International Research Journal of Gastroenterology and Hepatology

Volume 7, Issue 1, Page 1-13, 2024; Article no.IRJGH.111013

Non Alcoholic Fatty Liver Disease; Disease Burden, Management, and Future Perspectives

Peter Jerome Ishmael Villete Paulino [a*], Kimberly Morton Cuthrell [b] and Nikolaos Tzenios [c]

[a] Department of Biological Sciences, Vanguard University, Costa Mesa, California, US State.
[b] Saint James School of Medicine, Illinois, United States of America.
[c] Public Health and Medical Research, Charisma University, Grace Bay, Turks and Caicos Islands, UK.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/111013

Review Article

Received: 26/10/2023
Accepted: 29/12/2023
Published: 04/01/2024

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a significant and pertinent human ailment linked to a modified way of life, characterized by a fast increasing occurrence and prevalence in the majority of countries worldwide. Non-alcoholic fatty liver disease (NAFLD) can lead to significant health problems at various stages of chronic liver disease, including cirrhosis and related consequences such as hepatocellular carcinoma (HCC) and decompensation (such as bleeding from esophageal varices, accumulation of fluid in the abdomen, and impaired brain function due to liver dysfunction). In addition to hepatic problems, non-alcoholic fatty liver disease (NAFLD) patients frequently experience the metabolic syndrome, type 2 diabetes (T2D), and cardiovascular disease (CVD). While the current comprehension of the fundamental pathways in relation to NAFLD is growing, the

**Corresponding author: E-mail: ppaulino@lbcc.edu;*

precise pathophysiological impact of NAFLD on T2D and CVD remains incompletely known. One of the main theories suggests that a sub-clinical pro-inflammatory milieu is caused by lipotoxicity, insulin resistance (IR), and the intestinal microbiota. The primary foundation of the treatment involves lifestyle adjustment, which encompasses weight reduction, nutritional intervention, and consistent physical activity. While achieving this aim may be challenging for numerous patients, it is advisable for treating physicians to recommend and provide support for it. A variety of therapy choices, ranging from non-invasive management and medical intervention to surgical techniques (such as bariatric surgery), have been created with different results, particularly for the non-invasive treatment methods. The range of innovative therapeutic techniques is extensive, with several intriguing candidates. Collectively, NAFLD represents a significant healthcare concern that is projected to escalate in the future. Consequently, it is imperative for physicians from many disciplines to enhance their understanding of this condition to effectively address it with their patients.

Keywords: Non alcoholic; liver dysfunction; fatty liver disease; lipotoxicity; disease burden.

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a prevalent etiology of chronic hepatic disorder on a global scale. NAFLD is a range of the illness distinguished by the presence of fatty liver when there are no other identifiable reasons for the buildup of fat in the liver (such as excessive alcohol consumption) [1-3]. NAFLD encompasses a spectrum of liver conditions, ranging from the less harmful non-alcoholic fatty liver (NAFL) to the more severe non-alcoholic steatohepatitis (NASH). Non-alcoholic fatty liver disease has the potential to advance to fibrosis and cirrhosis [4]. In NAFLD, the liver contains excess fat without any signs of inflammation. However, in non-alcoholic steatohepatitis (NASH), the liver still has excess fat but is accompanied with inflammation and cell death in the liver lobes. Theinflammation and cell death can eventually result in the development of fibrosis and cirrhosis [5-8].

Prior to the mid-2000s, NASH was commonly regarded as a significant condition that primarily affected obese females [9]. It was frequently linked to Type 2 Diabetes Mellitus (T2DM) and had a relatively mild prognosis. These factors were indicative of an increased risk for cardiovascular disease, stroke, and diabetes. NAFLD has experienced a significant increase in occurrence in Western countries, with a global prevalence rate of 25% [9,10]. NAFLD is increasingly prevalent as a chronic liver condition in Western industrialized nations, especially among those with central obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and metabolic syndrome [10, 11].

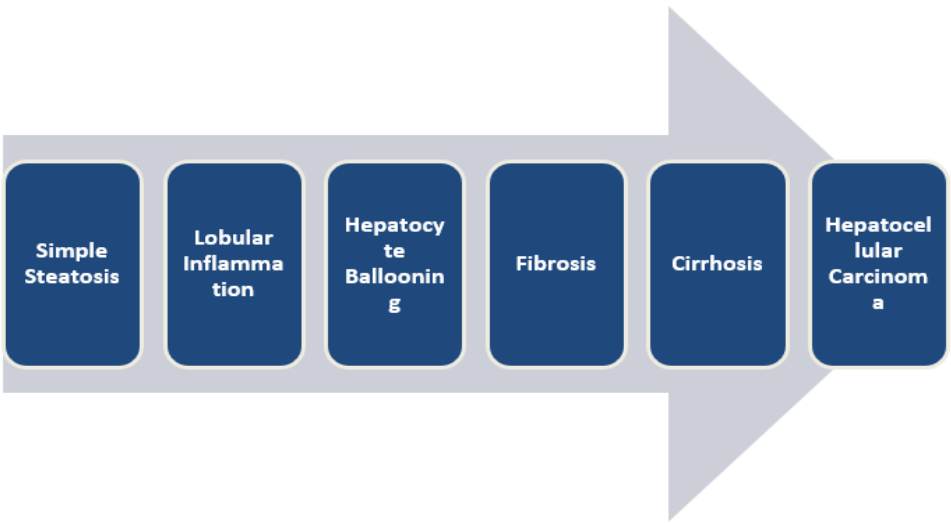

Fig. 1. From NAFLD To HCC

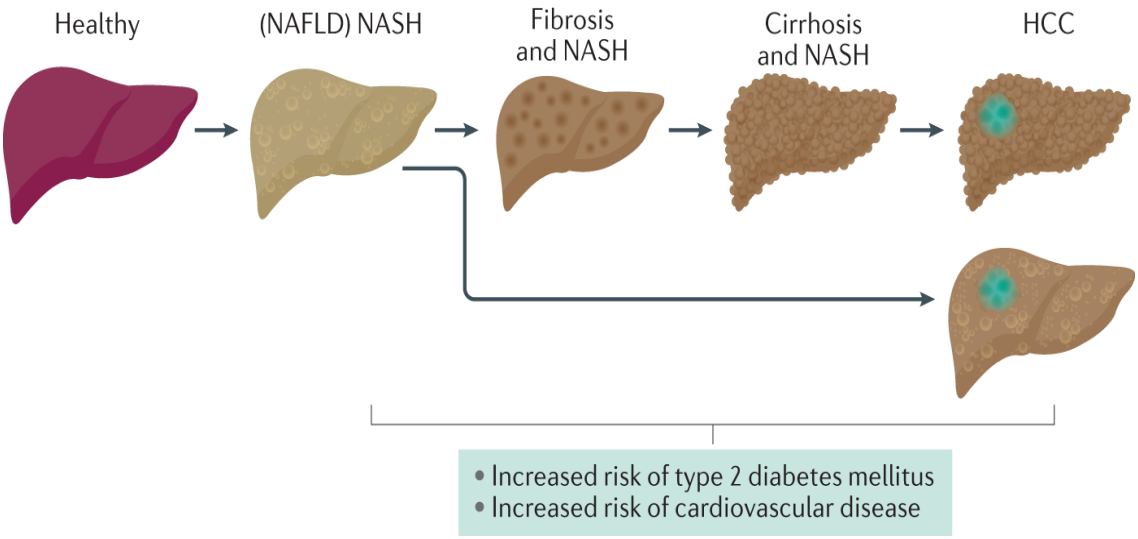

Fig. 2. Progression of NAFLD [12]

When it comes to diagnostic examinations, the most reliable method to examine any type of liver inflammation or damage is a liver biopsy. Liver biopsies are highly valuable in diagnosing NAFLD and related conditions. The findings from these biopsies might vary, ranging from the presence of triglyceride deposits as droplets in the liver cells to more severe types of non-alcoholic steatohepatitis (NASH). NASH is often defined by the aforementioned lipid droplets present in liver cells, accompanied by inflammation and varying levels of liver fibrosis. Most people with hepatic steatosis have a non-progressive form of the illness. However, a small subset of these patients may develop NASH, as described earlier. NASH can advance to liver failure and even hepatocellular cancer [13].

The US guidelines for managing NAFLD define NAFLD as the presence of steatosis with at least 5% fat infiltration in imaging or histology, and the absence of alcohol, drug, or viral-induced steatosis. Patients with non-alcoholic fatty liver disease (NAFLD) may exhibit high levels of liver enzymes [15, 16].

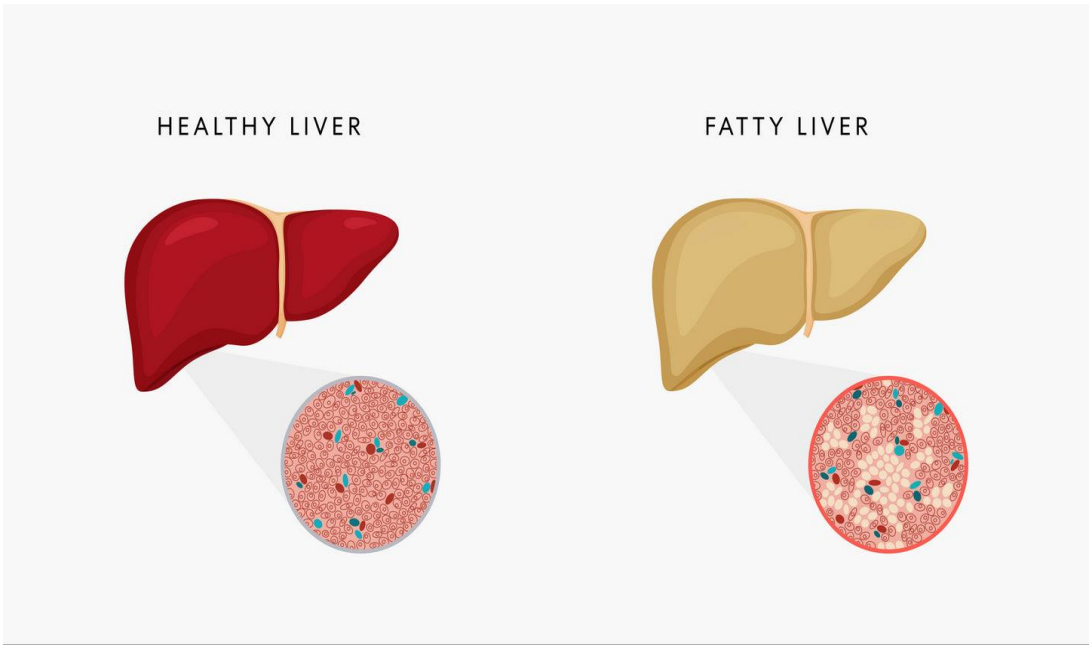

Fig. 3. Healthy Vs Fatty Liver [14]

Patients diagnosed with NAFLD may exhibit one or more elements of the metabolic syndrome (MS), such as systemic hypertension, dyslipidemia, insulin resistance, or overt diabetes. Mounting data suggests that visceral obesity is a risk factor for non-alcoholic fatty liver disease NAFLD [17]. Additionally, it is important to consider that metabolic syndrome (MS) is a recognized risk factor for the development of cardiovascular disease. According to existing literature, cardiac and vascular disorders appear to be the primary cause of death in these patients. However, the precise pathophysiological pathways that link cardiovascular disease and NAFLD are not yet fully comprehended. Insulin resistance is believed to be a shared element in the development of both conditions [18, 19].

Assessing atypical liver enzyme levels in an otherwise healthy patient can provide a difficulty even for a seasoned practitioner. NAFLD is a prevalent cause for atypical liver function test findings in individuals who donate blood. The liver function test identifies the presence of elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in up to 90% of cases, after ruling out other causes of liver illness [20, 21]. According to the 2014 data from the World Health Organization Global Health Observatory, the prevalence of obesity among those aged 18 and above is 15% among women and 11% among men worldwide. An assessment examining the frequency of NASH determined that around 5.7–17% of the population in the United States is impacted by this condition [22-25].

2. PATHOPHYSIOLOGY OF NAFLD

The progression of NASH is an intricate phenomenon that remains incompletely comprehended. Recently, there has been a significant amount of animal research focused on studying the pathophysiology of NAFLD and NASH. The research mostly examines the effects of several dietary models, such as high fructose, high fat, or methionine/choline deficient diet (MCD). According to this collection of information, it has been proposed that the progression of NASH occurs in two distinct stages. The initial stage of this process involves the accumulation of fat in the liver, leading to an elevation in insulin resistance. The second phase of this process entails cellular and molecular alterations characterized by oxidative stress and the oxidation of fatty acids in the liver. These changes are caused by various factors, including cytokine injury, hyperinsulinemia, hepatic iron and/or lipid peroxidation, variations in the extracellular matrix, disturbances in energy homeostasis, and alterations in immune system function. The emergence of insulin resistance is a complex process. In the context of metabolic syndrome (MS), similar to many individuals with NASH, the escalation of fat mass and the process of adipocyte differentiation are crucial factors in the development of insulin resistance [26-30].

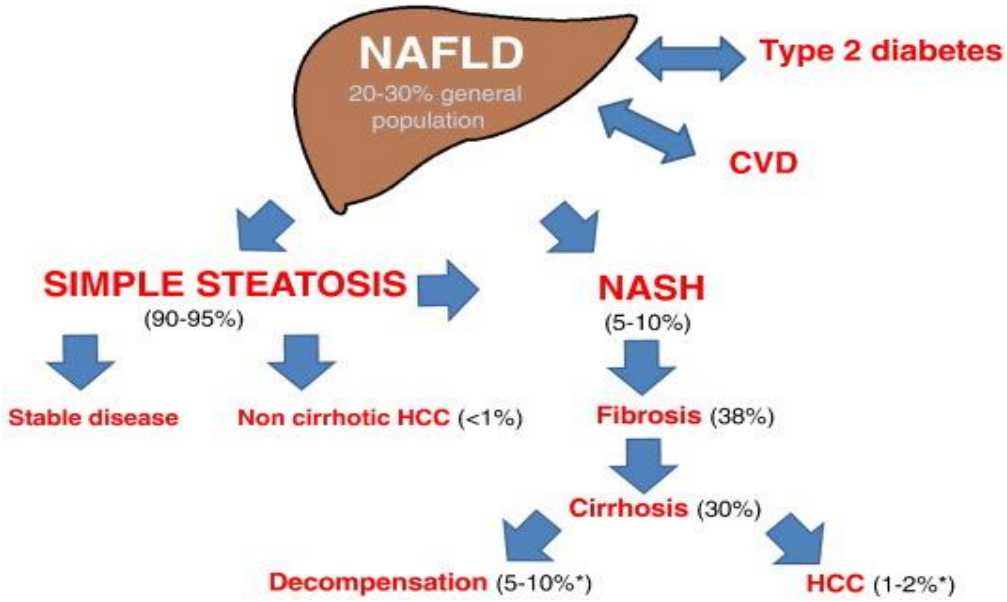

Fig. 4. Pathophysiology of NAFLD [31]

NAFLD can be categorized into two different subtypes. The first form of NAFLD is closely associated with metabolic syndrome, and it is widely believed that insulin resistance is the main underlying mechanism responsible for its development. The second variant of NAFLD is associated with infectious diseases that might result in the development of hepatic steatosis. In this scenario, infections such as hepatitis C and HIV can be a contributing factor. However, it is also linked to the use of certain medications (such as total parenteral nutrition, glucocorticoids, tamoxifen, tetracycline, amiodarone, methotrexate, valproic acid, and vinyl chloride), as well as exposure to specific toxins or the presence of inherited or acquired metabolic disorders (such as lipodystrophy, cachexia, or intestinal bypass surgery) [32-34].

3. RISK FACTORS

Individuals with NAFLD typically exhibit features commonly seen in metabolic syndrome (MS), along with the accompanying risk factors for cardiovascular disease[35]. As previously mentioned, NAFLD is strongly associated with metabolic syndrome and obesity [36]. Type 2 diabetes mellitus (T2DM) and dyslipidemia are recognized as significant risk factors for NAFLD [37]. Research has demonstrated a higher occurrence of cardiovascular disease (CVD) in individuals with NAFLD, regardless of whether they had diabetes or not. Hence, NAFLD is commonly linked to an unhealthy way of living, and there is evidence indicating that modifying unhealthy lifestyles can lower transaminase levels and enhance NAFLD [38]. A study on patients with T2DM discovered a higher occurrence of peripheral vascular, coronary, and cerebrovascular diseases in individuals with NAFLD compared to those without NAFLD [39]. The prevalence of coronary, cerebrovascular, and peripheral vascular disease was significantly higher in subjects with NAFLD, even after accounting for normal cardiovascular disease risk factors, medication usage, and diabetes-related variablesMore than 20 investigations, including both prospective and retrospective ones, have examined the connection between NAFLD and cardiovascular disease, and it has been determined that cardiovascular disease poses a significant and immediate risk [29]. This finding is consistently being supported by ongoing studies [40, 41].

Fig. 5. Risk factors of NAFLD

The association between NAFLD and smoking is a subject of debate. Smoking is a significant contributor to the occurrence of chronic, non-communicable diseases (NCD) worldwide, including cancer, T2DM, respiratory problems, and cardiovascular conditions [42]. Research conducted on rats with obesity revealed that exposure to cigarette smoke intensified the histopathological severity of non-alcoholic fatty liver disease (NAFLD) [43]. A cross-sectional study conducted on individuals with NAFLD observed that the prevalence of liver substantial fibrosis and advanced hepatic fibrosis was significantly greater among smokers compared to non-smokers. A comprehensive analysis of 20 published studies conducted a systematic review and meta-analysis, revealing a strong correlation between smoking and NAFLD [44]. The study also emphasized the need for additional research to elucidate the underlying processes of this association. Although smoking was previously believed to be a significant risk factor for the development of NAFLD, a study involving 933 patients (368 smokers and 565 non-smokers as controls) found no difference in the occurrence of NAFLD between the two groups (22.2% versus 29%), including heavy smokers who consumed more than 20 packs of cigarettes per year [45].

4. ETIOLOGY Of NAFLD

- **Insulin Resistance and Metabolic Syndrome:** The primary cause of NAFLD is often linked to metabolic risk factors, including insulin resistance, obesity, high levels of fats in the blood (hyperlipidemia), and conditions like type 2 diabetes. These factors contribute to the accumulation of fat in the liver [46].
- **Genetic Predisposition:** Genetic factors can influence an individual's susceptibility to NAFLD. Certain genetic mutations or variations may increase the risk of developing the condition [47].
- **Dietary Factors:** Consuming a diet high in calories, especially from sugars and unhealthy fats, can contribute to the development of NAFLD [48].
- **Lifestyle Factors:** Sedentary lifestyles and lack of physical activity are associated with an increased risk of NAFLD [49].
- **Other Medical Conditions:** Certain medical conditions like polycystic ovary syndrome (PCOS), sleep apnea, and hypothyroidism are linked to a higher risk of NAFLD [50].

5. EPIDEMIOLOGY

The prevalence of NAFLD has been rising globally, in parallel with the increasing rates of obesity and metabolic syndrome. Key epidemiological points include:

- **Global Prevalence:** NAFLD is one of the most common liver diseases worldwide. Its prevalence varies by region, but it is estimated that around 25% of the global population has NAFLD [51].
- **Association with Obesity:** Obesity is a significant risk factor for NAFLD. A substantial portion of obese individuals have NAFLD, and the prevalence increases with higher body mass index (BMI) [52].
- **Age and Gender:** NAFLD can affect individuals of all ages, including children. However, it is more prevalent in middle-aged and older adults. Men tend to have a higher prevalence of NAFLD compared to premenopausal women, but after menopause, the risk in women increases [53].
- **Ethnic and Geographic Variations:** There are variations in NAFLD prevalence among different ethnic groups and geographical regions. Certain populations, such as Hispanics and Asians, may have a higher predisposition to NAFLD [54].
- **Association with Other Conditions:** NAFLD is often associated with other health conditions like cardiovascular disease, type 2 diabetes, and chronic kidney disease, making it a significant health concern due to its potential complications [55].

Understanding the causes and epidemiology of NAFLD is crucial for developing effective prevention strategies and treatments, especially given its increasing prevalence worldwide. Regular exercise, maintaining a healthy weight, and adopting a balanced diet are essential preventive measures against NAFLD.

6. DIAGNOSIS

NAFLD is a condition characterized by the accumulation of fat in the liver cells, not due to alcohol consumption. Diagnosis typically involves a combination of medical history, physical examination, blood tests, imaging studies, and sometimes a liver biopsy [56, 57].

- **Medical History and Physical Examination:** The doctors take detailed medical histories to understand the patient's risk factors, such as obesity, diabetes, high cholesterol, or metabolic syndrome. A physical examination may reveal an enlarged or tender liver [58].
- **Laboratory Tests:** Blood tests are commonly used to assess liver function and rule out other liver diseases. These tests may include liver enzymes (AST, ALT), markers of liver function (bilirubin, albumin), and other markers such as gamma-glutamyl transferase (GGT) and alkaline phosphatase. Elevated liver enzymes can indicate liver inflammation or damage [59].
- **Imaging Studies:** Various imaging techniques help in diagnosing and assessing the extent of NAFLD. Ultrasound is often the first imaging test used, showing fat accumulation in the liver. Other imaging methods like computed tomography (CT) scans or magnetic resonance imaging (MRI) can provide more detailed information [60].
- **Fibrosis Assessment:** As NAFLD can progress to more severe conditions like non-alcoholic steatohepatitis (NASH) and fibrosis, assessing the degree of fibrosis is crucial for prognosis. Non-invasive methods like transient elastography (FibroScan) or magnetic resonance elastography (MRE) are used to assess liver stiffness, indicating the degree of fibrosis without the need for a liver biopsy [61, 62].
- **Liver Biopsy:** In some cases, a liver biopsy may be recommended, especially if the diagnosis is uncertain or if there is a need to determine the severity of liver damage and rule out other liver conditions that typically involves taking a small sample of liver tissue for microscopic examination [63, 64].
- **Serum Biomarkers and Scoring Systems:** Some emerging serum biomarkers and scoring systems (like NAFLD Fibrosis Score, FIB-4 index, etc.) are used to assess the risk of advanced fibrosis in NAFLD without the need for a liver biopsy [65, 66].

The diagnosis and management of NAFLD should be done by healthcare professionals. The approach to diagnosis may vary based on individual patient characteristics and available resources [67].

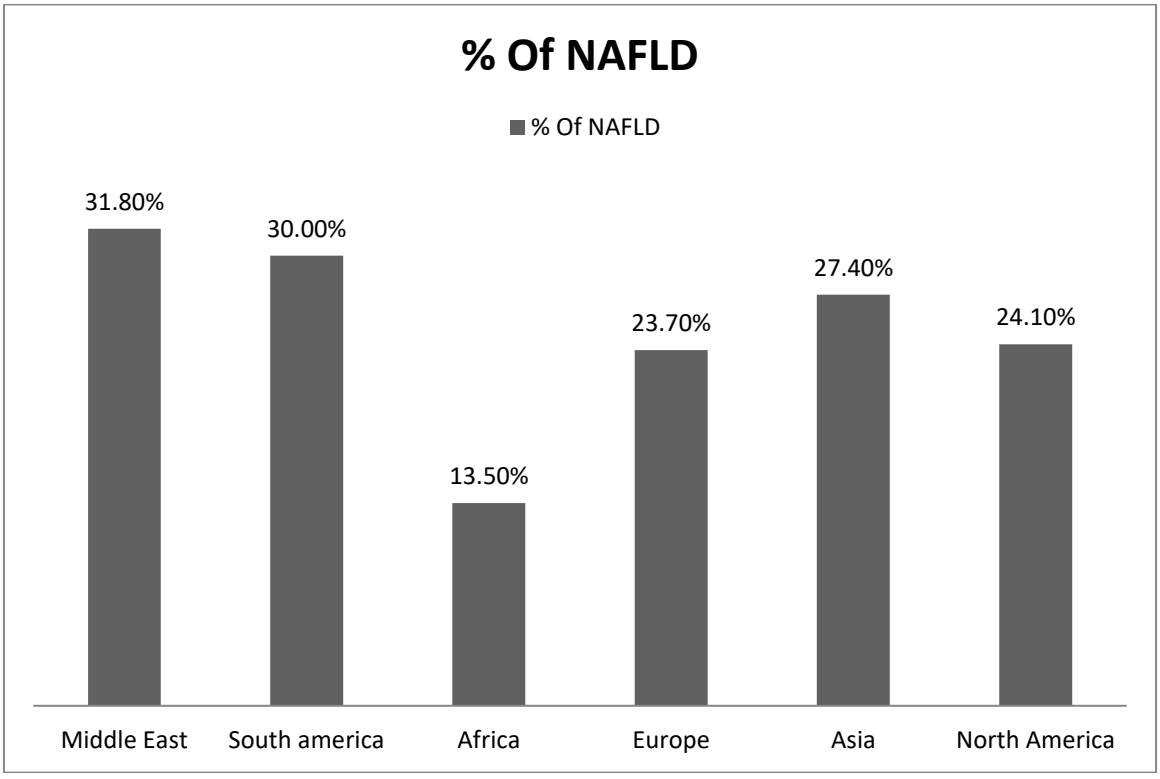

Fig. 6. Epidemiology of NAFLD

7. MANAGEMENT

NAFLD is a prevalent liver condition characterized by an accumulation of fat in the liver cells in individuals who consume little to no alcohol. It encompasses a spectrum of liver disorders, ranging from simple fatty liver (steatosis) to non-alcoholic steatohepatitis (NASH), which involves liver inflammation and can progress to fibrosis, cirrhosis, and even liver failure in severe cases. As the incidence of NAFLD continues to rise globally, the development of effective treatment options becomes increasingly crucial [68, 69].

7.1 Lifestyle Modifications

- **Dietary Changes:** A fundamental aspect of managing NAFLD involves adopting a balanced, healthy diet. This typically includes reducing the intake of sugars, saturated fats, and processed foods while increasing consumption of fruits, vegetables, whole grains, and healthy fats like those found in nuts, avocados, and fish [70].
- **Weight Management:** Weight loss, particularly for individuals who are overweight or obese, is a cornerstone of NAFLD treatment. Gradual weight reduction, typically around 5-10% of body weight, has shown substantial improvements in liver health and can lead to a reduction in liver fat [71].
- **Regular Exercise:** Physical activity plays a pivotal role in NAFLD management. Exercise, along with dietary changes, aids in weight loss and helps improve insulin sensitivity, reducing liver fat and inflammation [72].

7.2 Medications

- **Insulin Sensitizers:** Certain medications, like pioglitazone and metformin, are used off-label to improve insulin sensitivity, manage blood sugar levels, and potentially reduce liver inflammation in NAFLD patients with insulin resistance or diabetes [73, 74].
- **Antioxidants and Cytoprotective Agents:** Vitamin E, due to its antioxidant properties, has been studied in NASH patients and has shown some promise in reducing liver inflammation and fibrosis [75].
- **Lipid-Lowering Medications:** Statins or other lipid-lowering drugs may be prescribed to manage cholesterol levels, which can help in reducing liver fat accumulation [76].

7.3 Clinical Interventions

- **Bariatric Surgery:** For severely obese individuals with NAFLD or NASH, bariatric surgery might be considered in cases where lifestyle changes have not been successful in achieving weight loss. Studies have shown improvements in liver histology following significant weight reduction post-surgery [77, 78].
- **Clinical Trials:** Ongoing research investigates various pharmaceutical agents targeting different pathways involved in NAFLD/NASH pathogenesis. These trials explore new drug classes focusing on liver fat metabolism, inflammation, and fibrosis [79].

7.4 Liver Transplantation

In advanced stages of NAFLD-associated liver disease, such as cirrhosis or liver failure, liver transplantation remains the definitive treatment option. However, due to the rise in NAFLD cases, transplantation resources might face challenges in meeting the demand [80]. The management of NAFLD involves a multidisciplinary approach, integrating lifestyle modifications, medications, and sometimes surgical interventions. Patients should consult with healthcare professionals for personalized treatment plans and ongoing monitoring to mitigate disease progression and reduce the risk of complications. Moreover, early detection and intervention play a vital role in preventing NAFLD from advancing to more severe stages [81].

Non-Alcoholic Fatty Liver Disease (NAFLD) has emerged as a pressing global health concern in recent decades. Characterized by the accumulation of fat in the liver, NAFLD encompasses a spectrum of conditions ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and eventually liver failure. As the prevalence of NAFLD continues to rise worldwide, there is an urgent need for innovative approaches and future perspectives in its treatment.

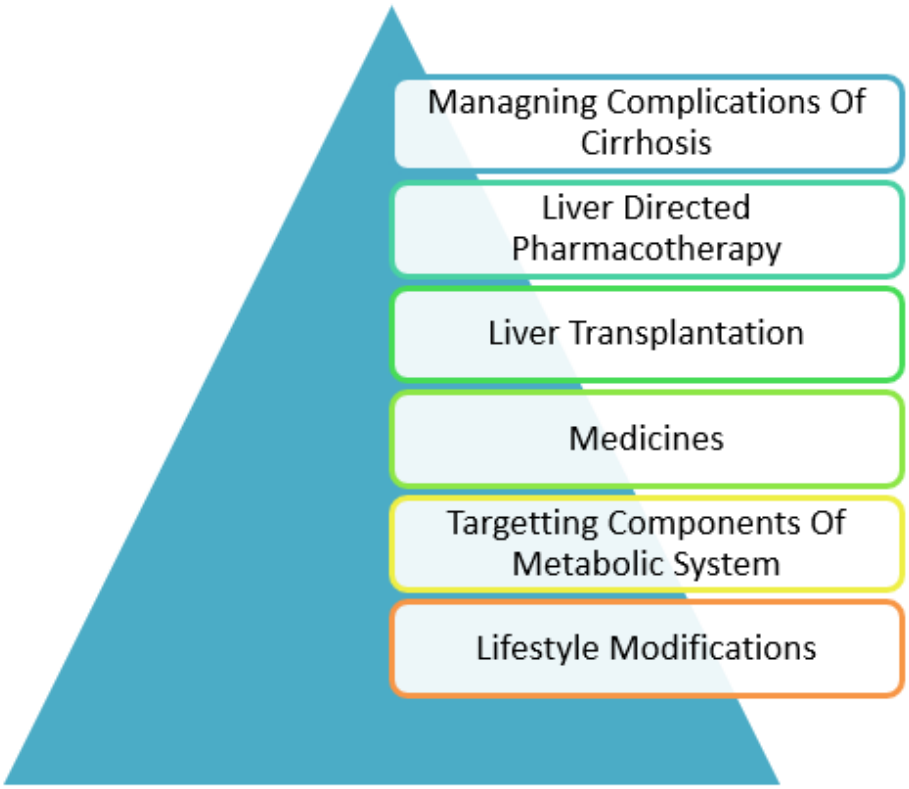

Fig. 7. Management options for NAFLD

8. FUTURE PERSPECTIVES

The current management of NAFLD primarily involves lifestyle modifications such as dietary changes, increased physical activity, and weight loss. However, these measures can be challenging to implement and sustain, and they might not be sufficient for many patients, particularly those with advanced stages of the disease [82]. Research in the field of NAFLD treatment has been dynamic, aiming to address the complexity of the condition. Pharmaceutical companies and researchers are actively investigating various drug targets and compounds that could effectively treat NAFLD and NASH. Some of these drugs focus on reducing liver fat accumulation, inflammation, and fibrosis. Several medications targeting metabolic pathways, such as insulin sensitizers, antioxidants, lipid-lowering agents, and anti-fibrotic drugs, are in different stages of clinical trials. These drugs hold potential for altering the natural course of NAFLD progression [83, 84]. Advancements in genomics and precision medicine offer hope for tailored treatments based on an individual's genetic makeup and disease characteristics. Identifying specific genetic variants associated with NAFLD susceptibility and progression could lead to personalized therapeutic strategies, optimizing treatment efficacy and minimizing adverse effects [85].

Growing evidence suggests a strong association between gut microbiota and NAFLD. Manipulating the gut microbiome through probiotics, prebiotics, or fecal microbiota transplantation shows promise in improving liver health by modulating inflammation, metabolic function, and gut barrier integrity [86, 87]. Innovative approaches involving cellular and gene therapies are being explored to target liver regeneration, repair damaged tissues, and modulate metabolic pathways. Techniques like gene editing and stem cell transplantation hold potential for addressing the underlying molecular mechanisms of NAFLD [88]. Integration of technology and digital health tools, such as mobile applications, wearable devices, and artificial intelligence, can aid in monitoring patients, providing personalized interventions, and promoting adherence to lifestyle modifications and medication regimens [89].

Despite these promising future perspectives, challenges remain in translating these advancements into clinical practice. Rigorous research, ensuring safety and efficacy, regulatory approvals, and accessibility of novel treatments to diverse populations are crucial considerations.

9. CONCLUSIONS

There is a rising occurrence of NAFLD and NASH, which is directly linked to the growing prevalence of obesity and diabetes. NAFLD and NASH are the principal causes responsible for the escalating incidence of hepatocellular carcinoma (HCC), which is the predominant form of liver cancer. Currently, there is no authorized therapy for NAFLD and NASH. Evaluations have been conducted on novel non-invasive diagnostic markers, such as miRNAs, for the prospective diagnosis of NAFLD. Timely detection of the advancement of NAFLD to liver fibrosis, cirrhosis, or HCC is of utmost significance due to the irreversible or challenging reversibility of severe liver disease. PPARs, GLP-1, miRNAs, and KLFs are important molecules that can be targeted for treating metabolic illnesses including NAFLD and NASH. Preclinical investigations and clinical trials have been conducted to assess prospective therapeutic interventions for NAFLD and NASH, such as synbiotics, pan-caspase inhibitors, CCR2/5 antagonists, FXR agonists, and other similar approaches. Utilizing a comprehensive approach, such as integrating medical treatment with physical activity, may have the potential to decrease the duration of treatment and enhance the overall outcome.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Abu-Shanab A, E. Quigley, the role of the gut microbiota in nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol. 2010;7.
2. Ahmed A, Wong RJ, Harrison SA, Nonalcoholic fatty liver disease review: Diagnosis, treatment, and outcomes. Clin Gastroenterol Hepatol. 2015;13.
3. Ajmera V, Belt P. Among patients with nonalcoholic fatty liver disease, modest alcohol use is associated with less improvement in histologic steatosis and steatohepatitis. Clin Gastroenterol Hepatol. 2018;16.
4. Batool S et al. Hepatocellular carcinoma in non-alcoholic fatty liver disease: Emerging burden. International Journal of Oncology. 2022;6:93-104.
5. Angula P, Hui JM, Marchesini G. The nafld fibrosis score: A noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007;45.
6. Angulo P. Obesity and nonalcoholic fatty liver disease. Nutr Rev. 2007;65.
7. Barsh G, Farooqi I, Rahilly SO. Genetics of body-weight regulation. Nature. 2000;404.
8. Bjelakovic G, Nikolova D, Gluud L. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: Systematic review and meta-analysis. JAMA. 2007;297.
9. Chalasani N, Younossi Z, Lavine JE. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the american association for the study of liver diseases. Hepatology. 2018;67.
10. Gawrieh S, Chalasani N. Emerging treatments for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Clin Liver Dis. 2018;22.
11. Kim D, Touros A, Kim WR. Nonalcoholic fatty liver disease and metabolic syndrome. Clin Liver Dis. 2018;22.
12. Tsochatzis EA. natural history of NAFLD: Knowns and unknowns. Nature Reviews Gastroenterology & Hepatology. 2022;19(3):151-152.
13. Loomba R, Lawitz E, Mantry PS. The ask1 inhibitor selonsertib in patients with nonalcoholic steatohepatitis: A randomized, phase 2 trial. Hepatology. 2018;67.
14. Alalwani J et al. The impact of health status, diet and lifestyle on non-alcoholic fatty liver disease: Narrative review. Clinical Obesity. 2022;12(4):e12525.
15. Marengo A, Jouness R, Bugianesi E. Progression and natural history of nonalcoholic fatty liver disease in adults. Clin Liver Dis. 2016;20.

16. Neuschwander-Tetri BA, Loomba R, AJ Sanyal, Farsenoid X. Nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (flint): A multicentre, randomised, placebo-controlled trial. Lancet. 2015;385.
17. Rich NE, Oji S, Mufti AR. Racial and ethnic disparities in nonalcoholic fatty liver disease prevalence, severity, and outcomes in the united states: A systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2017;16.
18. Younossi ZM. et al. Clinical and economic burden of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Clin Liver Dis. 2018;22.
19. Mantovani A, Petracca G, Csermely A, Beatrice G, Bonapace S, Rossi A et al. Non-alcoholic fatty liver disease and risk of new-onset heart failure: An updated meta-analysis of about 11 million individuals. Gut; 2022.
20. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol. 2000;35:569–582.
21. Climent M, Viggiani G, Chen YW, Coulis G, Castaldi A. microrna and ros crosstalk in cardiac and pulmonary diseases. Int J Mol Sci. 2020; 21.
22. Zhao Y, Wang Z. impact of trimethylamine n-oxide (TMAO) metaorganismal pathway on cardiovascular disease. J Lab Precis Med. 2020;5.
23. Roderburg C, Kostev K, Mertens A, Luedde T, Loosen SH. Non-alcoholic fatty liver disease (NAFLD) is associated with an increased incidence of extrahepatic cancer; 2022.
24. Adams LA et al. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut. 2017;66.
25. Afolabi PR et al. The characterisation of hepatic mitochondrial function in patients with non-alcoholic fatty liver disease (NAFLD) using the (13)c-ketoisocaproate breath test. J Breath Res. 2018;12.
26. Anstee QM et al. Risk of cardiomyopathy and cardiac arrhythmias in patients with nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol. 2018;15.
27. Aung LHH et al. Therapeutic potential and recent advances on targeting mitochondrial dynamics in cardiac hypertrophy: A concise review. Mol Ther Nucleic Acids. 2021;25.
28. Borges-Canha M et al. Association between nonalcoholic fatty liver disease and cardiac function and structure-a meta-analysis. Endocrine 2019;66.
29. Brown E et al. SGLT2 Inhibitors and glp-1 receptor agonists: Established and emerging indications. Lancet. 2021; 398.
30. Byrne CD, Targher G. Non-alcoholic fatty liver disease-related risk of cardiovascular disease and other cardiac complications. Diabetes Obes Metab. 2022;24.
31. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD) Metabolism. 2016;65(8):1038-1048.
32. Carlsson B et al. Review article: the emerging role of genetics in precision medicine for patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2020;51.
33. Chiu LS et al. The association of non-alcoholic fatty liver disease and cardiac structure and function-framingham heart study. Liver Int. 2020;40.
34. Dulai PS et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology. 2017;65.
35. Dunn MA et al. Hepatic steatosis in diabetic patients does not predict adverse liver-related or cardiovascular outcomes. Liver Int. 2013;33.
36. Eslam M et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol. 2020;73.
37. Estes C et al. Modeling NAFLD disease burden in china, france, germany, italy, japan, spain, united kingdom, and united states for the period. J Hepatol. 2018;69:2016–2030.
38. Houghton D et al. The degree of hepatic steatosis associates with impaired cardiac and autonomic function. J Hepatol. 2019;70.
39. Huber Y et al. Health-related quality of life in nonalcoholic fatty liver disease associates with hepatic inflammation. Clin Gastroenterol Hepatol. 2019;17.
40. Jacob JS, Ahmed A,. Cholankeril G. The impact of alteration in gut microbiome in the pathogenesis of nonalcoholic fatty liver disease. Curr Opin Infect Dis. 2021;34.

41. Jennison E, Byrne CD.The role of the gut microbiome and diet in the pathogenesis of non-alcoholic fatty liver disease. Clin Mol Hepatol. 2021;27.
42. Labenz C et al. Impact of non-alcoholic fatty liver disease on metabolic comorbidities in type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes. 2022;130.
43. Lan Y et al. Outcomes of subjects who are lean, overweight or obese with nonalcoholic fatty liver disease: A cohort study in china. Hepatol Commun. 2022;6.
44. Li W et al. Association between non-alcoholic fatty liver disease and risk of incident heart failure: A meta-analysis of observational studies. Ther Adv Chronic Dis.2022;13.
45. Loosen SH et al. Heart failure and depression: A comparative analysis with different types of cancer. Eur J Prev Cardiol. 2022;29.
46. Mantovani A et al. Risk of heart failure in patients with nonalcoholic fatty liver disease: JACC review topic of the week. J Am Coll Cardiol. 2022;79.
47. Mantovani A, Byrne CD, Targher G. Efficacy of peroxisome proliferator-activated receptor agonists, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors for treatment of non-alcoholic fatty liver disease: A systematic review. Lancet Gastroenterol Hepatol. 2022;7.
48. Mantovani A et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: An updated systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2021;6.
49. Mohamed-Ali V et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J Clin Endocrinol Metab. 1997;82.
50. Moschen AR et al. Anti-inflammatory effects of excessive weight loss: Potent suppression of adipose interleukin 6 and tumour necrosis factor alpha expression. Gut. 2010;59.
51. Patel VB et al. Role of the ace2/angiotensin axis of the renin-angiotensin system in heart failure. Circ Res. 2016;118:1–7
52. Rathmann W et al. Basic characteristics and representativeness of the german disease analyzer database. Int J Clin Pharmacol Ther. 2018;56.
53. Roderburg C et al. Heart failure is associated with an increased incidence of cancer diagnoses. ESC Heart Fail. 2021;8.
54. Romeo S et al. Genetic variation in pnpla3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet. 2008;40.
55. Romero-Gómez M, Zelber-Sagi S, Trenell M. treatment of NAFLD with diet, physical activity and exercise. J Hepatol. 2017;67.
56. Schiattarella GG et al. Gut microbe-generated metabolite trimethylamine-n-oxide as cardiovascular risk biomarker: a systematic review and dose-response meta-analysis. Eur Heart J. 2017;38.
57. Simon TG et al. Non-alcoholic fatty liver disease and incident major adverse cardiovascular events: Results from a nationwide histology cohort. Gut. 2022;71.
58. Sookoian S et al. Genetic variation in transmembrane 6 superfamily member 2 and the risk of nonalcoholic fatty liver disease and histological disease severity. Hepatology. 2015;61.
59. Stahl EP et al. Nonalcoholic fatty liver disease and the heart: Jacc state-of-the-art review. J Am Coll Cardiol. 2019;73.
60. Targher G et al. association between non-alcoholic fatty liver disease and impaired cardiac sympathetic/parasympathetic balance in subjects with and without type 2 diabetes-the cooperative health research in south tyrol (CHRIS)-NAFLD sub-study. Nutr Metab Cardiovasc Dis. 2021;31.
61. Targher G, Tilg H, Byrne CD. Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach. Lancet Gastroenterol Hepatol. 2021;6.
62. VanWagner LB et al. longitudinal association of non-alcoholic fatty liver disease with changes in myocardial structure and function: The CARDIA study. J Am Heart Assoc. 2020;9.
63. Zou B et al. Fatty liver index and development of cardiovascular disease: findings from the uk biobank. Dig Dis Sci. 2021;66.
64. Anstee QM, Day CP. the genetics of NAFLD. Nat Rev Gastroenterol Hepatol. 2013;10.
65. Younossi Z et al. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology. 2019;69.
66. Zhou J et al. Nonalcoholic fatty liver disease and cardiac remodeling risk:

Pathophysiological mechanisms and clinical implications. Hepatology. 2021;74.
67. Araki O et al. Distinct dysregulation of lipid metabolism by unliganded thyroid hormone receptor isoforms. Mol Endocrinol. 2009;23.
68. Armstrong MJ et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (lean): A multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet. 2016;387.
69. Artwohl M et al. Different mechanisms of saturated versus polyunsaturated ffa-induced apoptosis in human endothelial cells. J Lipid Res. 2008;49.
70. Ashraf NU, Sheikh TA. Endoplasmic reticulum stress and oxidative stress in the pathogenesis of non-alcoholic fatty liver disease. Free Radic Res. 2015;49.
71. Asrih M, Jornayvaz FR. Diets and nonalcoholic fatty liver disease: The good and the bad. Clin Nutr. 2014;33.
72. Baar MJB et al. SGLT2 inhibitors in combination therapy: from mechanisms to clinical considerations in type 2 diabetes management. Diabetes Care. 2018;41.
73. Balboa E et al. Mln64 induces mitochondrial dysfunction associated with increased mitochondrial cholesterol content. Redox Biol. 2017;12.
74. Barber MC, Price NT, Travers MT. Structure and regulation of acetyl-coa carboxylase genes of metazoa. Biochim Biophys Acta. 2005;1733.
75. Barbero-Camps E et al. Endoplasmic reticulum stress mediates amyloid beta neurotoxicity via mitochondrial cholesterol trafficking. Am J Pathol. 2014;184.
76. Basaranoglu M, Basaranoglu G, Bugianesi E. Carbohydrate intake and nonalcoholic fatty liver disease: fructose as a weapon of mass destruction. Hepatobiliary Surg Nutr. 2015;4.
77. BasuRay S et al. the PNPLA3 variant associated with fatty liver disease (I148m) accumulates on lipid droplets by evading ubiquitylation. Hepatology. 2017;66.
78. BasuRay S et al. Accumulation of pnpla3 on lipid droplets is the basis of associated hepatic steatosis. Proc Natl Acad Sci U S A. 2019;116.
79. Baumeister SE et al. Impact of fatty liver disease on health care utilization and costs in a general population: A 5-year observation. Gastroenterology. 2008; 134.
80. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: Epidemiology, pathophysiology, and management. JAMA. 2002;287.
81. Bellentani S, Marino M. Epidemiology and natural history of non-alcoholic fatty liver disease (NAFLD). Ann Hepatol. 2009;8.
82. Bellentani S et al. Prevalence of and risk factors for hepatic steatosis in northern italy. Ann Intern Med. 2000;132.
83. Bieghs V et al. Nash and atherosclerosis are two aspects of a shared disease: Central role for macrophages. atherosclerosis. 2012;220.
84. Bieghs V et al. trapping of oxidized LDL in lysosomes of kupffer cells is a trigger for hepatic inflammation. Liver Int. 2013;33.
85. Bijnen M et al. Adipose tissue macrophages induce hepatic neutrophil recruitment and macrophage accumulation in mice. Gut. 2018;67.
86. Bittencourt MS, Cerci RJ. Statin effects on atherosclerotic plaques: Regression or healing? BMC Med. 2015;13.
87. Adams LA et al. Nonalcoholic fatty liver disease increases risk of death among patients with diabetes: A community-based cohort study. Am J Gastroenterol. 2010;105.
88. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol. 2013;10.
89. Wong RJ et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015; 148.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/111013