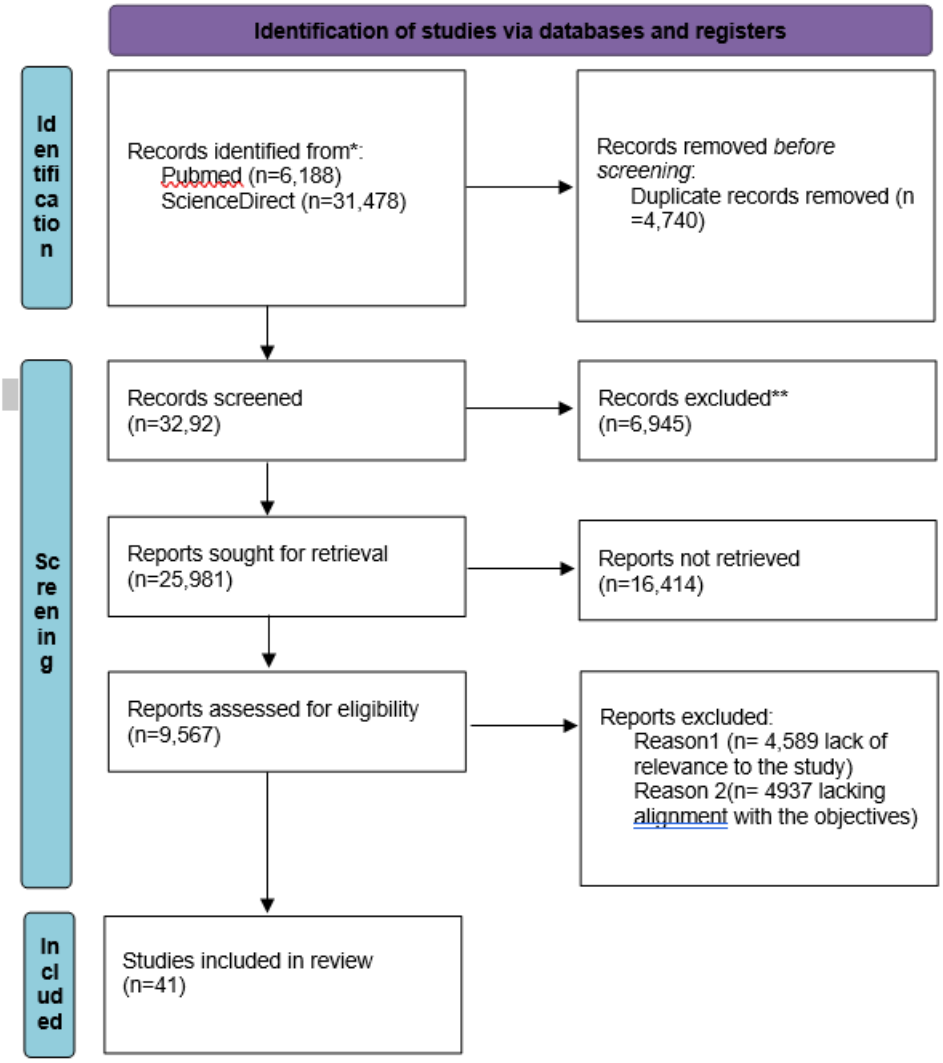

Figure 1: PRISMA flow chart

3. Findings

Risk Factors and Correlation Between NAFLD and T2DM

NAFLD shares a complex and bidirectional relationship with T2DM, as both significantly increases the risk of the other. Insulin resistance (IR) has a vital role in this interrelationship, by assisting in the manifestation of the pathogenesis of both conditions. T2DM not only predisposes individuals to develop NAFLD, but it also accelerates the progression of liver disease towards more severe stages such as NASH and liver cancer (Muzica et al., 2020; Juanola et al., 2021).

Obesity is a critical predisposing factor for NAFLD in individuals with T2DM, as it contributes to both insulin resistance and the accumulation of fat in the liver. Studies show that over 50% of T2DM patients also suffer from NAFLD. In Ghana, obesity was identified as an independent predictor of NAFLD, surpassing other

factors such as hypertension and dyslipidemia, highlighting the importance of addressing obesity in the management of T2DM and NAFLD (Wiafe et al., 2023). Additionally, gut microbiota is also involved in the interplay between NAFLD and T2DM, with a study on an Asian NAFLD cohort revealing that certain bacterial taxa, including Romboutsia, Clostridium, and Enterobacter, showing prominent connections with both NAFLD severity and impaired glucose metabolism, thereby linking the microbiome to markers such as fasting blood glucose and HbA1c (Si et al., 2021). Functional analysis has also suggested that patients with both these conditions demonstrate enriched endotoxin biosynthesis pathways, further implicating the microbiome in this bidirectional relationship (Si et al., 2021).

Metabolically, short-chain fatty acids (SCFAs) are emerging as important players in the development of NAFLD in T2DM. Research has shown a negative correlation between circulating levels of isobutyrate and methylbutyrate and the severity of NAFLD, independent of glycated hemoglobin (HbA1c) levels. This suggests that SCFAs may influence the progression of NAFLD in T2DM patients (Tsai et al., 2023). The risk of developing T2DM is also doubled in individuals with NAFLD compared to those without liver disease. The combination of obesity, insulin resistance, and hyperglycemia significantly increases the likelihood of developing T2DM, while the resolution of hepatic steatosis has been shown to reduce this risk by 39% to 82% (Lee et al., 2020).

T2DM significantly increases the risk of severe liver disease outcomes, including cirrhosis and liver-related death, with a hazard ratio (HR) of 2.25. This finding is concerning as the global prevalence of diabetes continues to rise, highlighting the need for early identification of individuals at high risk for liver complications (Jarvis et al., 2020). Furthermore, studies have demonstrated a strong correlation between NAFLD and insulin resistance, with 70.5% of T2DM patients exhibiting impaired insulin response. This relationship underscores the importance of managing insulin resistance to prevent the progression of NAFLD in T2DM patients (Rajendra et al., 2024).

Another emerging factor in the pathophysiology of NAFLD in T2DM is hyperglucagonaemia. Elevated glucagon levels have been associated with increased liver fat content, suggesting that glucagon resistance may play a critical role in the development and progression of NAFLD in T2DM. Further research is needed to understand the mechanisms linking glucagon resistance to metabolic disturbances in these patients (Rix et

al., 2024). Lastly, the OPG-RANKL-RANK axis is being explored as a potential mediator in the relationship between NAFLD and T2DM. Elevated osteoprotegerin (OPG) levels have been linked to metabolic dysfunction and cardiovascular disease, suggesting that this signaling pathway may contribute to the increased risk of NAFLD in T2DM (Vachliotis & Polyzos, 2023). These findings highlight the multifaceted nature of the relationship between NAFLD and T2DM, emphasizing the need for comprehensive management strategies targeting obesity, insulin resistance, and metabolic dysregulation.

Prevalence of NAFLD Among Patients with T2DM

The prevalence of NAFLD in individuals with T2DM is alarmingly high worldwide. Epidemiological studies show that individuals with T2DM are at a two-fold increased risk of developing NAFLD, and vice versa, demonstrating the strong link between these conditions. NAFLD currently affects up to 25% of the general adult population, with an increasing incidence in children. Given that T2DM impacts approximately 463 million people globally, the rising number of NAFLD cases is closely tied to this metabolic disorder, as individuals with NAFLD often exhibit abnormal glucose metabolism, making them more prone to developing T2DM. Furthermore, those diagnosed with NAFLD are at an elevated risk for cardiovascular, renal, and oncological diseases, particularly when coupled with T2DM (Tanase et al., 2020).

Recent shifts in the classification of NAFLD to metabolic associated fatty liver disease (MAFLD) have led to a surge in diagnoses, with a 68.89% rise in cases among T2DM patients. This redefinition, which includes those previously diagnosed with NAFLD but now categorized under the broader scope of MAFLD, emphasizes the connection between metabolic dysfunction and liver disease. MAFLD(+)/NAFLD(-) patients were found to be at a significantly higher risk for adverse cardiovascular events, advanced fibrosis, and mortality compared to those with the dual diagnosis. The presence of viral hepatitis in this group further increased the likelihood of advanced fibrosis (odds ratio: 6.77) and mortality (hazard ratio: 1.75), highlighting the importance of managing co-morbidities. However, some concerns have emerged about the premature adoption of the MAFLD definition, as it could potentially lead to over-diagnosis and complicate clinical decision-making (Muthiah et al., 2023).

In India, a study found that 57% of T2DM patients were affected by NAFLD, with a higher rate observed in males (54.6%). Among those with NAFLD, 26% developed nonalcoholic steatohepatitis (NASH), and 37.3%

had mild to moderate steatosis, while 26.6% exhibited severe steatosis. This highlights the high prevalence of NAFLD in the eastern region of India, particularly in individuals with T2DM (Sinha & Bankura, 2023). Similarly, a study in another part of India revealed that 80.4% of T2DM patients had NAFLD, significantly higher than the 53.3% observed in non-diabetic participants. Factors such as age (25-45 years), obesity, increased waist circumference, elevated triglycerides, lower HDL, and the use of sulfonylureas and metformin were strongly associated with the increased risk of NAFLD in this group (Almahmoud et al., 2021).

In a study of clinically significant liver fibrosis (CSLF) among T2DM patients, 22.7% were found to have CSLF, with 58.9% exhibiting steatosis. Factors associated with CSLF included higher BMI, elevated AST and ALT levels, and lower platelet counts. Interestingly, most patients with CSLF had normal transaminase levels, emphasizing the need for more accurate diagnostic methods (Deb et al., 2024). Furthermore, a study conducted by Heidari et al. (2017) found that 86.66% of T2DM patients had NAFLD, with 68% of these patients being female and 32% male. The study also noted the high prevalence of diabetic nephropathy, with microalbuminuria in 32% and macroalbuminuria in 10% of the participants (Heidari et al., 2017).

In South Asia, the prevalence of NAFLD is notably high, with a pooled prevalence of 26.9% in the general population, increasing to 54.1% among those with metabolic diseases. Urban populations have a higher prevalence (32.9%) compared to rural populations (22.6%), though the difference was not statistically significant (Niriella et al., 2023). In Latin America, NAFLD affects about 24% of the general population, but this prevalence rises significantly in high-risk groups such as those with T2DM or obesity, reaching 68% (Rojas et al., 2022).

In sub-Saharan Africa, a study conducted in Ghana found that 51.4% of individuals with T2DM had NAFLD, challenging the assumption that the prevalence of NAFLD is lower in this region (Wiafe et al., 2023). Similarly, research conducted at TH Jaffna revealed that 77.7% of T2DM patients had NAFLD, reinforcing the global trend linking T2DM with NAFLD, especially in patients with insulin resistance (Rajendra et al., 2024).

Factors Contributing to Severity in NAFLD Prevalence Among T2DM Patients

The progression and severity of non-alcoholic fatty liver disease (NAFLD) are closely linked to insulin resistance and type 2 diabetes mellitus (T2DM), with both conditions independently increasing the risk of

NAFLD development. There is a bidirectional relationship between NAFLD (or NASH) and T2DM, where impaired insulin sensitivity and hepatic lipid accumulation exacerbate liver damage. Specifically, lipids like diacylglycerol and ceramides disrupt insulin signaling, increasing hepatic glucose production and worsening insulin resistance. Additionally, individuals with NAFLD, especially those with NASH, face a higher risk of progression to cirrhosis and hepatocellular carcinoma (HCC). Elevated liver enzymes in NAFLD patients, particularly when unexplained by other conditions, are predictive of T2DM, with NAFLD patients having a more than twofold increased risk of T2DM (Ferguson & Finck, 2021).

NAFLD is highly prevalent among T2DM patients, with over 55% of T2DM individuals suffering from NAFLD, and approximately 37% having NASH. This emphasizes the need for integrated management approaches. Cardiovascular disease (CVD), a leading cause of death in T2DM patients, is closely associated with NAFLD, compounding health risks. Both CVD and NAFLD share common risk factors such as insulin resistance, obesity, and hypertension, and therapies that improve insulin sensitivity and reduce weight may benefit both conditions. Furthermore, the increasing severity of NAFLD correlates with worsening kidney function, particularly in NASH patients, underscoring the importance of renal monitoring in these individuals. A comprehensive treatment strategy targeting both liver and metabolic dysfunction may improve outcomes for this population (Ferguson & Finck, 2021).

Bile acids, through the farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5), regulate metabolism, inflammation, and lipid/carbohydrate metabolism, with their interaction with the gut microbiota influencing metabolic diseases like obesity, T2DM, and NASH. This points to the therapeutic potential of targeting bile acid signaling in NAFLD and T2DM (Talavera et al., 2017). T2DM has been shown to significantly increase the risk of hepatic decompensation and HCC in NAFLD patients, with elevated glycated hemoglobin being an independent predictor of these outcomes (Huang et al., 2023).

Metabolic dysfunction, including obesity, T2DM, hypertension, and dyslipidemia, contributes to the development of NAFLD, which may be redefined as metabolic dysfunction-associated fatty liver disease (MAFLD). Insulin resistance underpins fat accumulation in the liver, exacerbating inflammation, fibrosis, and carcinogenesis. Genetic factors and altered gut microbiota also influence the progression of the disease (Sakurai et al., 2021; Gonçalves et al., 2019). Moderate alcohol consumption has been associated with an

increased risk of advanced fibrosis in T2DM patients with NAFLD, suggesting a synergistic effect of alcohol and insulin resistance on disease progression (Blomdahl et al., 2021).

Dietary factors also influence NAFLD development in T2DM patients. A higher dietary inflammatory index (DII) is associated with increased NAFLD risk, while central obesity markers like trunk-to-leg fat ratio (TLR) and metabolic score for visceral fat (METS-VF) also show a strong correlation with NAFLD in diabetic individuals (Soltanieh et al., 2023). The duration of diabetes, BMI, hypertriglyceridemia, and HbA1c levels are significantly associated with NAFLD prevalence in T2DM patients, with prolonged disease duration and poor glycemic control contributing to both NAFLD and diabetic nephropathy (Heidari et al., 2017).

In the South Asian population, NAFLD is strongly linked to diabetes, hypertension, dyslipidemia, and metabolic syndrome, with gender not being a significant factor. Interestingly, a considerable proportion of NAFLD patients are non-obese, highlighting the role of metabolic diseases in NAFLD development (Niriella et al., 2023). In Latin America, T2DM and obesity are major risk factors for NAFLD, with individuals in these high-risk groups exhibiting a much higher prevalence of the disease compared to the general population (Rojas et al., 2022).

Altered amino acid profiles, including elevated levels of isoleucine and glutamate and reduced levels of glycine and serine, have been observed in NAFLD patients, indicating disruptions in metabolic pathways that contribute to liver fat accumulation and insulin resistance (Rix et al., 2024). Additionally, NAFLD in T2DM can progress from simple steatosis to more severe forms like NASH and fibrosis, with factors such as aging, diabetes duration, obesity, and insulin resistance playing significant roles in disease severity (Lee et al., 2020).

Discussion,

This systematic literature review highlights the complex relationship between NAFLD and T2DM, confirming the bidirectional association that exacerbates both conditions. Previous studies consistently demonstrate that NAFLD, particularly in its progressive form of non-alcoholic steatohepatitis (NASH), is a significant risk factor for the worsening of insulin resistance, increased hepatic glucose production, and overall metabolic dysfunction. The prevalence of NAFLD in individuals with T2DM has been well documented, with over 55% of T2DM patients showing concurrent NAFLD, and around 37% of these cases progressing to NASH (Ferguson & Finck, 2021). This aligns with findings from our review, as the

accumulation of lipids such as diacylglycerol and ceramides in the liver disrupts insulin signaling, leading to both hepatic and systemic insulin resistance.

Additionally, the review affirms that the progression of NAFLD is closely tied to other metabolic conditions, including obesity, hypertension, and dyslipidemia, all of which are common among individuals with T2DM. The review reiterates that individuals with both conditions face significantly higher risks of adverse liver outcomes, such as hepatic decompensation and hepatocellular carcinoma (Huang et al., 2023). These findings emphasize the critical need for early detection of NAFLD in patients with T2DM and the importance of developing therapeutic strategies that simultaneously address metabolic dysfunction and liver disease.

The literature also highlights the role of bile acid signaling as a potential therapeutic target in the management of both T2DM and NAFLD. Receptors like farnesoid X receptor (FXR) and G protein-coupled bile acid receptor 1 (TGR5) have been shown to regulate key metabolic pathways, including lipid and glucose metabolism, and play a role in controlling inflammation (Talavera et al., 2017). Targeting these pathways could offer a dual benefit in treating both T2DM and NAFLD, a promising avenue for future research and potential therapeutic interventions.

Moreover, genetic factors, gut microbiota imbalances, and environmental influences are increasingly recognized as contributing factors to the progression of NAFLD in T2DM patients. Several studies have indicated that genetic predisposition and changes in the gut microbiome contribute to liver fat accumulation, inflammation, and fibrosis, which in turn increase the risk of hepatocellular carcinoma (Sakurai et al., 2021; Gonçalves et al., 2019). These factors, along with insulin resistance, form a complex network that drives the progression of NAFLD in T2DM patients, emphasizing the importance of a multifaceted approach to treatment that takes genetic and environmental influences into account.

The review also highlights the growing global prevalence of NAFLD, particularly in regions where metabolic conditions like obesity and T2DM are on the rise. Studies from South Asia (Niriella et al., 2023) and Latin America (Rojas et al., 2022) show that lifestyle factors, dietary habits, and regional metabolic patterns significantly influence the development and progression of NAFLD, adding a regional dimension to the understanding of these diseases. These findings suggest that tailored interventions that consider regional and population-specific factors may be necessary for effective management.

Furthermore, the involvement of microRNAs (miRNAs) in regulating processes such as lipid metabolism, inflammation, and insulin resistance has been a subject of increasing interest. miRNAs are now considered as potential biomarkers and therapeutic targets for both NAFLD and T2DM, with several studies highlighting their role in the pathogenesis of these conditions (Fang et al., 2021). The exploration of miRNA-based therapies may provide new opportunities for treating these diseases, particularly in cases where conventional treatments are less effective.

Conclusion

This study strengthens the understanding of the bidirectional relationship between NAFLD and T2DM, emphasizing the need for integrated management strategies. The findings reveal that insulin resistance, obesity, dyslipidemia, and other metabolic abnormalities are key contributors to the pathogenesis of both conditions. Moreover, the increased risk of progression to more severe liver disease in T2DM patients with NAFLD underscores the importance of early intervention to prevent liver-related complications such as cirrhosis and hepatocellular carcinoma. Future clinical approaches should focus on improving insulin sensitivity, managing metabolic dysfunction, and utilizing targeted therapies that address both liver and metabolic health.

Future Directions

Further research is needed to explore the underlying molecular mechanisms linking NAFLD and T2DM. Specifically, studies should investigate the role of bile acid signaling pathways in regulating lipid and carbohydrate metabolism in patients with these conditions. Additionally, the influence of genetic factors and gut microbiota imbalances in NAFLD progression should be explored, as they may provide novel targets for personalized therapies. Longitudinal studies could help clarify the temporal relationship between metabolic dysfunction and liver disease progression, shedding light on potential biomarkers for early detection of severe liver outcomes, including cirrhosis and hepatocellular carcinoma. Lastly, clinical trials evaluating interventions that target both insulin resistance and liver dysfunction, such as lifestyle modifications, pharmacological therapies, and bile acid receptor agonists, could offer valuable insights into effective treatments for this dual pathology.

5. Acknowledgements

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