Non-Alcoholic Fatty Liver Disease (NAFLD) and its Impact on Health: Risk Factors and Management

Tajassum Khan[1,*], Namrah Abid[2], Iffat Khalid[2], Ayesha Sohail[1], Laiba Zahid[3], Zainab Fatima[2], Bisma Zafar[2] and Arooj Binyamin[1]

[1]Department of Epidemiology and Public Health, University of Agriculture, Faisalabad, Pakistan
[2]National Institute of Food Science and Technology, University of Agriculture, Faisalabad, Pakistan
[3]Department of Food, Nutrition and Home Science, University of Agriculture, Faisalabad, Pakistan
*Corresponding author: tajassumkhan0123@gmail.com

Abstract

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver disorders characterized by excessive fat accumulation in the liver, affecting individuals without significant alcohol consumption. It ranges from isolated steatosis (NAFL) to non-alcoholic steatohepatitis (NASH), which may progress to cirrhosis and hepatocellular carcinoma (HCC). NAFLD is closely associated with metabolic syndrome, including obesity, type 2 diabetes, and dyslipidemia, increasing cardiovascular risk. Diagnosis relies on imaging modalities such as ultrasound, MRI, and CT, though liver biopsy remains the gold standard for assessing NASH. Pathogenesis involves insulin resistance, oxidative stress, and inflammatory pathways. Management focuses on lifestyle modifications like weight loss and exercise, which have proven effective in reducing liver fat and improving metabolic health. Pharmacological treatments, including pioglitazone and vitamin E, are reserved for patients with confirmed NASH, while emerging therapies like GLP-1 agonists show promise. Comprehensive management of metabolic risk factors is crucial in mitigating the disease's progression and associated comorbidities. Despite advancements, further research is needed to clarify the natural history of NAFLD and optimize therapeutic strategies.

Keywords: Fatty liver, Liver fibrosis, Cirrhosis, Metabolic syndrome, Insulin resistance, Obesity, Type 2 diabetes, Inflammation

Cite this Article as: Khan T, Abid N, Khalid I, Sohail A, Zahid L, Fatima Z, Zafar B and Binyamin A, 2025. Non-alcoholic fatty liver disease (NAFLD) and its impact on health: risk factors and management. In: Ismael SS, Nisa QU, Nisa ZU and Aziz S (eds), Diseases Across Life: From Humans to Land and Sea. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 257-263. https://doi.org/10.47278/book.HH/2025.187

A Publication of Unique Scientific Publishers

Chapter No: 25-037

Received: 14-Jan-2025
Revised: 15-Apr-2025
Accepted: 18-May-2025

Introduction

The term "non-alcoholic fatty liver disease" (NAFLD) was first introduced by Schaffner in 1986 (Han et al., 2023). It is defined by an excessive accumulation of fat in the liver, often associated with insulin resistance, and is identified histologically when more than 5% of hepatocytes show steatosis (Cobbina & Akhlaghi, 2017). The annual prevalence of NAFLD, based on abdominal ultrasound, is around 48.2 cases per 1,000 persons (range: 13.4–77.7). Using the index of hepatic steatosis, it is approximately 21.1 cases per 1,000 people per year. NAFLD is a histological continuum that starts with isolated steatosis, sometimes referred to as non-alcoholic fatty liver (NAFL), and advances to cirrhosis, hepatocellular carcinoma (HCC), and non-alcoholic steatohepatitis (NASH) (Chang et al., 2016; Kang et al., 2021). Hepatocyte fat buildup, lobular inflammation, and ballooning degeneration of these cells are characteristics of NASH. While NASH was acknowledged as a more severe variant linked to an elevated risk of liver-related problems and mortality from both liver-related and non-liver causes, NAFL was traditionally thought to be a benign illness (Bence & Birnbaum, 2021).The degree of steatosis and the stage of fibrosis can be assessed non-invasively. Ultrasonography is less successful in detecting lower grades of fat accumulation, but it is quite sensitive and specific for diagnosing moderate to severe steatosis (Karanjia et al., 2016). Shear wave and transient elastography are non-invasive methods for determining the stage of fibrosis(Barr et al., 2015). While magnetic resonance elastography (MRE) shows potential for fibrosis assessment, magnetic resonance imaging (MRI) offers precise quantification of steatosis (Ozturk et al., 2023). In contrast, liver biopsy is necessary for a conclusive diagnosis of steatohepatitis due to the necro inflammatory alterations, notably lobular inflammation and ballooning. We still do not fully understand how NAFLD develops naturally. Prior research frequently used small, carefully chosen patient groups with varying follow-up periods those with histologically diagnosed NAFLD who were referred to specialized tertiary care facilities (Neuberger et al., 2020). It is unclear whether the morbidity rates documented in previous research can be general to community-based exercise, where patients may present with milder disease, because there are yet insufficient studies on population-based to determine the long-term prognosis of NAFLD (Benedict & Zhang, 2017). A thorough grasp of NAFLD and its effects on health is the objective of this chapter. It examines the main risk factors that lead to NAFLD, such as genetic predisposition, lifestyle factors, and metabolic abnormalities. In order to decrease the impact of NAFLD on public health, the chapter also covers diagnostic approaches and efficient management strategies, such as pharmaceutical interventions, lifestyle changes, and new therapeutic choices.

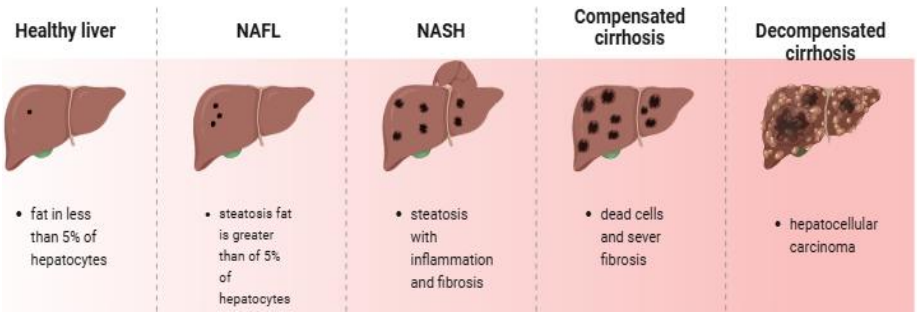

Fig. 1: Non-alcoholic fatty liver disease progresses through several stages. It begins with non-alcoholic fatty liver, marked by the accumulation of fat in otherwise healthy liver cells. Without intervention, NAFL can advance to a more serious condition known as non-alcoholic steatohepatitis, which involves not only fat buildup but also liver inflammation and fibrosis. As NASH progresses, it can lead to cirrhosis and, in severe cases, hepatocellular carcinoma (Guo et al., 2022).

Traditional Definition and Classifications

NASH, NAFL, and NASH-related cirrhosis are all included in the general term non-alcoholic fatty liver disease. The inflammatory subtype of NAFLD, known as NASH, is characterized by inflammation, perhaps accompanied by fibrosis, steatosis, and ballooning of the liver cells (Savari & Mard, 2024). According to the American Association for the Study of Liver Diseases' (AASLD) 2018 guidelines, NAFLD biopsies should be categorized into three severity ratings: NAFL, NAFL with inflammation, and NASH. Although they are not intended for diagnosis, scoring systems like the NAFLD Activity Score (NAS) are used to monitor histological changes in NAFLD, particularly in drug studies. Scores for steatosis, inflammation, and ballooning are added by NAS, which has a range of 0 to 8. Studies have demonstrated that NAS levels (e.g., NAS ≥5) can misclassify patients even though they potentially correlate with NASH. NAS should therefore be utilized with caution and not just as a diagnostic tool (Chalasani et al., 2018).

Non-alcoholic fatty liver (simple steatosis)

The hallmark of NAFL is hepatocellular steatosis, or the buildup of fat in the liver cells; a steatosis level of more than 5% is necessary for diagnosis. It may be micro vesicular or macro vesicular, which is typical in NAFLD (Benedict & Zhang, 2017). Once thought to be benign, NAFL is now thought to have the potential to advance, with fibrosis occurring in about 25% of cases. Nearly 64% of patients with simple steatosis may develop NASH within a few years, according to studies. Inflammation and fibrosis are frequently correlated with the severity of steatosis. Even in simple situations, follow-up is advised because fibrosis development is seen in about 30–40% of NAFL patients (Friedman et al., 2018). For individuals without metabolic concerns, the European Association for the Study of the Liver (EASL) recommends monitoring for two to three years. Although there is disagreement over surveillance for higher-risk NAFL patients, risk factors for advancement include diabetes, high blood pressure, low AST/ALT ratio, and liver damage from alcohol, toxins or other disorders (Thursz et al., 2018).

Non-alcoholic steatohepatitis without fibrosis

Chronic liver inflammation is a feature of NASH, which was first detected in 1980. It is thought to be very varied, particularly depending on the presence of fibrosis. Although histological diagnosis is uncommon, hepatocellular ballooning, lobular inflammation, and steatosis must be confirmed by biopsy in order to diagnose NASH, which makes estimating prevalence challenging. Older age, Hispanic ethnicity, and metabolic illnesses (such as diabetes, obesity, and hypertension) are risk factors for progression. NAS, Fibrosis-4 index, APRI, ELF panel, and elastography procedures are examples of diagnostic instruments (Pu et al., 2024).

Non-alcoholic steatohepatitis with fibrosis

Fibrosis usually starts as perisinusoidal or pericellular fibrosis in zone 3 of NASH and develops into more complex forms such as portal, periportal, bridging fibrosis, and ultimately cirrhosis (Takahashi & Fukusato, 2014). Hepatic decompensation, HCC, and liver-related mortality are among the severe liver outcomes that are closely associated with advanced fibrosis, and the risks rise with the severity of the fibrosis. According to observational research, fibrosis is a significant predictor of NAFLD patients' overall and liver-specific death (Xu et al., 2016). A systematic review of 4,428 patients with biopsy-confirmed NAFLD, including 2,875 with NASH, revealed that as fibrosis progressed, there was an increase in mortality and liver-related events (Tong et al., 2022). Greater fibrosis stages were associated with greater mortality rates, according to another study. For example, early fibrosis (F0–F2) had 0.32 fatalities per 100 person-years, while advanced fibrosis (F4) had 1.76. Therefore, fibrosis reduction is the main goal of clinical studies for NASH therapy (Brennan et al., 2023).

NASH-related cirrhosis

NASH can develop into "burn-out" NASH, when steatosis and inflammation are no longer visible, in cases of severe fibrosis or cirrhosis. This could result in a diagnosis of cryptogenic cirrhosis. Visible histological indicators of NASH are usually absent in NASH-related cirrhosis, which is frequently macro nodular (Ota et al., 2022). Patients with cryptogenic cirrhosis frequently have recurrence of these illnesses after liver transplantation, and they share demographic characteristics with those with NASH-cirrhosis, such as high rates of obesity and metabolic risk factors. The existence of cirrhosis complications, the elimination of other causes, and cirrhosis risk factors are necessary for the diagnosis of NASH cirrhosis. Women over 50 who suffer from obesity, diabetes, or dyslipidemia make up the majority of NASH-cirrhosis patients (Ota et al., 2022). Compared to cirrhosis caused by hepatitis C, advanced NASH fibrosis has a decreased incidence of HCC and liver-related comorbidities, and its 10-year survival rate is 81.5%. Patients with NASH-cirrhosis are more likely to develop diabetes and chronic renal disease, and as metabolic risk factors become more common, the number of liver transplants associated to NASH is increasing (Heyens et al., 2021).

PATHOPHYSIOLOGY OF NAFLD/NASH

The process by which NASH develops is intricate and poorly understood. The pathogenesis of NAFLD and NASH has been extensively studied in recent years using animals, mostly focusing on the variations in dietary models (high fructose, high fat, or methionine/choline deficient diet (MCD)) (Erbas et al., 2018). NASH development has been proposed to be a two-step process based on this body of research. Deposition of fat in the liver is the initial stage of this process, which will raise insulin resistance. This process's second phase consists of cellular and molecular changes carried on by oxidative stress and the oxidation of fatty acids in the liver as a result of several causes, including cytokine damage, hyperinsulinemia, hepatic iron and/or lipid peroxidation, extracellular matrix variation, energy homeostasis, and immune system dysfunction (Berardo et al., 2020). Insulin resistance develops through a complex mechanism. Increased fat mass and adipocyte differentiation are important factors in the development of insulin resistance in the context of MS, as is the situation for many NASH patients. There are two different forms of NAFLD. Insulin resistance is thought to be the main pathophysiological mechanism for the first kind of NAFLD, which has a limited association with metabolic syndrome (Pouwels et al., 2022). Liver steatosis is a possible consequence of viral diseases that are linked to the second kind of NAFLD. HIV and hepatitis C infections may be the cause in this instance, but it is also linked to certain toxins, inherited or acquired metabolic diseases (such as lipodystrophy, cachexia, or intestinal bypass surgery), and medications (total parenteral nutrition, glucocorticoids, tamoxifen, tetracycline, amiodaron, methotrexate, valproic acid, vinyl chloride (S.-H. Lee et al., 2022)

RISK FACTOR

The metabolic syndrome (MS), which includes obesity, type 2 diabetes mellitus (T2DM), and dyslipidaemia all of which are risk factors for cardiovascular disease (CVD) is intimately linked to NAFLD (Hayden, 2023). Regardless of diabetic status, studies show that NAFLD patients have a higher prevalence of CVD, and that altering one's lifestyle can enhance liver health by reducing transaminase levels. NAFLD is associated with a higher incidence of peripheral vascular, cardiac, and cerebrovascular diseases in individuals with type 2 diabetes. The high correlation between NAFLD and CVD is supported by numerous research, confirming that CVD is a major issue for people with NAFLD (C. H. Lee et al., 2022). Although smoking is a known risk factor for non-communicable diseases (NCDs) worldwide, its precise effect on NAFLD differs, therefore the relationship between smoking and NAFLD is still unclear. While there is conflicting evidence regarding whether smoking raises the risk of NAFLD on its own, some research indicates that smoking may exacerbate the severity of liver fibrosis. To fully understand smoking's impact in the development of NAFLD, more research is required (NCD Alliance, 2010).

IMPACT OF NAFLD ON HEALTH

The impact of NAFLD on the course of other liver diseases is a matter of concern. T2DM development is linked to both HCV infection and NAFLD. Together, NAFLD and HCV's impact on T2DM may lead to a vicious cycle of ill health that ultimately raises all-cause mortality as well as cardiovascular and liver-related complications (Hazlehurst et al., 2016). On the other hand, using direct-acting antiviral medications to eradicate HCV and reduce fatty liver may lower the incidence of T2DM and enhance patient outcomes. Additional research is required to validate initial findings (Geddawy et al., 2017). There is a complex link between HBV infection and NAFLD. HBV infection may decrease the progression of fatty liver-associated illness in patients with NAFLD infection. However, fatty liver-induced liver disease worsens after HBV Sero clearance (either naturally or by treatment). Since Sero clearance and NAFLD are both linked to aging, more research is required (Zeng et al., 2020). Lastly, a new NHANES study indicates that metabolic syndrome may make the effects of excessive alcohol consumption on mortality worse. These findings point to a substantial overlap between NAFLD and alcohol-related liver damage. It is significant to note that NAFLD includes patients with cryptogenic cirrhosis in addition to these liver disorders. Recent biopsy results, despite their controversy, indicated that patients with cryptogenic cirrhosis may have worse outcomes even though they are part of the spectrum of NASH (Younossi et al., 2019).

DIAGNOSIS OF NAFLD

Hepatomegaly, lipomatosis, acanthosis nigricans, fatigue, and discomfort in the right upper quadrant are among the symptoms that some NAFLD patients may experience, even if the majority may not exhibit any (Chalasani et al., 2018). End-stage liver disease may also be present in a significant percentage of cirrhosis patients. NASH is commonly detected via medical assessments for other causes, and it might be asymptomatic in 48–100% of cases. Although clinical symptoms of chronic liver failure are rare in this population, one study found that 25% of patients showed splenomegaly at diagnosis. A diagnosis of NASH or NAFLD is often made as a result of irregular liver function tests such as ALT and AST or the inadvertent observation of hepatic steatosis on radiologic abdominal findings (Delvin et al., 2014).

Laboratory findings

Serum indicators such as aminotransferases (AST, ALT) are mildly to increase after laboratory testing. However, patients with NAFLD or associated conditions may have atypical AST and ALT levels. Stated differently, increased or normal AST and ALT values do not indicate the presence of NAFLD (Oh et al., 2017). ALT elevations are more prevalent than AST elevations in NAFLD patients. Compared to ordinary steatosis, NASH typically has higher ALT levels. individuals with NAFLD frequently have raised serum ferritin levels, and 6–11% of individuals have increased transferrin saturation (Pouwels et al., 2022). Clotting factors and alkaline phosphatase (ALP) are other relevant markers. ALP can be abnormal in patients with NAFLD and even raised two to three times the upper limit of its normal value. Furthermore, the diagnosis of NAFLD may benefit from further test results. Patients with chronic progressive illness may have elevated levels of both albumin and bilirubin. Laboratory measurements of clotting times may be abnormal in people with cirrhosis. Patients with cirrhosis typically exhibit thrombocytopenia, a lengthy prothrombin time, and concurrent neutropenia (Pouwels et al., 2022).

Imaging of NAFLD

The diagnosis of liver diseases such as NAFLD and NASH can be supported by a variety of imaging modalities; however, none of them are

commonly used to differentiate between the (histological) subtypes of NAFLD or NASH. Abdominal ultrasonography (US), computed tomography (CT) scans, or MRI can all be used to detect certain liver diseases. NAFLD is considered by imaging abnormalities such as increased echogenicity on ultrasound, decreased hepatic attenuation on CT, and elevated fat signal on MRI (Ajmera & Loomba, 2021).

Ultrasound

Due to diffuse fatty infiltration, US frequently shows a bright liver or a hyperechoic texture. When it comes to identifying increasing fibrosis and steatosis, US has a sensitivity of 89 and a specificity of 93%. Nonetheless, the most widely used modality in clinical practice and the least expensive is the US. Patients that are obese have lower US sensitivity (Petzold, 2022).Steatosis may be indicated by the US displaying hyperechogenic liver tissue in comparison to the spleen or kidney echogenicity. But in these cases, the US's sensitivity is only 60–94% (Khov et al., 2014).

Magnetic resonance spectroscopy (MRS), CT, and MRI

Both imaging techniques can identify steatosis, but they are not sensitive enough to identify inflammatory or fibrotic liver processes. Unfortunately, MRS is (not now) generally available and has a higher sensitivity to identify the previously stated disease processes. The sensitivity of CT, MRI, and MRS to identify hepatic steatosis was 33, 50, and 88%, respectively. The three had respective specificities of 100, 83, and 63% for detecting hepatic steatosis (S. S. Lee & Park, 2014).

MANAGEMENT STRATEGIES FOR NAFLD

Pharmacological treatments, if there is evidence of severe fibrosis or NASH, and dietary and lifestyle modifications for weight loss are all part of the current care of NAFLD (Lange et al., 2021).

Lifestyle and diet modification

Poor dietary habits (high consumption of sugar, soft drinks, meat, and saturated fats, and low intake of fiber, omega-3s, and vitamins) and inactivity are common characteristics of the unhealthy lifestyles of patients with NAFLD (Ratziu et al., 2015). Even little weight loss can improve insulin resistance and dramatically lower liver fat. Few randomized controlled trials (RCTs) have been done on the effectiveness of food and lifestyle changes, and complex therapies involving several specialists are frequently not feasible for normal care (Petersen et al., 2005). Histological improvement in NASH has been seen with a 7% weight loss, and calorie restriction is crucial for both liver function and weight management. Because of its good fats, the Mediterranean diet may help with insulin resistance and liver fat even if it doesn't result in weight loss (Chalasani et al., 2018). By reducing inflammation, bariatric surgery can eliminate or lessen NASH and fibrosis in obese people, even if it is not a first-line treatment for NASH. In addition to lowering the risk of T2DM, hypertension, and liver fat, physical activity also lowers mortality and improves general health by reducing sedentary time. It can be difficult to stick to lifestyle changes over the long term, therefore for long-lasting effects, a combination of calorie restriction and exercise with reasonable goals is advised (Cardoso et al., 2021)

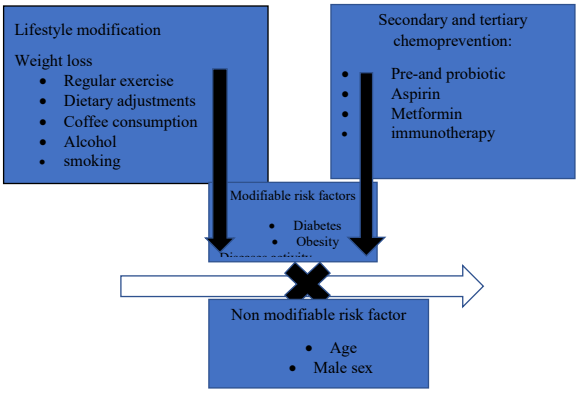

Fig. 2: The progress of risk factors of HCC in NAFLD have been identified, both controllable and non-modifiable. Modifiable risk factors may be the focus of chemoprevention and lifestyle measures. NAFLD stands for non-alcoholic fatty liver disease; HCC stands for hepatocellular cancer (Lange et al., 2021).

Pharmaceutical treatments

According to the American guidelines, only patients with biopsy-confirmed NASH should be treated when determining which NAFLD patients should receive medical attention. Current experimental medications (such as metformin, omega-3 fatty acids, and pentoxifylline) have conflicting effects and need more research (Leoni et al., 2018). The primary therapeutic groups and new developments consist of:

Insulin Sensitizers: The most researched is pioglitazone, which improves NASH by lowering inflammation, steatosis, and cell damage, albeit the effects fade when treatment is stopped. Risks like weight gain and cardiovascular consequences raise questions about its long-term safety (Ratziu et al., 2015).

Vitamin E: Although it has long-term hazards (such as hemorrhagic stroke and prostate cancer), vitamin E helps lessen inflammation and steatosis in non-diabetic people with biopsy-proven NASH. Vitamin E and pioglitazone have no effect on fibrosis, which is important because severe fibrosis raises the chance of death (El Hadi et al., 2018).

Obeticholic Acid: Reduces liver fibrosis, inflammation, and fat synthesis via activating the FXR receptor. According to recent research, it raises LDL cholesterol levels, which may raise cardiovascular concerns, but it improves all NASH histological characteristics. Early studies have demonstrated that ligarglutide, a GLP-1 agonist that increases insulin secretion and decreases glucose synthesis, can cure NASH. With few adverse effects on the gastrointestinal tract, it also promotes metabolic health and weight loss (Goto et al., 2018).

Control of underlying risk factors for metabolism

Treatment of related metabolic risk factors, including diabetes, hypertension, and dyslipidemia, is necessary for all individuals with NAFLD. Patients with T2DM with NAFLD may be treated with insulin, GLP-1 agonists, metformin, pioglitazone, or sulfonylureas (Jeong et al., 2024). In addition to reducing hypertension, antihypertensive drugs can also help when renin-angiotensin-aldosterone system blockers,

especially sartans, are taken. In the population with NAFLD, statins are safe to use. Apart from their positive impact on dyslipidemia, they also enhance liver function and lower the incidence of HCC (Dyson et al., 2015).

Conclusion

The spectrum of NAFLD, a common metabolic liver disease, ranges from benign steatosis to severe cirrhosis and fibrosis. Metabolic comorbidities, such as obesity, insulin resistance, and cardiovascular disease, play a major role in its progression. Smoking and virus infections can also make it worse. Disease progression can be slowed down and quality of life enhanced with early diagnosis and focused intervention, mostly through lifestyle changes and new pharmaceutical treatments. There may be more extensive and efficient treatment options available with novel therapeutic drugs that target fibrosis and metabolic health. To better understand the natural history of NAFLD and improve care strategies for long-term patient safety and health, more extensive, population-based research is necessary.

References

Ajmera, V., & Loomba, R. (2021). Imaging biomarkers of NAFLD, NASH, and fibrosis. *Molecular Metabolism*, *50(4)*, 101167. https://doi.org/10.1016/j.molmet.2021.101167

Barr, R. G., Ferraioli, G., Palmeri, M. L., Goodman, Z. D., Garcia-Tsao, G., Rubin, J., Garra, B., Myers, R. P., Wilson, S. R., Rubens, D., & Levine, D. (2015). Elastography Ultrasound. *Radiology Md (B.G.); Departments of Hepatology (R.P.M.) and Radiology*, *273*(3), 1–17. https://doi.org/10.1148/radiol.2015150619

Bence, K. K., & Birnbaum, M. J. (2021). Metabolic drivers of non-alcoholic fatty liver disease. *Molecular Metabolism*, *50*(12), 101143. https://doi.org/10.1016/j.molmet.2020.101143

Benedict, M., & Zhang, X. (2017). Non-alcoholic fatty liver disease: An expanded review. *World Journal of Hepatology*, *9*(16), 715–732. https://doi.org/10.4254/wjh.v9.i16.715

Berardo, C., Di Pasqua, L. G., Cagna, M., Richelmi, P., Vairetti, M., & Ferrigno, A. (2020). Nonalcoholic fatty liver disease and non-alcoholic steatohepatitis: Current issues and future perspectives in preclinical and clinical research. *International Journal of Molecular Sciences*, *21*(24), 9646. https://doi.org/10.3390/ijms21249646

Brennan, P. N., Elsharkawy, A. M., Kendall, T. J., Loomba, R., Mann, D. A., & Fallowfield, J. A. (2023). Antifibrotic therapy in nonalcoholic steatohepatitis: time for a human-centric approach. *Nature Reviews Gastroenterology and Hepatology*, *20*(10), 679–688. https://doi.org/10.1038/s41575-023-00796-x

Cardoso, A. C., de Figueiredo-Mendes, C., & A. Villela-Nogueira, C. (2021). Current management of NAFLD/NASH. *Liver International*, *41*(1), 89–94. https://doi.org/10.1111/liv.14869

Chalasani, N., Younossi, Z., Lavine, J. E., Charlton, M., Cusi, K., Rinella, M., Harrison, S. A., Brunt, E. M., & Sanyal, A. J. (2018). The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*, *67*(1), 328–357. https://doi.org/10.1002/hep.29367

Chang, Y., Jung, H. S., Cho, J., Zhang, Y., Yun, K. E., Lazo, M., Pastor-Barriuso, R., Ahn, J., Kim, C. W., Rampal, S., Cainzos-Achirica, M., Zhao, D., Chung, E. C., Shin, H., Guallar, E., & Ryu, S. (2016). Metabolically healthy obesity and the development of nonalcoholic fatty liver disease. *American Journal of Gastroenterology*, *111*(8), 1133–1140. https://doi.org/10.1038/ajg.2016.178

Cobbina, E., & Akhlaghi, F. (2017). Non-alcoholic fatty liver disease (NAFLD) - pathogenesis, classification, and effect on drug metabolizing enzymes and transporters. *Drug Metabolism Reviews*, *49*(2), 197–211. https://doi.org/10.1080/03602532.2017.1293683

Delvin, E., Patey, N., Dubois, J., Henderson, M., & Lévy, É. (2014). Pediatric non-alcoholic fatty liver disease. *Journal of Medical Biochemistry ,34* (1),10-12. https://doi.org/10.2478/jomb-2014-0059

Dyson, J. K., Anstee, Q. M., & McPherson, S. (2015). Non-alcoholic fatty liver disease: A practical approach to treatment. *Postgraduate Medical Journal*, *91*(1072), 92–101. https://doi.org/10.1136/postgradmedj-2013-100404rep

El Hadi, H., Vettor, R., & Rossato, M. (2018). Vitamin E as a treatment for nonalcoholic fatty liver disease: Reality or myth? *Antioxidants*, *7*(1),12-14. https://doi.org/10.3390/antiox7010012

Erbas, O., Erdogan, M. A., Khalilnezhad, A., Gürkan, F. T., Yiğittürk, G., Meral, A., & Taskiran, D. (2018). Neurobehavioral effects of long-term maternal fructose intake in rat offspring. *International Journal of Developmental Neuroscience*, *69*(6), 68–79. https://doi.org/10.1016/j.ijdevneu.2018.07.001

Friedman, S. L., Neuschwander-Tetri, B. A., Rinella, M., & Sanyal, A. J. (2018). Mechanisms of NAFLD development and therapeutic strategies. In *Nature Medicine ,24* (7),6-8. https://doi.org/10.1038/s41591-018-0104-9

Geddawy, A., Ibrahim, Y. F., Elbahie, N. M., & Ibrahim, M. A. (2017). Direct acting anti-hepatitis C virus drugs: Clinical pharmacology and future direction. *Journal of Translational Internal Medicine*, *5*(1), 8–17. https://doi.org/10.1515/jtim-2017-0007

Goto, T., Itoh, M., Suganami, T., Kanai, S., Shirakawa, I., Sakai, T., Asakawa, M., Yoneyama, T., Kai, T., & Ogawa, Y. (2018). Obeticholic acid protects against hepatocyte death and liver fibrosis in a murine model of nonalcoholic steatohepatitis. *Scientific Reports*, *8*(1), 1–13. https://doi.org/10.1038/s41598-018-26383-8

Guo, X., Yin, X., Liu, Z., & Wang, J. (2022). Non-Alcoholic Fatty Liver Disease (NAFLD) Pathogenesis and Natural Products for Prevention and Treatment. *International Journal of Molecular Sciences*, *23*(24), 2-3. https://doi.org/10.3390/ijms232415489

Han, S. K., Baik, S. K., & Kim, M. Y. (2023). Non-alcoholic fatty liver disease: Definition and subtypes. *Clinical and Molecular Hepatology*, *29*(3), 8-9. https://doi.org/10.3350/cmh.2022.0424

Hayden, M. R. (2023). Overview and New Insights into the Metabolic Syndrome: Risk Factors and Emerging Variables in the Development of Type 2 Diabetes and Cerebrocardiovascular Disease. *Medicina (Lithuania)*, *59*(3), 24-28. https://doi.org/10.3390/medicina59030561

Hazlehurst, J. M., Woods, C., Marjot, T., Cobbold, J. F., & Tomlinson, J. W. (2016). Non-alcoholic fatty liver disease and diabetes. *Metabolism:*

Clinical and Experimental, *65*(8), 1096–1108. https://doi.org/10.1016/j.metabol.2016.01.001

Heyens, L. J. M., Busschots, D., Koek, G. H., Robaeys, G., & Francque, S. (2021). Liver Fibrosis in Non-alcoholic Fatty Liver Disease: From Liver Biopsy to Non-invasive Biomarkers in Diagnosis and Treatment. *Frontiers in Medicine*, *8*(6), 1–20. https://doi.org/10.3389/fmed.2021.615978

Jeong, D., Wong, S., Karim, M. E., Manges, A. R., Makuza, J. D., Bartlett, S. R., Velásquez García, H. A., Luster, D., Adu, P. A., Binka, M., Yu, A., Krajden, M., & Janjua, N. Z. (2024). Treatment of HCV with direct-acting antivirals on reducing mortality related to extrahepatic manifestations: a large population-based study in British Columbia, Canada. *The Lancet Regional Health - Americas*, *29(2)*, 1–13. https://doi.org/10.1016/j.lana.2023.100658

Kang, S. H., Lee, H. W., Yoo, J., Cho, Y., Kim, S. U., Lee, T. H., & Jang, B. K. (2021). KASL clinical practice guidelines : Management of non-alcoholic fatty liver disease. *Clinical and Molecular Hepatology,* 27(3), 363–401.

Karanjia, R. N., Crossey, M. M. E., Cox, I. J., Fye, H. K. S., Njie, R., Goldin, R. D., & Taylor-Robinson, S. D. (2016). Hepatic steatosis and fibrosis: Non-invasive assessment. *World Journal of Gastroenterology*, *22*(45), 9880–9897. https://doi.org/10.3748/wjg.v22.i45.9880

Khov, N., Sharma, A., & Riley, T. R. (2014). Bedside ultrasound in the diagnosis of nonalcoholic fatty liver disease. *World Journal of Gastroenterology*, *20*(22), 6821–6825. https://doi.org/10.3748/wjg.v20.i22.6821

Lange, N. F., Radu, P., & Dufour, J. F. (2021). Prevention of NAFLD-associated HCC: Role of lifestyle and chemoprevention. *Journal of Hepatology*, *75*(5), 1217–1227. https://doi.org/10.1016/j.jhep.2021.07.025

Lee, C. H., Lui, D. T. W., & Lam, K. S. L. (2022). Non-alcoholic fatty liver disease and type 2 diabetes: An update. *Journal of Diabetes Investigation*, *13*(6), 930–940. https://doi.org/10.1111/jdi.13756

Lee, S.-H., Park, S.-Y., & Choi, C. S. (2022). Insulin Resistance: From Mechanisms to Therapeutic Strategies. *Diabetes & Metabolism Journal*, *46*(1), 15–37. https://doi.org/10.4093/dmj.2021.0280

Lee, S. S., & Park, S. H. (2014). Radiologic evaluation of nonalcoholic fatty liver disease. *World Journal of Gastroenterology*, *20*(23), 7392–7402. https://doi.org/10.3748/wjg.v20.i23.7392

Leoni, S., Tovoli, F., Napoli, L., Serio, I., Ferri, S., & Bolondi, L. (2018). Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis. *World Journal of Gastroenterology*, *24*(30), 3361–3373. https://doi.org/10.3748/wjg.v24.i30.3361

Neuberger, J., Patel, J., Caldwell, H., Davies, S., Hebditch, V., Hollywood, C., Hubscher, S., Karkhanis, S., Lester, W., Roslund, N., West, R., Wyatt, J. I., & Heydtmann, M. (2020). Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology. *Gut*, *69*(8), 1382–1403. https://doi.org/10.1136/gutjnl-2020-321299

Oh, R. C., Hustead, T. R., Ali, S. M., & Pantsari, M. W. (2017). Mildly Elevated Liver Transaminase Levels: Causes and Evaluation. *American Family Physician*, *96*(11), 709–715.

Ota, S., Hamada, M., Muramatsu, K. I., Takeuchi, I., & Yanagawa, Y. (2022). Possible Development of Burn-Out Nonalcoholic Steatohepatitis under Long-Term Steroid Use. *Case Reports in Gastroenterology*, *16*(3), 557–562. https://doi.org/10.1159/000526570

Ozturk, A., Olson, M. C., Samir, A. E., & Venkatesh, S. K. (2023). *Liver fibrosis assessment: MR and US Elastography*. *47*(9), 3037–3050. https://doi.org/10.1007/s00261-021-03269-4.Liver

Petersen, K. F., Dufour, S., Befroy, D., Lehrke, M., Hendler, R. E., & Shulman, G. I. (2005). Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. *Diabetes*, *54*(3), 603–608. https://doi.org/10.2337/diabetes.54.3.603

Petzold, G. (2022). Role of Ultrasound Methods for the Assessment of NAFLD. *Journal of Clinical Medicine*, *11*(15), 45-58. https://doi.org/10.3390/jcm11154581

Pouwels, S., Sakran, N., Graham, Y., Leal, A., Pintar, T., Yang, W., Kassir, R., Singhal, R., Mahawar, K., & Ramnarain, D. (2022). Non-alcoholic fatty liver disease (NAFLD): a review of pathophysiology, clinical management and effects of weight loss. *BMC Endocrine Disorders*, *22*(1), 1–9. https://doi.org/10.1186/s12902-022-00980-1

Pu, F., Lin, J., Wei, Y., Li, J., Liao, X., Shi, L., Zeng, X., & Hu, W. (2024). Association of dietary behavior patterns of middle-aged and older adults with their obesity metabolic phenotype: a cross-sectional study. *BMC Public Health*, *24*(1) 43-45. https://doi.org/10.1186/s12889-024-19781-3

Ratziu, V., Goodman, Z., & Sanyal, A. (2015). Current efforts and trends in the treatment of NASH. *Journal of Hepatology*, *62*(1), 65–75. https://doi.org/10.1016/j.jhep.2015.02.041

Savari, F., & Mard, S. A. (2024). Nonalcoholic steatohepatitis: A comprehensive updated review of risk factors, symptoms, and treatment. *Heliyon*, *10*(7), 28468. https://doi.org/10.1016/j.heliyon.2024.e28468

Takahashi, Y., & Fukusato, T. (2014). Histopathology of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *World Journal of Gastroenterology*, *20*(42), 15539–15548. https://doi.org/10.3748/wjg.v20.i42.15539

Thursz, M., Gual, A., Lackner, C., Mathurin, P., Moreno, C., Spahr, L., Sterneck, M., & Cortez-Pinto, H. (2018). EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. *Journal of Hepatology*, *69*(1), 154–181. https://doi.org/10.1016/j.jhep.2018.03.018

Tong, X. fei, Wang, Q. yi, Zhao, X. yan, Sun, Y. meng, Wu, X. ning, Yang, L. ling, Lu, Z. zhao, Ou, X. juan, Jia, J. dong, & You, H. (2022). Histological assessment based on liver biopsy: the value and challenges in NASH drug development. *Acta Pharmacologica Sinica*, *43*(5), 1200–1209. https://doi.org/10.1038/s41401-022-00874-x

Xu, F., Moorman, A. C., Tong, X., Gordon, S. C., Rupp, L. B., Lu, M., Teshale, E. H., Spradling, P. R., Boscarino, J. A., Trinacty, C. M., Schmidt, M. A., & Holmberg, S. D. (2016). All-cause mortality and progression risks to hepatic decompensation and hepatocellular carcinoma in patients infected with Hepatitis C virus. *Clinical Infectious Diseases*, *62*(3), 289–297. https://doi.org/10.1093/cid/civ860

Younossi, Z. M., Stepanova, M., Ong, J., Yilmaz, Y., Duseja, A., Eguchi, Y., El Kassas, M., Castellanos-Fernandez, M., George, J., Jacobson, I. M.,

Bugianesi, E., Wong, V. W. S., Arrese, M., de Ledinghen, V., Romero-Gomez, M., Mendez-Sanchez, N., Ahmed, A., Wong, R., Papatheodoridis, G., … Afendy, A. (2019). Effects of Alcohol Consumption and Metabolic Syndrome on Mortality in Patients With Nonalcoholic and Alcohol-Related Fatty Liver Disease. *Clinical Gastroenterology and Hepatology*, *17*(8), 1625-1633.e1. https://doi.org/10.1016/j.cgh.2018.11.033

Zeng, H., Li, L., Hou, Z., Zhang, Y., Tang, Z., & Liu, S. (2020). Direct-acting antiviral in the treatment of chronic hepatitis c: Bonuses and challenges. *International Journal of Medical Sciences*, *17*(7), 892–902. https://doi.org/10.7150/ijms.43079