CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://zenodo.org/records/10044988

https://www.iajps.com/volumes/volume10-october-2023/11-issue-10-october-23/

Available online at: http://www.iajps.com *Review Article*

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD): A REVIEW OF PATHOPHYSIOLOGY AND CLINICAL MANAGEMENT

Elham Yahya Baamer[1], Zainab Naji Alaithan[2], Abdullah Mohammad Alshumrani[3], Mohammed Hamdan Alwabisi[4], Mohammed Yousef A Alali[5], Aram Faleh Alharbi[5], Haytham Nabil Alhazmi[6], Anan Ali Baamer[7], Abdulmajeed Abed M Aljuaid[8], Ashwaq Fathi Aldossary[9], Rashed Abdullah Bati Alsaeedi[10], Fatimah Ahmed Althubyani[11], Deyala Mohammed Badawi[12], Bayan Mohammed H Alhashidi[12]

[1] National Guard Hospital – Jeddah – Saudi Arabia
[2] King Faisal University-Hufof – Saudi Arabia
[3] King Abdull Aziz General Hospital – Jeddah – Saudi Arabia
[4] King Fahad Hospital -Tabuk – Saudi Arabia
[5] Royal College Of Surgeons - Dublin – Ireland
[6] King Fahad Hospital – Medinah – Saudi Arabia
[7] Health Control Center In King Abdulaziz International Airport – Jeddah– Saudi Arabia
[8] Security Forces Hospital – Makkah – Saudi Arabia
[9] King Fahad Military Medical City – Dhahran – Saudi Arabia
[10] Jeddah University – Jeddah – Saudi Arabia
[11] Alqiblatin Primary Healthcare - Almadinah Almunawara – Saudi Arabia
[12] King Abdulaziz University – Jeddah – Saudi Arabia

Abstract:

Introduction: *The harmful effects of non-alcoholic fatty liver disease (NAFLD) are becoming a significant problem for public health due to the rising incidence of diabetes and obesity worldwide. In the Western world, NAFLD is the most prevalent chronic liver disease. Metabolic problems such as central obesity, dyslipidemia, hypertension, hyperglycemia, and recurrent abnormalities in liver function tests are all intimately related to NAFLD. In general, NAFLD is a term used to describe a wide range of liver diseases, including fibrosis, inflammation, and hepatocyte injury. This is typically detected through a liver biopsy and can take a variety of forms, from lesser forms (steatosis) to more severe forms (cirrhosis, advanced fibrosis, non-alcoholic steatohepatitis, and liver failure). A precise diagnosis of NASH and NAFLD is essential since severe fibrosis is the main indicator of morbidity and liver-related death in these patients. The gold standard for diagnosing NAFLD continues to be histologic assessment with liver biopsy. The presence of hepatic steatosis, ballooning, and lobular inflammation with or without fibrosis is required for the diagnosis of NAFLD. Once the diagnosis is made, the pillars of treatment are still weight loss, dietary changes, and the management of the underlying metabolic syndrome. Once a diagnosis is made, the fundamentals of therapy continue to be dietary advice and lifestyle changes, weight loss, and the treatment of the underlying metabolic syndrome, all of which show promise but are challenging to sustain. Guidelines prescribe pioglitazone and vitamin E in some people.*

Aim of the study: *Clinicians encounter difficulties due to the complexity of NAFLD and related diseases, especially its association with metabolic syndrome. The pathophysiology of NAFLD, risk factors, diagnostic techniques, and conservative and surgical treatment options are all summarised in this review. An overview of NAFLD and available treatments is provided in this review.*

Methodology: *The present review is a comprehensive research of PUBMED since the year 1995 to 2023*

Conclusion: *The management of these patients has grown more challenging due to the expanding obesity pandemic and the increased frequency of concomitant disorders, including T2DM and NAFLD. There are several therapy options; however, there isn't much high-quality research that compares them with one another. Prospective studies addressing the remaining uncertainties regarding the relationship between insulin resistance, fatty liver, and fibrosis progression should be made accessible soon, given the rising popularity of bariatric surgery.*

Keywords: *Non-alcoholic fatty liver disease (NAFLD), obesity, dyslipidemia, hypertension, hyperglycemia, liver failure etc.*

Corresponding author:
Elham Yahya Baamer,
National Guard Hospital – Jeddah – Saudi Arabia

QR code

Please cite this article in Elham Yahya Baamer et al . ***Non-alcoholic fatty liver disease (nafld): A review of pathophysiology and clinical management****, Indo Am. J. P. Sci, 2023; 10 (10).*

INTRODUCTION:

A prominent cause of chronic liver disease globally is non-alcoholic fatty liver disease (NAFLD). Hepatic steatosis, a symptom of NAFLD, occurs when no other reasons for secondary hepatic fat accumulation (such as excessive alcohol use) can be found. Non-alcoholic steatohepatitis (NASH) falls on the extreme end of the severity range between non-alcoholic fatty liver (NAFL), which is a more benign disorder, and NAFLD. Fibrosis and cirrhosis can develop from NAFLD. Hepatic steatosis is present in NAFLD without any signs of inflammation, but it is coupled with lobular inflammation and apoptosis in NASH, which can result in fibrosis and cirrhosis. [1, 2]

NASH was previously regarded as a serious condition with a relatively benign prognosis that mostly affected obese females and was associated with Type 2 Diabetes Mellitus (T2DM) and other risk factors for diabetes, cardiovascular disease, and stroke. With a 25% global prevalence, the incidence of liver disease (NAFLD) has significantly increased in Western nations. In Western industrialized nations, NAFLD is a chronic liver disease that is becoming increasingly prevalent, especially in people who have central obesity, type 2 diabetes, dyslipidemia, and metabolic syndrome. [1, 2]

The US guidelines for NAFLD management describe NAFLD as a no alcohol, drug, or viral-induced steatosis and b) steatosis with 5% fat infiltration in imaging or histology. Elevated liver enzymes may be seen in NAFLD patients. The metabolic syndrome (MS), which includes systemic hypertension, dyslipidemia, insulin resistance, and overt diabetes, is frequently present in patients with NAFLD. Visceral obesity is increasingly being shown to be a risk factor for NAFLD, and it must also be considered well-recognized that Metabolic syndrome increases the chance of developing cardiovascular disease. The pathophysiological pathways relating to cardiovascular disease and NAFLD are not fully known; however, based on current literature, it appears that cardiac and vascular disorders are the major causes of death in these patients.[3]

Insulin resistance is thought to have a role in the pathophysiology of both conditions. Even an experienced practitioner may find it difficult to evaluate abnormal liver enzyme levels in a patient who is otherwise healthy. When blood donors have abnormal liver test findings, NAFLD is frequently at blame. Once other causes of liver illness are ruled out, it identifies an asymptomatic rise of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in up to 90% of cases. According to data from the World Health Organization's Global Health Observatory in 2014, 11% of men and 15% of women worldwide who are 18 years of age or older are obese. According to a study assessing the prevalence of NASH, 5.7-17% of Americans are thought to be affected.[4]

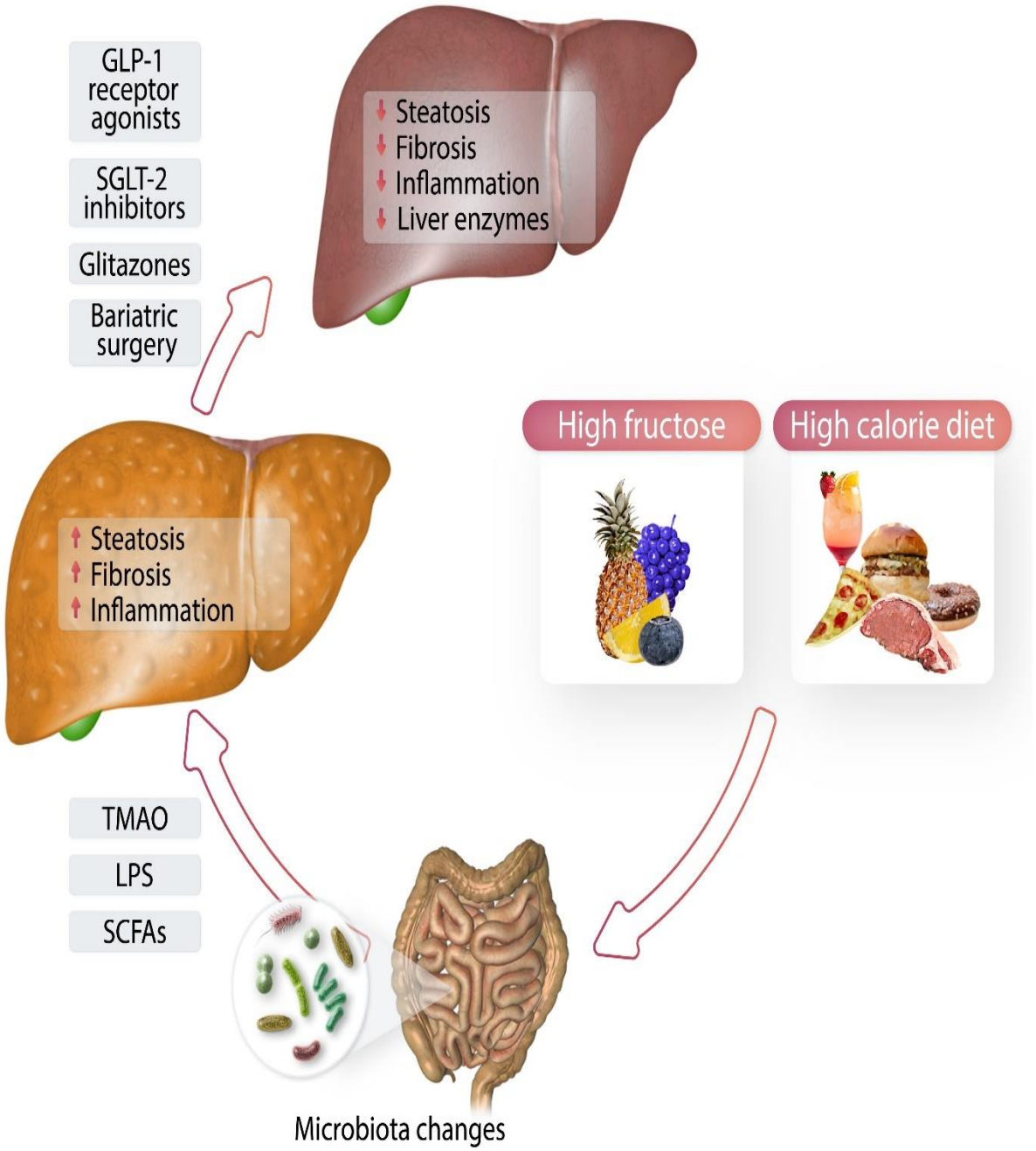

Fig. 1 Depicting overview of NAFLD and Glucagon-like peptide 1 receptor antagonists, sodium-glucose transporter 2 inhibitors, Fibroblast Growth Factor analogs, Farnesoid X receptor agonists, and peroxisome proliferator-activated receptor agonists as some of the most effective therapy options. [5]

Pathophysiology

The clinical spectrum of NAFLD ranges from mild steatosis to cirrhosis as the final stage of liver disease, which serves as an example of the pathophysiology's complexity and heterogeneity. The liver undergoes changes related to metabolism due to a variety of circumstances. Overnutrition can cause dysbiosis in the gastrointestinal tract, and pro-inflammatory responses in the liver can be brought on by the movement of microbial-associated molecular patterns into the systemic circulation through increased permeability of the intestinal barrier and into the liver via the portal vein. However, some dietary elements

can also directly activate illness-related disease processes in liver tissue.[6]

1. Lipotoxicity

The buildup of lipid droplets in hepatocytes is one of the histopathologically distinct characteristics of NAFLD. As a result, it has long been believed that lipids and substances derived from lipids may play a role in the development of disease. Possessing the SNP rs738409, I148M in PNPLA3 increases one's genetic susceptibility to NAFLD development.20 Within the hepatocyte, this protein is near to lipid droplets. The I148m mutation in PNPLA3 results in abnormal fatty acid remodeling in hepatocytes. Additionally, this variant causes a buildup of PNPLA3 on lipid droplets because it is less likely to be degraded via the ubiquitination route than the wild-type protein. [7]

Free cholesterol is another substance that may have lipotoxic effects. Comparing NAFLD patients to lean and obese controls, the expression of 3-hydroxy-3-methylglutaryl (HMG) CoA reductase, the rate-limiting enzyme in cholesterol synthesis, is up-regulated. This up-regulation was followed by a dephosphorylation that increased the activity of the HMG CoA reductase enzyme and the amount of free cholesterol generated.[5,13]

2. Dietary Components Affecting NAFLD

In addition to consuming too many calories and gaining weight repeatedly, fructose has a significant role in the onset and development of NAFLD. In the diet, fructose is obtained from processed foods and sweetened beverages. By improving the substrates for fatty acid synthesis through the actions of aldolase B and ketohexokinase, as well as by activating transcription factors like sterol regulatory element-binding protein 1c (SREBP1c) and others, fructose promotes lipogenesis. The intake of total calories, fat, and carbs was comparable between NAFLD and NASH patients, according to a recent small study involving pediatric and teenage NAFLD patients.[8]

3. Microbiome, the intestine, and NAFLD

Numerous studies have emphasized the significance of dysbiosis in the onset of various stages of liver disease. On the level of phylum, family, genus, and species, these microbial alterations were described. For instance, Ruminococcaceae or Bifidobacteriaceae were described as being decreased in NAFLD patients compared to healthy controls, but Proteobacteria seemed to be increased in NAFLD47.In contrast, Robinsoniella is an example of a genus that is elevated in NAFLD. Faecalibacterium prausnitzii, a relatively anti-inflammatory bacterial strain, is decreased in NAFLD patients.[9,10]

Metabolites produced by bacteria can affect the liver's metabolism and inflammatory responses. When compared to healthy people, NAFLD patients have different feces metabolomic signatures. Short-chain fatty acids (SCFAs), which are dietary components like butyrate, propionate, and acetate, are converted by bacterial enzymes into some metabolically active compounds. These metabolites are bioactive substances that are more prevalent in the stool of NAFLD patients and are primarily bound to G protein-coupled receptors (GPCRs). Trimethylamine-N-oxide (TMAO), which is made in the liver from trimethylamine (TMA), is another dietary metabolite that has been linked to NAFLD and other diseases. Choline, carnitine, and phosphatidylcholine can all be metabolized into TMA by the gut flora.[11,12]

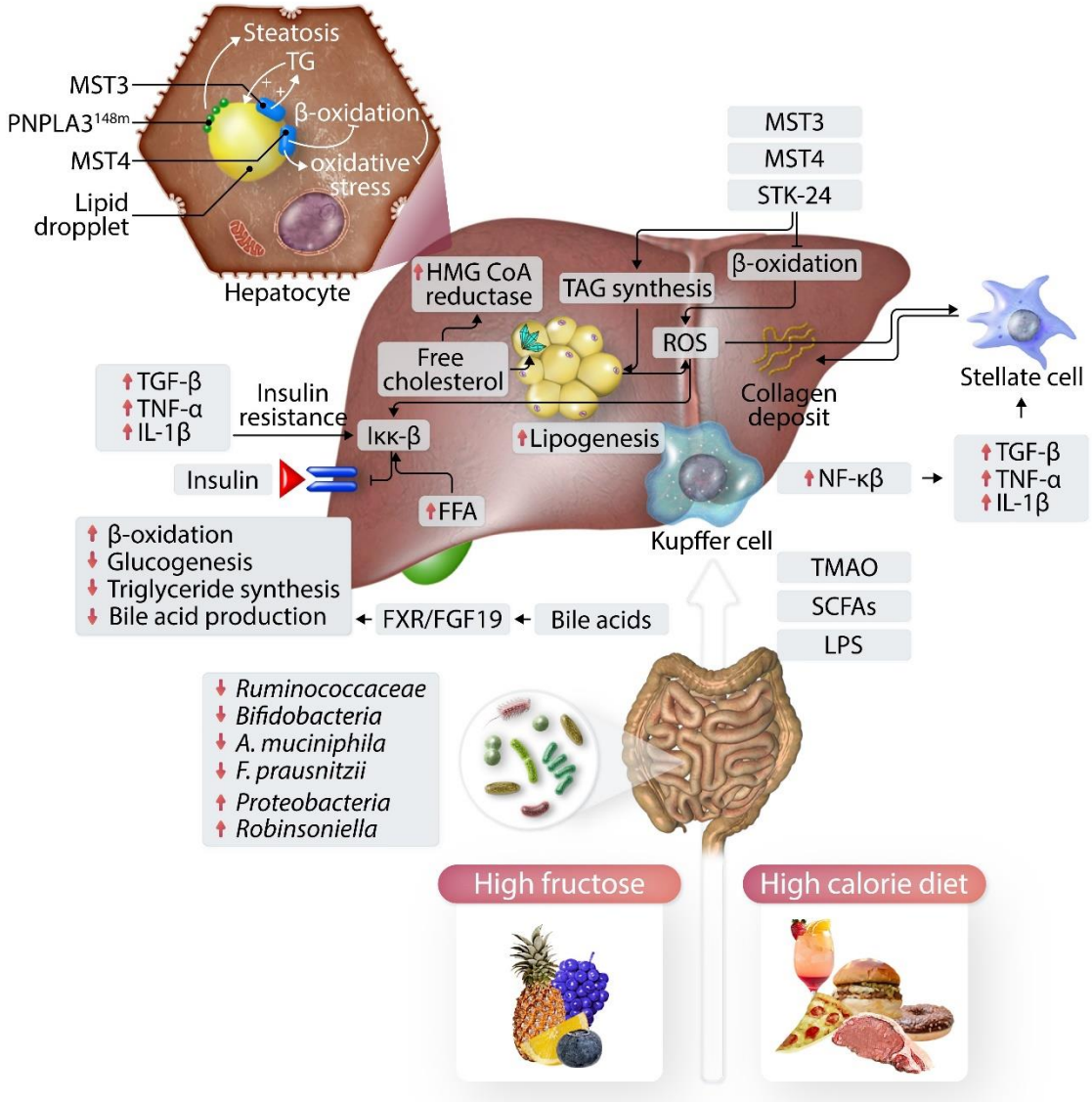

Fig. 2 Non-alcoholic fatty liver disease (NAFLD) has a complex pathophysiology. Diet and dietary components affect the intestinal microbiota and have an impact on steatosis and hepatic inflammation. By modifying IKK-, FFAs, reactive oxygen species (ROS), and low-grade inflammation influence insulin resistance. Elevated amounts of free cholesterol and lipogenesis aggravate cellular stress (lipotoxicity) further. LPS stimulates the production of pro-inflammatory cytokines by hepatic Kupffer cells. The gut bacteria metabolises components of the diet to produce SCFAs and TMAO. When several mechanisms work together to cause inflammation (such as the release of pro-inflammatory cytokines), stellate cells are activated to generate collagen and cause fibrogenesis. Mammalian sterile 3 and 4, similar to 20; NF-B, Reactive oxygen species, short chain fatty acids, triacylglycerol, nuclear factor of activated B cells, SCFA, transforming growth factor beta; Trimethylamine-N-oxide and tumour necrosis factor alpha are the two terms used.[5]

Risk Factors

NAFLD patients typically exhibit MS-like traits along with the cardiovascular disease risk factors that go along with it. As previously mentioned, NAFLD and metabolic syndrome are closely associated, and obesity, type 2 diabetes (T2DM), and dyslipidemia are thought to be significant risk factors for NAFLD. Studies have indicated that patients with NAFLD, both with and without diabetes, have a higher frequency of cardiovascular disease (CVD). As a result, NAFLD is typically linked to an unhealthy lifestyle, and there is evidence that making changes to an unhealthy lifestyle can lower transaminase levels and improve NAFLD. Patients with T2DM discovered that participants with

NAFLD had higher rates of peripheral vascular, coronary, and cerebrovascular disorders than those without, as well as higher rates of peripheral vascular, cerebrovascular, and heart disease.[14]

Management

Signs and Symptoms

Acanthosis nigricans, hepatomegaly, fatigue, and lipomatosis are some of the symptoms that NAFLD patients may report. The majority of NAFLD patients may not experience any symptoms. End-stage liver disease can manifest in a sizable portion of cirrhosis patients. It can be asymptomatic in about 48–100% of cases, and it is frequently found during examinations by clinicians for other conditions. Rarely do individuals with chronic liver failure present with splenomegaly at the time of diagnosis. Abnormal liver function tests, such as aminotransferases (ALT and AST), or the accidental discovery of hepatic steatosis on radiologic abdominal abnormalities very frequently rule out a diagnosis. During a physical examination, hepatomegaly may be seen, which is due to fatty liver infiltration.[15]

Laboratory Findings

Serum indicators, including aminotransferases (AST, ALT), are mild to moderately increased during laboratory tests. However, in patients with NAFLD or other associated disorders, the AST and ALT levels can vary. To put it another way, both increased and normal AST and ALT levels do not always indicate the presence of NAFLD. ALT elevations are more typical in NAFLD patients than AST elevations. In comparison to ordinary steatosis, NASH typically has higher ALT levels. Patients with NAFLD frequently have raised blood ferritin levels, and 6–11% of them also have enhanced transferrin saturation.[16]

Alkaline phosphatase (ALP) and coagulation factors are additional interesting markers. ALP can be abnormal and even 2-3 times the upper limit of its normal range in NAFLD patients. Additional test results may also be useful in the diagnosis of NAFLD. Patients with chronic progressive diseases may have high amounts of both albumin and bilirubin. Laboratory assessments of clotting times may be abnormal in cirrhotic patients. The majority of the time, individuals with cirrhosis also have concurrent neutropenia, thrombocytopenia, and a protracted prothrombin time. [17]

Imaging

Various imaging techniques can be utilized to diagnose liver diseases, including NAFLD. Ultrasounds, magnetic resonance imaging (MRI), or computed tomography (CT) scans can detect certain liver conditions. Enhanced ultrasonic echogenicity, reduced hepatic attenuation on CT, and enhanced fat signal on MRI are all imaging findings in NAFLD patients.

1. Ultrasound (US)

   Because of the widespread fatty infiltration, the US frequently reveals a hyperechoic texture or a brilliant liver. When it comes to identifying increasing fibrosis and steatosis, the US has a sensitivity and specificity of 89 and 93%, respectively. However, the US is the most affordable approach and has been the modality utilized in clinical practice the most frequently. Patients who are obese have lower US sensitivity. Steatosis is suggested by the Ultrasound showing hyperechogenic liver tissue. However, the US is only 60-94% sensitive in these situations.[18]

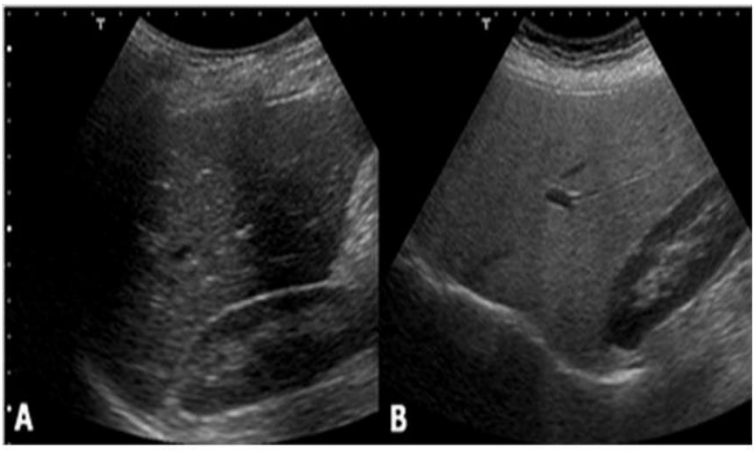

Fig. 3 Ultrasound imaged with no difference in (A) cortex echogenicity of the liver and kidney while (B) kidney parenchyma compared with hyperechoic liver. [19]

2. CT, MRI, and Magnetic resonance spectroscopy (MRS)
   Although both imaging techniques are capable of detecting steatosis, they are not sensitive enough to identify hepatic inflammatory or fibrotic processes. Unfortunately, despite the fact that MRS has a higher sensitivity to identify the disease processes already discussed, it is (not yet) commonly used. Generally speaking, the sensitivity of CT, MRI, and MRS to identify hepatic steatosis was 33, 50, and 88%, respectively. The three tests' relative specificities for detecting hepatic steatosis were 100, 83, and 63%. [20]

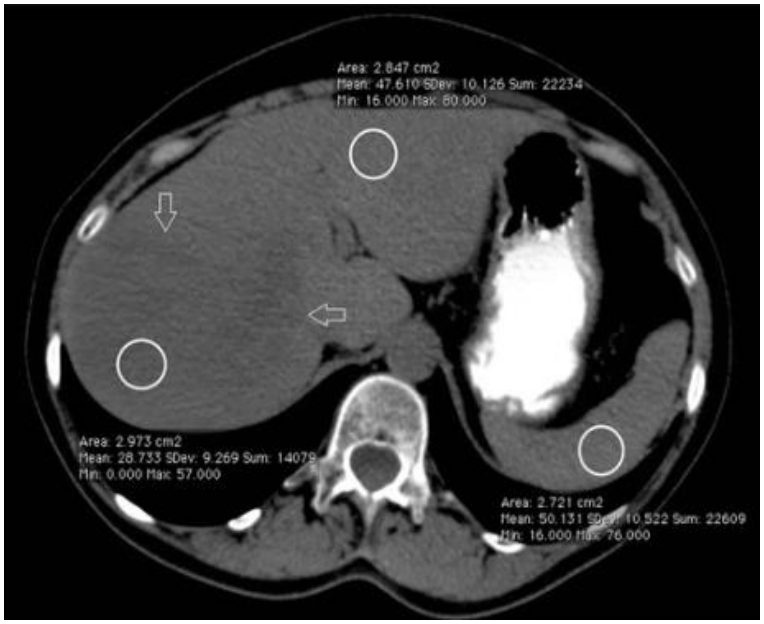

Fig. 4 CT-Scan Depicting Due to uneven fat accumulation, the posterior section of the right lobe has a regionally shaped hypodense area (arrows).[21]

Metabolic disorders like obesity, diabetes, and insulin resistance are frequently linked to NAFLD. Patients with NAFLD must be managed and treated in order to increase their prognosis because NAFLD is linked to increased mortality from CVD and problems relating to the liver. In order to improve intrahepatic inflammation and fibrosis and treat concomitant metabolic illnesses, treatments for NAFLD include both pharmaceutical and non-pharmacologic alternatives. These treatments aim to lower the incidence and mortality of CVD and liver-related comorbidities.[22]

Insulin sensitizers include Pioglitazone, Metformin, and GLP-1 agonist Liraglutide. Pioglitazone causes mitochondrial oxidative dysfunction, which in turn lessens hepatocellular damage and insulin resistance in the liver, muscle, and adipose tissue. It was anticipated that metformin, a routinely prescribed medication for T2DM, would be helpful in treating people with NASH because it lessens insulin resistance in the muscles and liver. Additionally, metformin lowers the expression of tumor necrosis factor- and inhibits hepatic fat synthesis and glucose excretion via triggering adenosine monophosphate-activated protein kinase. GLP-1 activator It is now legal to use Liraglutide, a synthetic long-acting GLP-1 receptor agonist, to treat both diabetes and obesity.[23]

Antioxidants like Vitamin E reduce liver inflammation and lessen oxidative stress, which exacerbates NASH. Due to the risk of prostate cancer and hemorrhagic stroke, vitamin E use over an extended period of time is also accompanied by safety issues. Vitamin E in high doses (>400 IU/day) is linked to an increased death rate despite the fact that the data is debatable, necessitating safety measures. [23]

Lipid-lowering drugs are used with patients with CVD. It is crucial to alter the risk factors for CVD because it is the leading cause of death in NAFLD patients. Dyslipidemia must be prevented and treated in order to reduce the risk of atherosclerotic plaques and carotid intima-media thickness, both of which contribute to CVD. Patients with NAFLD and dyslipidemia may benefit from lipid-lowering medications such as statins (hydroxy-methylglutaryl coenzyme A reductase inhibitors). [23]

Even modest weight loss can have an effect, especially in people with milder disease. Steatosis can be improved by 3%–5% by weight loss, although NASH and fibrosis are usually improved by weight loss of >10%. Losing weight while maintaining it is difficult. Long-term weight loss lowers adipose tissue stress and raises peripheral insulin sensitivity, which may decrease the tendency toward liver injury. Obesity and NAFLD are linked to a diet high in extra calories, especially extra saturated fats, refined carbs, and sugar-sweetened beverages. Excessive fructose consumption increases the risk of NAFLD. Different levels of caloric restriction and dietary changes (such as diets low in fat content, low-carbohydrate, saturated or unsaturated fat diets, intermittent fasting, Mediterranean diet, etc.) are equivalent in their capacity to treat NAFLD.[24]

Bariatric surgery: NAFLD is becoming more and more recognized as a comorbid condition that can benefit from bariatric surgery, even though the current accepted criteria are BMI -40 kg/m2 regardless of the presence of metabolic disease. BMI - 35 kg/m2, along with diseases (T2DM or pre-DM, uncontrolled hypertension, osteoarthritis of the hip or knee, and urinary incontinence). [24]

CONCLUSION:

NAFLD is one of the most significant and important human disorders linked to a changed lifestyle, with an increasing incidence and prevalence in the majority of nations worldwide. Throughout the many stages of chronic liver disease, including cirrhosis and related complications like HCC and decompensation (e.g., oesophageal variceal hemorrhage, ascites, and hepatic encephalopathy), NAFLD can significantly increase the burden of disease. Patients with NAFLD frequently exhibit metabolic syndrome, T2D, and CVD, in addition to hepatic problems. Although we are learning more about the underlying processes of NAFLD, we still don't fully understand how NAFLD affects T2D and CVD from a pathophysiological standpoint. The mainstay of the treatment is lifestyle adjustment, which includes food changes, frequent exercise, and weight loss. A variety of therapy strategies, from medical intervention and conservative management to surgical techniques (such as bariatric surgery), have been established with different results, particularly for the conservative treatment methods.

REFERENCES

1. **Ahmed A, Wong R J, & Harrison S A (2015).** Non-alcoholic fatty liver disease review: diagnosis, treatment, and outcomes. *Clinical Gastroenterology and Hepatology*, *13*(12), 2062-2070.
2. **Machado M V, & Diehl A M (2016).** Pathogenesis of non-alcoholic steatohepatitis. *Gastroenterology*, *150*(8), 1769-1777.
3. **Dixon J B, Bhathal P S, & O'brien P E (2001).** Non-alcoholic fatty liver disease: predictors of non-alcoholic steatohepatitis and liver fibrosis in the severely obese. *Gastroenterology*, *121*(1), 91-100.
4. **Clark J M, Brancati F L, & Diehl, A M (2003).** The prevalence and etiology of elevated aminotransferase levels in the United States. The American journal of gastroenterology, 98(5), 960-967.
5. **Grande C, Grabherr F, & Tilg H (2023)**. Non-alcoholic fatty liver disease: pathophysiological concepts and treatment options. *Cardiovascular research*, cvad095.
6. **Méndez-Sánchez N, Bugianesi E, Gish R G, Lammert F, Tilg H, Nguyen M H, & Awny S. (2022).** Global multi-stakeholder endorsement of the MAFLD definition. The lancet Gastroenterology & hepatology, 7(5), 388-390.
7. **BasuRay S, Smagris E, Cohen J C, & Hobbs H H (2017)**. The PNPLA3 variant associated with fatty liver disease (I148M) accumulates on lipid droplets by evading ubiquitylation. Hepatology, 66(4), 1111-1124.
8. **Herman M A, & Samuel V T. (2016).** The sweet path to metabolic demise: fructose and lipid synthesis. Trends in Endocrinology & Metabolism, 27(10), 719-730.
9. **Hoyles L, Fernandez-Real J M, Federici M, Serino M, Abbott J, Charpentier J, & Dumas M E (2018**). Molecular phenomics and metagenomics of hepatic steatosis in non-diabetic obese women. *Nature medicine*, *24*(7), 1070-1080.
10. **Zhu L, Baker S S, Gill C, Liu W, Alkhouri R, Baker R D, & Gill S R (2013).** Characterization of gut microbiomes in non-alcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. Hepatology, 57(2), 601-609.
11. **Rau M, Rehman A, Dittrich M, Groen A K, Hermanns H M, Seyfried F, & Geier A (2018).** Fecal SCFAs and SCFA-producing bacteria in gut microbiome of human NAFLD as a putative link to systemic T-cell activation and advanced disease. United European gastroenterology journal, 6(10), 1496-1507.
12. **Brown A J, Goldsworthy S M, Barnes A A, Eilert M M, Tcheang L, Daniels D, & Dowell S**

J (2003). The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. Journal of Biological Chemistry, 278(13), 11312-11319.

13. **Min H K, Kapoor A, Fuchs M, Mirshahi F, Zhou H, Maher J, & Sanyal A J (2012).** Increased hepatic synthesis and dysregulation of cholesterol metabolism is associated with the severity of non-alcoholic fatty liver disease. Cell metabolism, 15(5), 665-674.
14. **Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, & Arcaro G (2007).** prevalence of non-alcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. *Diabetes care*, *30*(5), 1212-1218.
15. **Mahlapuu M, Caputo M, Xia Y, & Cansby E (2022).** GCKIII kinases in lipotoxicity: Roles in NAFLD and beyond. Hepatology Communications, 6(10), 2613-2622.
16. **Mofrad P, Contos M J, Haque M, Sargeant C, Fisher R A, Luketic V A, & Sanyal A J (2003).** Clinical and histologic spectrum of non-alcoholic fatty liver disease associated with normal ALT values. Hepatology, 37(6), 1286-1292.
17. **NOGUCHI H, TAZAWA Y, NISHINOMIYA F, & TAKADA G (1995).** The relationship between serum transaminase activities and fatty liver in children with simple obesity. Pediatrics International, 37(5), 621-625.
18. **Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati F L, Guallar E, & Clark J M (2011).** Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. *Hepatology*, *54*(3), 1082-1090.
19. **Di Martino M, Koryukova K, Bezzi M, & Catalano C (2017)**. Imaging features of non-alcoholic fatty liver disease in children and adolescents. *Children*, *4*(8), 73.
20. **Borra R J, Salo S, Dean K, Lautamaki R, Nuutila P, Komu M, & Parkkola R (2009).** Non-alcoholic fatty liver disease: rapid evaluation of liver fat content with in-phase and out-of-phase MR imaging. *Radiology*, *250*(1), 130-136.
21. **Chartampilas E (2018).** Imaging of non-alcoholic fatty liver disease and its clinical utility. *Hormones*, *17*(1), 69-81.
22. **Ekstedt M, Franzén L E, Mathiesen U L, Thorelius L, Holmqvist M, Bodemar G, & Kechagias S (2006)**. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology*, *44*(4), 865-873.
23. **Kang S H, Lee H W, Yoo J J, Cho Y, Kim S U, Lee T H, & Cho Y K (2021).** KASL clinical practice guidelines: Management of non-alcoholic fatty liver disease. *Clinical and molecular hepatology*, *27*(3), 363.
24. **Rinella M E, Neuschwander-Tetri B A, Siddiqui M S, Abdelmalek M F, Caldwell S, Barb D, & Loomba R (2023).** AASLD practice guidance on the clinical assessment and management of non-alcoholic fatty liver disease. *Hepatology*, 10-1097.