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Review Article

A Systematic Review on Non-Alcoholic Fatty Liver Disease (NAFLD)

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ABSTRACT

The most prevalent chronic liver disease in Western nations, nonalcoholic fatty liver disease (NAFLD), affects about 25% of adults. NAFLD is typically regarded as the liver-related manifestation of the disease of metabolism because it is often linked to additional metabolic comorbidities like being overweight, diabetes type 2, mellitus, or dyslipidemia. NAFLD is linked to both preclinical and clinical cardiovascular disease (CVD), in addition to the potential for liver-related morbidity and mortality. Non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFL) are the two histological subtypes of NAFLD. Although ≥5% hepatic steatosis without hepatocyte damage is what is meant by NAFL, NASH is defined as the existence of lobular inflammation and hepatocyte damage (such as hepatocyte ballooning) in conjunction with hepatic steatosis, either with or without fibrosis. NAFLD is commonly characterized as the liver-related symptom of metabolic disease because it is frequently associated with other metabolic comorbidities such as obesity, type 2 diabetes, or dyslipidemia. NAFLD is associated with both experimental and clinical heart disease (CVD), as well as

the risk of liver-related mortality and morbidity. Nonalcoholic fatty liver disorder (NAFLD) is the most common chronic liver condition in Western nations, affecting approximately 25% of adults. The first phase of NAFLD/NASH is the buildup of fat in the liver, which is frequently associated with metabolic syndrome (MetS) disorders such weight gain, diabetes, type 2 dyslipidemia, and hypertension. According to research, NAFLD is marked mostly by hepatocyte dysfunction and steatosis in the beginning stages, which is followed by scarring and/or damage in the late stages. This review article highlights the pathophysiology of non-alcoholic fatty liver disease (NAFLD), the impact of nutrition in NAFLD, and the involvement of mitochondrial dysfunction and hereditary variables in raising the incidence of NAFLD condition. This article also discusses the methods for treating non-alcoholic fatty liver disease (NAFLD), which mostly involve weight loss and the use of various drugs such as pioglitazone, rosiglitazone, metformin, atorvastatins, and vitamin E.

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INTRODUCTION:

The most prevalent chronic liver disease in Western nations, nonalcoholic fatty liver disease (NAFLD), affects about 25% of adults. NAFLD is typically regarded as the liver-related manifestation of the disease of metabolism because it is often linked to additional metabolic comorbidities like being overweight, diabetes type 2, mellitus, or dyslipidemia. NAFLD is linked to both preclinical and clinical cardiovascular disease (CVD), in addition to the potential for liver-related morbidity and mortality. Non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFL) are the two histological subtypes of NAFLD. Although ≥5% hepatic steatosis without hepatocyte damage is what is meant by NAFL, NASH is defined as the existence of lobular inflammation and hepatocyte damage (such as hepatocyte ballooning) in conjunction with hepatic steatosis, either with or without fibrosis.

Most individuals with non-alcoholic fatty liver disease (NAFLD) are affected by early stages of the disease and frequently have other cardiometabolic risk factors. Finding these people may help identify individuals with high cardiometabolic risk factors who could benefit from therapeutic therapies meant to prevent atherosclerosis cardiovascular disease (CVD) and progressing non-alcoholic fatty liver disease (NAFLD). There is mounting evidence that individuals with non-alcoholic fatty liver disease (NAFLD) are significantly more likely to develop high blood pressure, coronary heart disease, and cardiac arrhythmias, all of which can lead to a higher risk of cardiovascular morbidity and death[1].

In this review article, the pathogenesis of NAFLD along with the role of diet in NAFLD as well as the role of genetic factors and mitochondrial dysfunction in increasing the incidences of NAFLD disorder is being highlighted. This article also highlights the treatment strategies of NAFLD which mainly includes loss of weight along with the use of different medications like Pioglitazone, Rosiglitazone, Metformin, Atorvastatin, and Vitamin E.

PATHOGENESIS OF NAFLD:

NAFLD & NASH:

The initial stage of NAFLD/NASH is fat accumulation in the liver, which is often linked to metabolic syndrome (MetS) conditions such obesity, type 2 diabetes, dyslipidemia, and hypertension [2]. Excess lipid buildup in the liver can be caused by several causes, including increased visceral adipose tissue (AT) lipolysis, hepatic de novo lipogenesis (DNL), and a high calorie/fat diet. Isotope labeling indicates that the primary cause is excessive free fatty acid (FFA) flow from the AT to the liver (59%), followed by DNL (26%), and excess

calories and lipids in the diet (15%) [3]. NASH increases the likelihood of developing cirrhosis and HCC compared to simple steatosis, which is considered more benign [4]. Pathological signals from other organs, such as the gut and the AT, or the parenchymal and non-parenchymal liver cell population interact intricately to cause the evolution of simple steatosis into NASH [5]. Several pathogenic triggers, such as hepatocyte death, AT-secreted chemicals, and intestinal infections, can induce inflammation and fibrogenesis by activating local macrophages (Kupffer cells [KCs]) [6], which then draw monocytes and leukocytes from the circulation. The activation of hepatic stellate cells (HSCs) leads to increased extracellular matrix production and deposition [7].

So far, several pathogenic processes linked with insulin resistance and MetS are involved in the development and progression of NAFLD (Fig.1), including fat accumulation, lipotoxicity, oxidative stress, mitochondrial dysfunction, and changes in the gut-liver axis signaling [5].

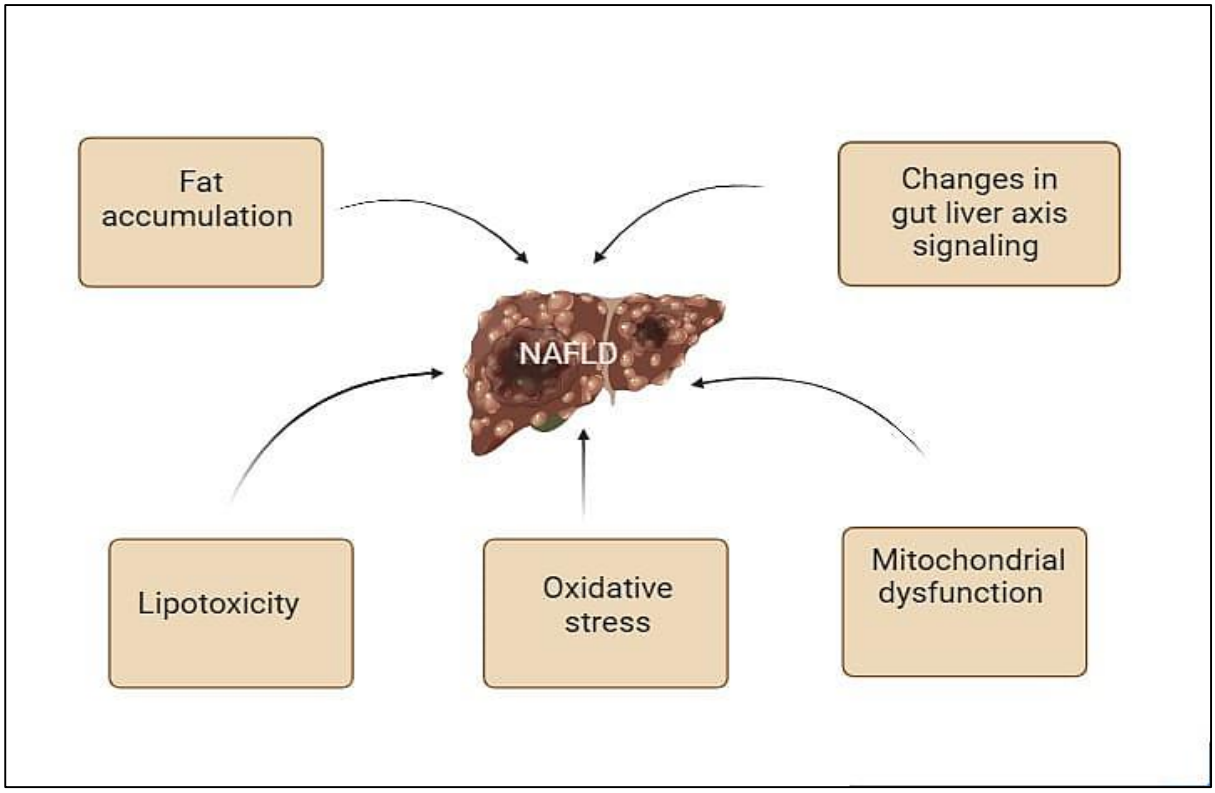

Figure 1: Pathogenic Processes Involved in NAFLD

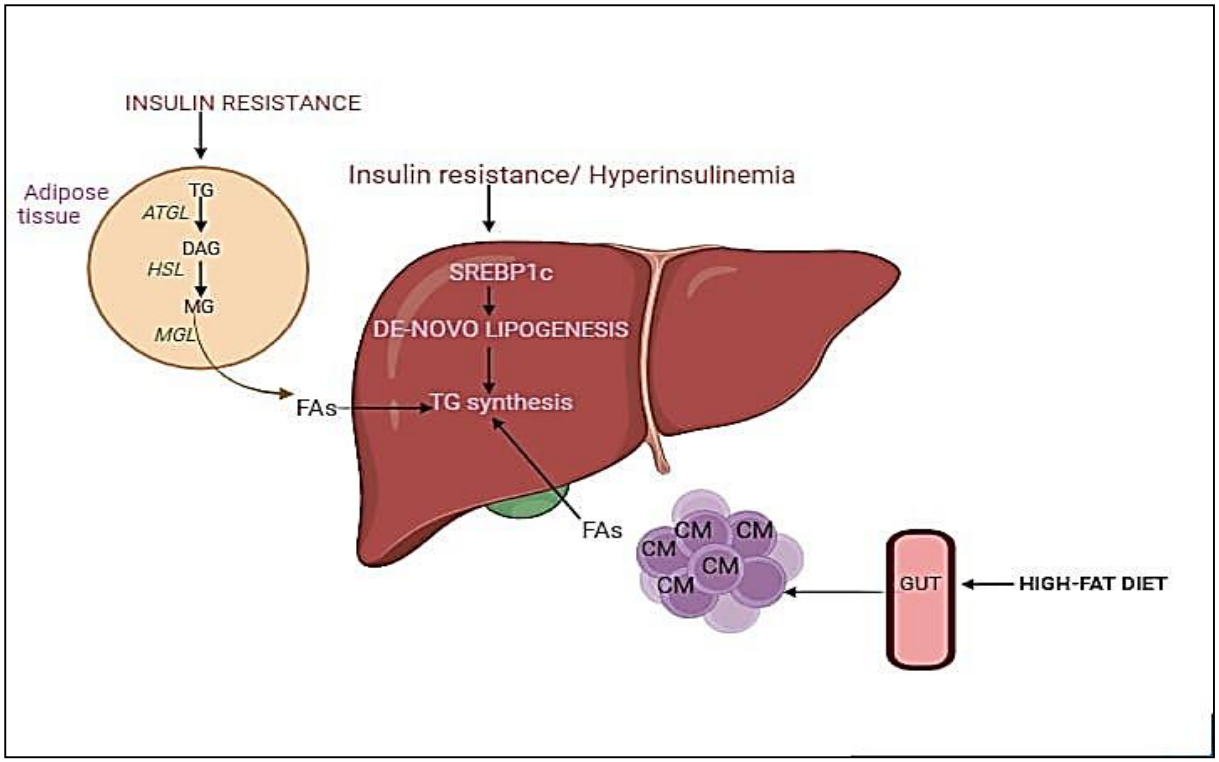

Figure 2: Pathogenesis of Hepatic Steatosis

Figure 2 shows the pathogenesis of hepatic steatosis, Insulin resistance causes TG breakdown through the hydrolase activity of particular enzymes such as ATGL, HSL, and MGL, resulting in a flux of FFAs toward liver. Furthermore, insulin resistance and hyperinsulinemia can stimulate hepatic DNL via the transcription factor SREBP1c. Finally, dietary FAs, which are absorbed in the gut and incorporated as TGs into chylomicrons, might accumulate in the liver. (HSL- Hormone sensitive lipase; MGL- Monoglyceride lipase).

1.1. Liver cells and NAFLD

The liver plays a crucial role in lipid metabolism by facilitating lipid intake, production, oxidation, and transport to other organs. The liver's cell population consists primarily of parenchymal cells, with hepatocytes accounting for around 78% [8]. Non-parenchymal cells include liver sinusoidal endothelial cells (LSECs), Kupffer cells (KCs), hepatic stellate cells (HSCs), and hepatic natural killer cells (NK cells). Although hepatocytes are responsible for vital liver functions including lipid metabolism, KCs also play a significant role in liver inflammation [9]. KCs make about 30% of sinusoidal cells[7] and 80-90% of macrophages in the human body[10]. Upon liver injury, Kupffer cells get activated and release inflammatory cytokines and chemokines that further contribute to the pathogenesis of NAFLD[11]. The balance between proinflammatory M1 KCs and anti-inflammatory M2 KCs regulates liver inflammation[12]. Via the portal circulation, the liver is exposed to various

substances, like nutrients and gut-derived bacterial products, which gets eliminated by KCs[13]. Various inflammatory cytokines, including TNF-α, IL-1β, IL-6, IL-12, IL-18 and chemokines are being produced by KCs[11]. HSCs are normally inactive, but when exposed to Lipotoxicity and inflammation, they activate and convert into myofibroblast like cells, secreting more collagen and inducing fibrosis[14]. Little is known about how LSEC lipotoxicity affects the progression of NAFLD. Lipotoxicity of LSEC can reduce nitric oxide and raise reactive oxygen species (ROS) levels, leading to oxidative stress and NASH[15]. The various liver cells' roles in non-alcoholic fatty liver disease (NAFLD) and the signals that parenchymal and non-parenchymal cells use to communicate with one another are currently being studied[15].

1.2 Key concepts of the two-hit hypothesis

Simply put, dysregulated mitochondrial cholesterol metabolism, as found in IR, can be hepatotoxic, resulting in the subsequent inflammatory response found in NASH. Various study approaches, including animal models, NAFLD stage, patient cohort, and gender differences, have yielded conflicting results on the involvement of cholesterol metabolites in NAFLD development and the role of lipids [16]. There's still uncertainty about when NAFLD truly begins. Early signs, like mild enzyme elevations, are often overlooked. Many models focus only on advanced disease stages and use animals that don't reflect human biology, missing key features like insulin resistance [17].

According to studies, NAFLD is characterized mostly by hepatocyte inflammation and steatosis in the early stages, followed by fibrosis and/or cirrhosis in the late stages [18]. However, the pathophysiology of NAFLD is not completely known. In 1998, scientists suggested the "two-hit" hypothesis to explain why steatosis (the first "hit") and other factors linked with free radicals (the second "hit") are required for NASH progression [19]. The "multiple hits" idea has gained popularity in recent years, supported by animal models and descriptive clinical trials [20]. The first major issue is macrophage-driven inflammation in visceral fat, leading to insulin resistance. At the same time, abnormal fat breakdown floods the liver with fatty acids, triggering toxic lipid buildup, stress responses, inflammation, cell death, and eventually fibrosis.

[20]. Furthermore, mitochondrial dysfunction, lifestyle, and epigenetic and genetic variables all influence the onset and progression of NAFLD [21].

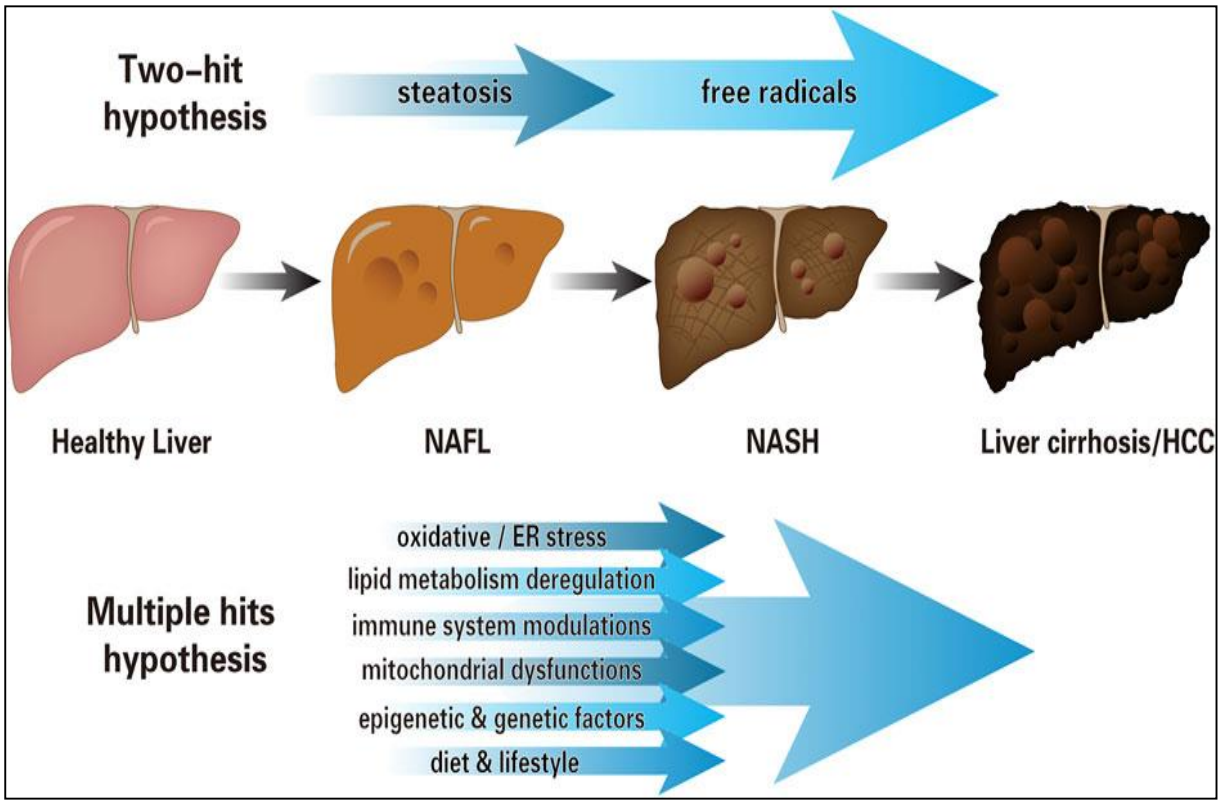

Figure 3: Schematic representation illustrating cognition toward the progression of NAFLD

Figure 3 shows the pathogenesis of NAFLD. A schematic illustration of cognition towards the progression of NAFLD, from the "two-hit" hypothesis to the "multiple hits" hypothesis. The early "two-hit" idea states that the first "hit" is steatosis, which leads to the second "hit": oxidative stress, endotoxin, and so on. The "multiple hits" hypothesis considers several parallel hits jointly affect the NAFLD pathogenesis, which includes, but is not limited to, oxidative and/or ER stress, lipid metabolism deregulation, immune system modulations, mitochondrial dysfunctions, lifestyle, and epigenetic and genetic factors (NAFL, non-alcoholic fatty liver, i.e., simple steatosis without hepatocellular injury; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma; ER, endoplasmic reticulum.

1.3 Mechanism of fat accumulation in the liver

Insulin resistance is the primary pathogenetic event associated with the development of hepatic steatosis. Insulin resistance prevents AT from responding to insulin's anti-lipolytic function, resulting in TG breakdown and the production of FFAs and glycerol [22]. Enzymes with hydrolase activity, including adipose TG lipase (ATGL), hormone-sensitive lipase, and monoglyceride lipase, facilitate enzymatic cleavage [23]. Lack of AT lipolysis inhibition results in a huge release of FFAs, which can be taken up by the liver and accumulate as TG [24]. Higher insulin

levels can improve hepatic lipid metabolism by increasing TG synthesis, especially in insulin resistance [25]. In the liver, DNL is an important path that leads to lipid accumulation. Glycolysis substrates(acetyl-CoA) begin a multistep process that leads to the synthesis of FFAs, which are ultimately transformed into TG. De novo lipogenesis is controlled by two transcriptional factors: SREBP1c and ChREBP. Insulin signaling activates SREBP1c through two pathways [26]. The insulin receptor mediates the first mechanism, which activates the phosphoinositide-3 kinase/protein kinase B pathway [27]. The second is dependent on the nuclear receptor liver X receptor, namely the hepatic isoform alpha, which phosphorylates SREBP1c [28]. In contrast, ChREBP is activated when glucose levels rise, ramping up glycolysis in the liver. Its byproducts trigger ChREBP to turn on genes that drive fat production, like ACC and FAS.[28]. Dietary factors play a significant role in the development of NAFLD. Western diets high in fat have been linked to insulin resistance, dyslipidemia, and metabolic/cardiovascular disease [29]. Eating or drinking too much sugar—especially fructose—has been linked to NAFLD. Unlike glucose, fructose ramps up fat-making genes and slows fat burning in the liver, leading to fat buildup. [30, 31]. Lifestyle adjustments can significantly improve metabolic abnormalities, hepatic steatosis, and inflammation associated with NAFLD, highlighting the importance of the western diet in its development [32-34]. Fig.4 represents the risk factors involve in the development of NAFLD.

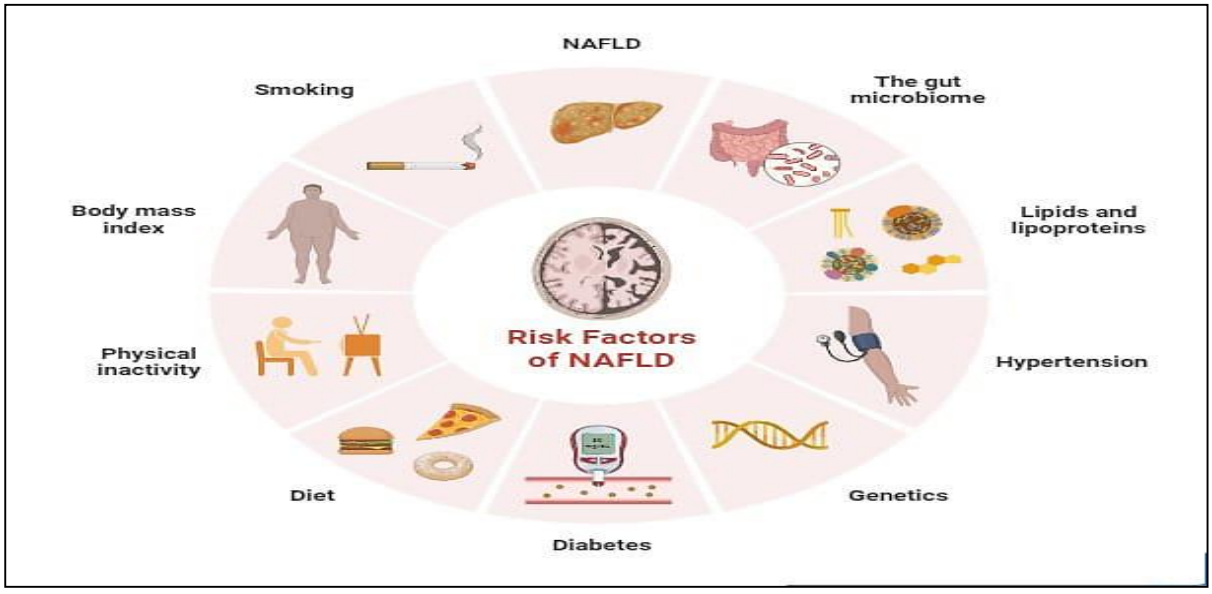

Figure 4: Risk factors of NAFLD

1.4 Role of Diet in NAFLD/NASH

It is commonly known that the development of NAFLD and the transition to NASH may be influenced by the diet's quantitative (calorie intake) and qualitative (kind of nutrients provided) aspects[35] . Although there is little doubt that overeating increases the risk of steatohepatitis and hepatic steatosis [36, 37], certain food substrates are more steatogenic than others. Fructose, for instance, is a pro-inflammatory lipogenic component that might result in TNF-α overproduction and oxidative stress [38]. Nearly all of the fructose is converted to fructose-1-phosphate, a molecule that enters the metabolic pathway for glycolysis and provides substrates for de novo lipogenesis [39] . Additionally, bacterial growth and increased intestinal permeability have been closely linked to fructose-induced NAFLD[40]. In addition, fructose ingestion on a daily basis has been linked to increased liver fibrosis in NAFLD patients[41] , a relationship that may be mediated by the depletion of hepatic ATP[42]. Drinking high-calorie beverages is linked to a higher risk of developing NASH and liver steatosis because they contain large amounts of sucrose, or sugar [43].

Conversely, coffee appears to have a hepato-protective impact on NAFLD patients [44]. This is probably because coffee contains a number of antioxidants and caffeine, which has anti-inflammatory characteristics for the liver [45]. Similarly, monounsaturated fats, which are common in the Mediterranean diet, have been demonstrated to help improve NAFLD and lessen the severity of IR [46, 47]. Moderate alcohol use has also been proposed to have a protective effect on NAFLD, despite the seeming controversy around these studies [48].

1.5 Role of Intestinal Microbiota

A growing body of research suggests that the gut microbiota may play a role in the etiology and progression of NAFLD [49-53]. Humans have different microbiota enterotypes [54]. An "obese" microbiota, defined as having a higher ability to absorb energy from the diet, appears to be capable of determining a substantially bigger increase in total body fat when compared to an individual colonized by the so-called "lean" microbiota [49]. The intestinal microbiota alters the host's energy balance by converting resistant starch and non-starch polysaccharides into short-chain fatty acids (SCFA), which are then absorbed by the intestinal epithelium [55].

In addition to accumulating fatty acids in hepatocytes, gut microbiota can trigger inflammation and contribute to the advancement of liver injury. Patients with NAFLD have greater intestinal permeability and bacterial proliferation in the small intestine compared to healthy

controls [50, 51]. Lipopolysaccharides (LPS) is a highly toxic bacterial product that acts as a TLR ligand, activating the inflammatory cascade and affecting insulin signaling, obesity, liver fat buildup, and the development of NASH [56].

The gut microbiota can create enzymes that convert dietary choline into hazardous chemicals, such as methylamines, which can reach the liver. The liver converts them into trimethylamine-N-oxide, which can cause inflammation and liver damage [57]. Microbiota dysbiosis can lead to NASH by lowering choline levels and increasing methylamine levels [52, 58] (Figure.5).

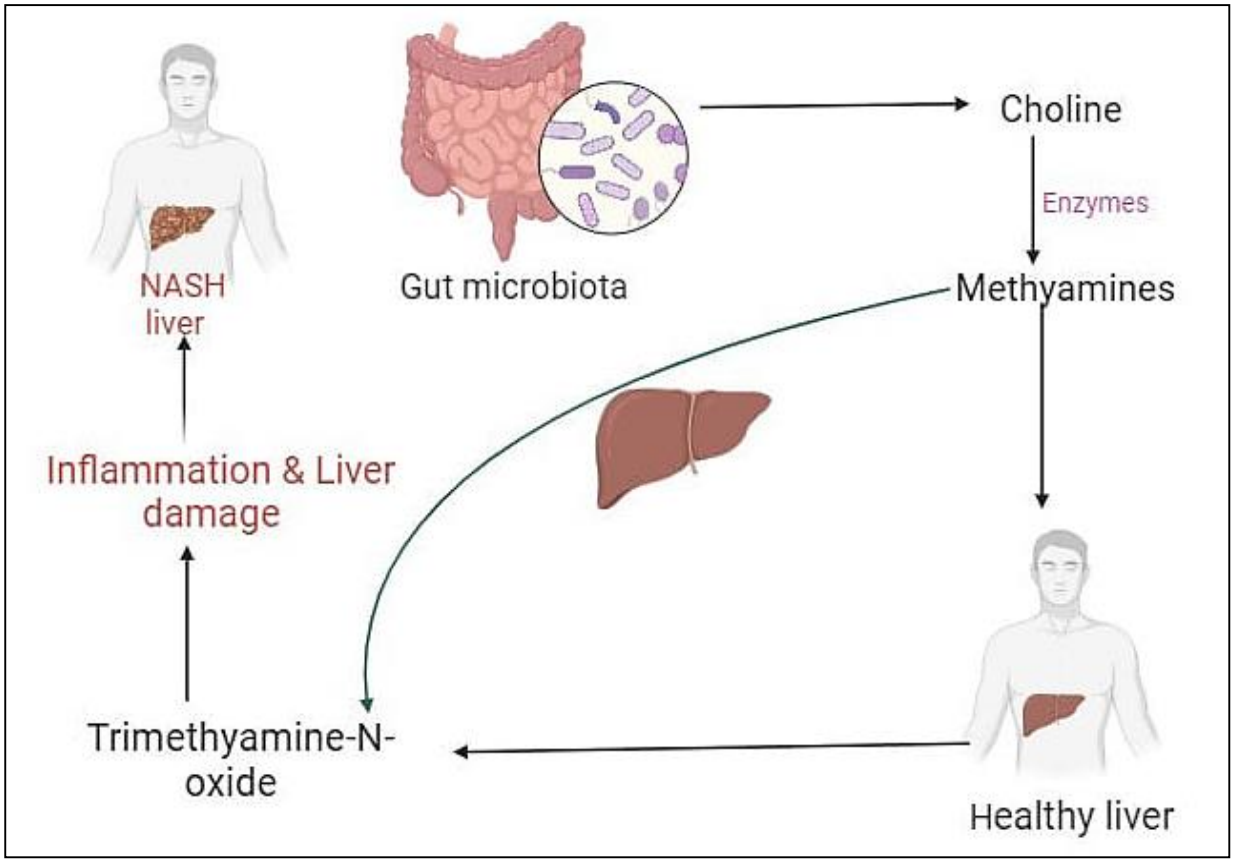

Figure 5: Microbiota dysbiosis

1.6 Role of Genetic and Epigenetic factors

Variants in one or more genes, particularly single nucleotide polymorphisms, can impact multiple processes, including the liver's uptake of FFAs, oxidative stress, endotoxin response, and cytokine synthesis and activity. They therefore appear to be essential for the onset and progression of NAFLD [59]. Single nucleotide polymorphisms of the patatin-like phospholipase domain-containing protein 3 (PNPLA3), namely the variant I148M (rs738409 C/G), have been linked to the development and progression of NAFLD in multiple studies [59-62] . The adiponutrin protein, which is encoded by the PNPLA3 gene, has a lipolytic effect on triglycerides [60]. Higher expression of SREBP-1c and decreased de novo lipogenesis are linked to the PNPLA3 148M allele [60]. This polymorphism is also linked to a higher degree of liver fibrosis and a higher prevalence of steatosis in humans [60, 61]. PNPLA3 polymorphism appears to be significantly associated with liver damage in people who also have concurrent causes of liver injury (e.g., HBV or HCV infection) [61]. A meta-analysis of 23 studies verified the noteworthy correlation between a greater risk of NAFLD and NASH and the PNPLA3 polymorphism [62]. There's a greater chance that NAFLD's pathogenesis involves at least one TM6SF2 gene variation.

Some research has focused on the possible influence of epigenetics on the development of non-alcoholic fatty liver disease (NAFLD), in addition to the involvement of genetic variations. Histone modifications, DNA methylation, and microRNA (miRNA) activity are examples of stable transcriptional alterations that are referred to as epigenetic modifications. They do not alter the basic DNA sequences, but they are able to modify their translation. Epigenetics plays a significant role in maintaining cellular homeostasis by adapting to environmental changes during evolution [63]. Disrupting this equilibrium may raise the risk of developing NAFLD [64]. Dietary deficiencies in methyl group donors, such as betaine, choline, and folate, have a significant impact on DNA methylation, a key factor in simple steatosis and NASH [65].

Folate levels influence the expression of genes involved in FFA synthesis, and a lack of folate appears to contribute to triglyceride accumulation inside the liver cells [66]. Sirtuins, also known as the Silent Information Regulator-2 family, are proteins that have deacetylase activity. Reduced SIRT1 expression or activity has been linked to increased risk of NAFLD in both animal and human studies [67].

Non-coding microRNAs (miRNAs) are also known to affect epigenetic gene expression processes. MiRNAs are short, single-stranded RNA molecules that regulate gene expression, including proliferation, apoptosis, differentiation, and cell growth [68]. MiRNA expression and circulating levels have been linked to NAFLD and NASH etiology. Individuals with NASH express different miRNAs, which are related with changes in glucose and lipid metabolism [69].

MiR-122 is mostly expressed in the liver, and inhibiting it reduces plasma cholesterol levels and alters the expression of liver genes involved in cholesterol and fatty acid production [70].

1.7 Role of Mitochondrial Dysfunction and Endoplasmic Reticulum Stress

NAFLD affects how mitochondria work and look, disrupting energy production, fat breakdown, and even damaging their structure and DNA, which worsens liver function over time [71]. In fact, respiratory oxidation collapses if the mitochondrial and peroxisomal processes are unable to control the increase in lipid flow. This results in a disturbance of lipid homeostasis, the production of toxic metabolites, and an excess of reactive oxygen species (ROS) [72, 73]. These molecules drive oxidative stress, worsen mitochondrial damage, and fuel liver inflammation. Mitochondrial dysfunction is strongly linked to insulin resistance, obesity, and higher TNF-α levels [74]. Furthermore, ROS and oxidized LDL particles have the ability to activate hepatic stellate and Kupffer cells, which leads to the addition of collagen and secondary liver fibrosis[75]. Extra protein production, ER stress, and low ATP can cause unfolded proteins to build up. In response, the UPR tries to restore balance by reducing and fixing proteins [73]. If protein-folding issues persist, the UPR can trigger liver cell death. In NAFLD, it's activated by things like high blood sugar, cholesterol, oxidative stress, and low ATP. [76]. UPR, in turn, activates JNK, which can decide the inflammatory state and apoptosis implicated in the evolution of NASH [77], as well as the disruption of insulin signaling and eventual T2DM development [78]. UPR stimulates SREBP-1c, which leads to increased hepatic fat storage and ER stress [79]. X-box Binging Protein-1 (XBP-1) is a key regulator of UPR that interacts with the insulin signaling pathway through PI3K [80]. The interaction of PI3K and XBP-1 affects the cell's response to endothelial stress and the reaction itself [81], potentially linking hepatic steatosis, IR, and inflammation [20].

Treatment Strategies in NAFLD/NASH

About 25% of persons worldwide suffer from non-alcoholic fatty liver disease (NAFLD), a condition whose prevalence is

rising [2]. Cardiovascular illnesses and type 2 diabetes mellitus (T2DM) are the main causes of death for those with NAFLD, according to reports [82, 83]. Research from both basic and clinical studies has demonstrated that NAFLD adversely affects patients' health [84, 85]. Consequently, NAFLD therapy necessitates the use of suitable therapeutic approaches and medications.

The rise of nonalcoholic fatty liver disease (NAFLD) can be attributed to the global epidemic of metabolic syndrome, which is likely linked to increased affluence and sedentary lifestyles. In India, there is a growing prevalence of fatty liver [86, 87] disease and diabetes [88]. NAFLD is becoming an increasingly common cause of chronic liver disease in India [87, 89]. In India, patients with hepatocellular carcinoma frequently have biochemical and histological signs of metabolic syndrome and NAFLD [90, 91].

Losing weight is the most effective technique for treating NAFLD. The greatest ways to attain the latter are through dietary adjustments and increased exercise. For many obese patients with non-alcoholic fatty liver disease (NAFLD), losing weight can be an extremely difficult task. It is felt that people with NAFLD progression require pharmaceutical therapies.

Obesity and insulin resistance are two main risk factors for NAFLD development. Its precise etiology and relationship to the metabolic syndrome remain unclear; pathogenic mechanisms that have been suggested include oxidative stress, free radical production, and hepatic mitochondrial malfunction (including fatty acid oxidation impairment) [92, 93].

Nowadays, a number of pharmaceuticals used to treat type 2diabetes and dyslipidemia may also be effective treatments for fatty liver disease. One of the thiazolidinediones (TZDs), rosiglitazone, has been demonstrated in earlier research to be useful in treating fatty liver disease [94, 95]. However, the Food and Drug Administration (FDA) has limited the use of rosiglitazone due to reports that the medication raises the risk of heart attack [96].

Neither the European Medicines Agency (EMA) nor the United States Food and Drug Administration (USFDA) have approved any medication to treat NAFLD as of date. For this reason, using any medication to treat NAFLD must currently be regarded as "off-label use [97]." Although there is currently no approved medication for the treatment of nonalcoholic fatty liver disease (NAFLD) by US or European drug regulatory agencies, the global NAFLD epidemic has made pharmacological therapies essential. Emerging data has demonstrated these therapies' effectiveness in treating NAFLD,

and as a result, clinical practice guidelines from the American Association for the Study of Liver Diseases (AASLD) [98], the European Association for the Study of the Liver (EASL), and the Indian National Association for the Study of the Liver (IN ASL)[86] have recommended the use of currently available drugs for the treatment of NAFLD.

2.1 Current & Future Pharmacological Therapies

Table 1 lists the medications for treating non-alcoholic fatty liver disease (NAFLD) that are currently on the market, have undergone clinical trial testing, and have been recommended by professional bodies. Understanding disease pathways has led to the identification of treatment targets for NAFLD. The majority of these medications target various components of the metabolic syndrome that NAFLD patients experience. The two major phenomena that the medications that are now on the market to treat NAFLD have targeted are insulin resistance and oxidative stress.

To treat NAFLD, two insulin-sensitizing medications (pioglitazone [99-101], metformin [102-104]) and vitamin E [101, 105, 106] have been investigated in randomised controlled studies. There has been a meta-analysis evaluating these three medications' effects on NAFLD patients. It is unknown if pioglitazone and vitamin E together will benefit NAFLD patients in a synergistic way.

Weight gain, lactic acidosis (metformin), an increased risk of prostate cancer (vitamin E), and an increased incidence of congestive heart failure (pioglitazone) are the main side effects of these medications.

In NAFLD patients, ursodeoxycholic acid may enhance serum transaminase levels. This medication is simple to administer because of its relative safety. However, ursodeoxycholic acid is not advised by AASLD and EASL due to the poor quality of evidence in randomised trials on its efficacy (Table 1)

Table 1: List of current drugs used to treat NAFLD

LIST OF DRUGS, MOA & SIDE EFFECTS			Recommendation to treat NAFLD	
DRUGS	**MECHANISM OF ACTION**	**SIDE EFFECTS**	**AASLD[98]**	**EASL**
Pioglitazone	PPAR-ϒ agonist, decrease insulin resistance	Weight gain, fractures, may precipitate heart failure	Yes(use in patients with biopsy proven NASH, with/without type 2 DM)	Yes(use in patients with NASH, especially in diabetics)

Vitamin E	Antioxidant	Hemorrhagic, stroke, prostate cancer	Yes(use in nondiabetic patients with biopsy proven NASH)	Yes(use in non-diabetic, non-cirrhotic patients with NASH)
Statins	HMG CoA reductase inhibitor	Hepatitis	No(can use to treat dyslipidemia. Avoid in decompensated cirrhosis)	No(can use to treat dyslipidemia)
Metformin	Decreases insulin resistance	Lactic acidosis	No	No
Ursodeoxycholic acid	Decreases TNF-α, reduces oxidative stress and insulin resistance	Headache, GI side effect	No	No

2.1.1 How to treat?

1. Antioxidants/hepatoprotective drugs

- *Vitamin E:* It has been suggested that oxidative stress plays a significant part in the development of NASH [107, 108]. Since vitamin E is a well-known scavenger of free radicals, its use in the therapy of NASH has been anticipated. It has been previously reported that in adult NASH patients who were not responsive to dietary intervention, a year-long vitamin E treatment decreased serum transaminase activity and transformed growth factor-beta1 [109, 110]. Vitamin E significantly decreased blood hepatobiliary enzymes, hepatic steatosis, inflammation, and hepatocellular ballooning when compared to the control group, according to a random-effects model analysis of the five investigations [111]. Long-term vitamin E treatment (300 mg/day) for over 2 years in Japan has been shown to improve hepatic fibrosis in NASH patients, particularly those who have improved blood transaminase levels and insulin resistance [112]. Vitamin E is currently advised for biopsy-proven NASH patients without diabetes based on the PIVENS experiment, as it has been linked to histological improvement regardless of diabetes status [111].
- *Glutathione (GSH):* Glutathione (GSH), also known as L-glutamyl-Lcysteinyl-glycine, is a tripeptide found in all human cells that acts as an antioxidant. A pilot trial revealed that oral treatment of GSH (300 mg/day) for 4 months reduced ALT levels and

hepatic steatosis in Japanese NAFLD patients without significant fibrosis or uncontrolled diabetes. Large-scale clinical trials are necessary to confirm its efficacy [113] .

- *Ursodeoxycholic acid (UDCA):* Ursodeoxycholic acid (UDCA), covered by health insurance for chronic liver illnesses in Japan, has been shown to have anti-oxidative properties [114]. A large multicenter RCT found that normal doses of UDCA had no effect on liver histology in NASH. The guidelines do not currently prescribe UDCA for the treatment of NASH [115].

2. ***Peroxisome proliferator-activated receptor (PPAR) agonists*** (Fig.6)

- *PPARγ: Pioglitazone*, a peroxisome proliferator-activated receptor gamma (PPARγ) agonist, significantly reduced steatosis and necro inflammation in diabetic NASH when compared to placebo, according to two randomized, double-blind, placebo-controlled trials (RDBPCT) [99, 100]. Pioglitazone, however, raises a number of issues for widespread clinical usage, including elevated risks of pancreatic or prostate cancer, weight gain, fluid retention, bone fractures in women, and a rise in cardiovascular events. A selective PPARγ modulator (SPPARMγ) called INT131 is being developed for people with type 2diabetes. Similar to 45 mg of pioglitazone, INT131 showed dose-dependent decreases in HbA1c, but with less weight gain and fluid buildup [116]. Even though INT131 hasn't been the subject of any studies for the treatment of NASH, more will likely be expected in the future.
- *PPARα:* PPARα agonists like *Bezafibrate* and *Fenofibrate*, commonly used to treat hypertriglyceridemia, have not been shown to be effective in NASH/NAFLD. Bezafibrate is thought to be beneficial for breast cancer patients with tamoxifen-induced NASH [117].
  - ✓ *Saroglitazar*, a dual PPARα/γ agonist, is approved for treating dyslipidemia in diabetic patients in India. A Phase 2 RDBPCT comparing three dosages of saroglitazar (1, 2, or 4 mg) to placebo in NAFLD is now ongoing (EVIDENCES II; NCT03061721) [118].
  - ✓ *Elafibranor* (GFT505), an unlicensed dual agonist of PPARα/δ receptors, improves steatosis, inflammation, and fibrosis in mice models of NAFLD [119].

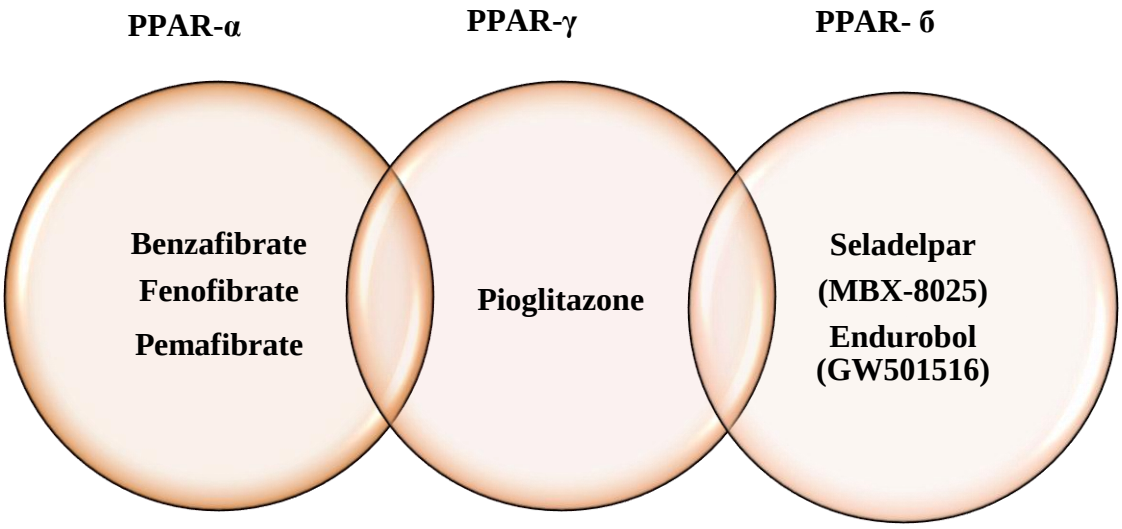

Figure 6: PPAR agonists for NAFLD/NASH

3. Antidiabetic drugs

T2DM is highly linked to NASH and liver-related deaths. The main challenge is determining which antidiabetic medications are most effective for NASH/NAFLD with diabetes. The ideal anti-diabetic treatment for NASH should reduce weight, reduce cardiovascular events, avoid HCC, be cost-effective, and improve quality of life [120]. The only approved diabetes therapy for NASH is *pioglitazone* [98, 115, 121, 122].

- *Metformin* is recommended as the first-line therapy for ADA/EASD because to its inexpensive cost, ability to reduce weight, prevent cardiovascular events, and safety profile. Metformin does not improve liver enzymes or histology in NASH/NAFLD, although it does reduce the risk of HCC and extra hepatic cancers.
- *Glucagon-like peptide 1 receptor agonists* (GLP-1RA) and *DPP4 inhibitors* are the two categories of *incretin-associated drugs*.

  Unfortunately, there is inconsistent data about the effectiveness of DPP4 inhibitors in NASH/NAFLD patients with diabetes, despite the limited number of patients participating in these trials[120].
- *Liraglutide*, a GLP-1 RA, has been shown to be effective in treating NASH patients in tests conducted in Japan (LEAN J study [123]) and Western countries (LEAN study [124]).
- Some benefits of *Dulaglutide* include weekly injection, a prefilled and

disposable device, and safety profiles comparable to those of other GLP-1RAs.

- *Semaglutide*, a novel GLP-1 RA. Compared to other GLP-1 RAs, semaglutide has three benefits. Initially, the SUSTAIN-6 study demonstrated the possible benefit of semaglutide in preventing cardiovascular events [125]. Secondly, according to the SUSTAIN 7 trail, semaglutide outperforms Dulaglutide in terms of weight loss and glucose management in patients with type 2 diabetes. Third, an oral semaglutide medication is currently being developed and will soon be used in clinical settings. Consequently, Dulaglutide or semaglutide will be the most promising GLP-1 RA among them when it comes to treating diabetic NASH [120, 126].
- It is unknown how SGLT2 inhibitors affect the histology of the liver. Takeda et al. described a case of NASH with T2DM in which *Ipragliflozin* treatment resulted in the resolution of steatosis, inflammation, and hepatocyte ballooning [127]. Additionally, Akuta et al. recently showed that three of the eight NAFLD patients saw improvements in their liver fibrosis and that all eight patients' hepatic steatosis was reduced with SGLT2 treatment [128].

  Serum transaminase activity in SGLT2 inhibitor-treated individuals were considerably lower than those in the placebo group, according to sub analyses of three RDBPCTs of SGLT2 inhibitor (*Canagliflozin* [129, 130], *Luseogliflozin* [131]) for the treatment of T2DM.

4. Lipid-altering agents

- *Ezetimibe:* Although there are contradictory findings, ezetimibe, a strong inhibitor of cholesterol absorption, has been investigated for the treatment of NASH/NAFLD [132, 133]. Following ezetimibe treatment, histological results (steatosis and inflammation) were observed without control arms [132, 133]. According to RDBPCT (MOZART) research, ezetimibe 10 mg taken orally every day for 24 weeks had no significant impact on hepatic steatosis when compared to a placebo [134].

  Statins may be used to treat dyslipidemia in NAFLD patients, who are at high risk for cardiovascular morbidity and mortality [98]. Statin usage may reduce liver inflammation, ameliorate fibrosis, and lower the risk of hepatocarcinogenesis [135].

- *Pemafibrate:* Pemafibrate, a new SPPARMα, was approved in Japan in 2017. In a phase 2 study in Japan, RDBPCT reduced serum transaminase levels and lipid profiles in dyslipidaemic patients while minimizing side effects [136]. Pemafibrate, which improves liver damage in a diet-induced mouse model of NASH [137], could be a viable treatment for human NASH. Clinical trials for NAFLD/NASH treatment in Japan are set to begin soon.
- *Aramchol:* Aramchol, a cholic-arachidic acid conjugate, can inhibit stearoyl-CoA desaturase (SCD). Aramchol was initially developed for the treatment of gallstone [138]. Nevertheless, rather than gallstone breakdown, hepatic fat buildup was significantly reduced in animal trials. In humans, the aramchol (300 mg/day) group showed a considerable reduction in hepatic fat content [139].
- *GS0076:* One important enzyme that controls the transformation of malonyl-CoA into acetyl-CoA is acetyl-CoA carboxylase (ACC) [140]. Malonyl-CoA is a crucial modulator of fatty acid metabolism, regulating the balance between fatty acid oxidation and de novo lipogenesis. GS-0976 is an experimental ACC inhibitor. This proof-of-concept trial is open-label and is being conducted on patients with NASH. The results showed that treatment was linked to statistically significant changes in liver fat content and noninvasive fibrosis markers in ten individuals who received oral GS-0976 20 mg once day for 12 weeks.

5. Anti-hypertensive drugs

- *Angiotensinogen receptor blocker:* There are no specific drugs that are preferred for controlling hypertension; nevertheless, some research indicates that angiotensinogen receptor blockers (ARB) may have anti-fibrotic effects in people with non-alcoholic steatohepatitis (NASH)

6. FXR ligand

- *Obeticholic acid (OCA):* Obeticholic acid (OCA) is a synthetic form of chenodeoxycholic acid, the natural bile acid, and a ligand of the farnesoid X receptor (FXR). FXR activation has been shown to decrease hepatic glucogenesis, lipogenesis, and steatosis in animal models [142].
- *INT-767:* As a dual agonist on FXR/Takeda G-protein-coupled receptor 5 (TGR5), INT-767 is an analogue of bile acid. INT-767 enhanced the histological characteristics of NASH in an animal model and controlled the activation of

hepatic monocytes [143]. It is known that TGR5 affects inflammation, bile composition and secretion, glucose homeostasis, and energy metabolism.

- *MGL-3196:* The main thyroxine (T4) receptor in the liver is thyroid hormone receptor β (THRβ). This receptor helps the body break down cholesterol and get rid of it through bile. A very specific THRβ agonist called MGL-3196 was initially developed to treat dyslipidemia, but it has also been demonstrated to lessen liver steatosis in rats given fat as food [144].

7. Anti-inflammatory and anti-apoptosis agents

- *Pentoxifylline:* A derivative of methylxanthine, pentoxifylline (PTX) reduces oxidative stress and exhibits anti-inflammatory properties. A RDBPCT shown that, in comparison to placebo, PTX therapy for a year greatly improved the histological characteristics of NASH [145]. However, this medicine is no longer accessible in Japan due to poor efficacy in treating the consequences of brain stroke.
- *Selonsertib:* Apoptosis signal-regulating kinase 1 (ASK1) is triggered by TNF-α, oxidative or ER stress, leading to apoptosis and fibrosis via the p38/JNK pathway [146]. Therefore, it has been suggested that inhibiting ASK1 is a good way to treat NASH.
- *Tipelukast:* Tipelukast, also known as MN-001, is a brand-new, orally bioavailable small-molecule drug that, in preclinical models, exhibits antifibrotic and anti-inflammatory properties through a variety of mechanisms, including leukotriene (LT) receptor antagonistic action, inhibition of phosphodiesterases (PDE), primarily 3 and 4, and inhibition of 5-lipoxygenase (5-LO) [142].
- *Emricasan:* In murine models of NASH, Emricasan, an irreversible caspase inhibitor, improves NAS and fibrosis [147].

8. Gut microbiome

- *IMM-124e:* IMM-24e is an IgG-rich extract of bovine colostrum from cows immunized against lipopolysaccharide (LPS). IMM-24e reduces liver exposure to gut-derived bacterial products and LPS. Ten patients with biopsy-proven NASH participated in an open-label, phase 1/2 clinical research that increased serum levels of GLP-1, adiponectin, and T regulatory cells, which in turn improved glycemic control and liver enzymes [148].
- *Solithromycin:* A powerful macrolide antibiotic of the next generation is called solithromycin. After receiving

solithromycin medication for 90 days, all six NASH patients showed reductions in their ALT level (mean reduction, 17.8 U/L) and NAS (mean reduction, 1.3) in a phase 2 open-label study [142].

- *TLR4 antagonist:* Long-acting and small molecule, JKB-121 functions well as a mild antagonist at the Toll-like receptor 4 (TLR4). It is a non-selective opioid antagonist that has been demonstrated in a methionine/choline deficient diet fed rat model of non-alcoholic fatty liver disease to protect the LPS-induced inflammatory liver injury. Inhibiting the TLR4 signaling pathway may help reduce inflammatory liver damage and fibrosis in NASH patients [56].

9. Anti-fibrotic agents

Advanced hepatic fibrosis is the leading cause of death in NASH patients [4, 149], highlighting the need for effective anti-fibrotic treatments. Several anti-fibrotic medicines have been developed to treat advanced NASH.

- *Cenicriviroc:* Cenicriviroc (CVC) is a C-C motif chemokine receptor-2/5 (CCR2/5) antagonist aimed to reduce inflammation. This drug also has antifibrotic properties and improves insulin sensitivity. CCR2-mediated macrophage migration into adipose tissue is speculated to have led to insulin resistance and T2DM. Using a CCR2 antagonist improved glycemic markers slightly compared to the placebo group [150]. A CCR5 antagonist may reduce the migration, activation, and proliferation of collagen-producing hepatic stellate cells[151].
- *Simtuzumab (SIM):* SIM is a monoclonal antibody directed against lysyl oxidase-like 2 (LOXL-2), an enzyme that cross-links collagen and is over expressed when fibrosis advances [152].
- *Galectin-3 antagonist:* The expression of the protein galectin-3, which is crucial for the progression of hepatic fibrosis, was elevated in NASH, with macrophages around lipid-laden hepatocytes exhibiting the highest expression. The galectin-3 inhibitor GR-MD-02 significantly reduced collagen deposition and NASH activity while also improving liver histopathology in mouse models [153].

2.2 Key developments in the management of NASH/NAFLD

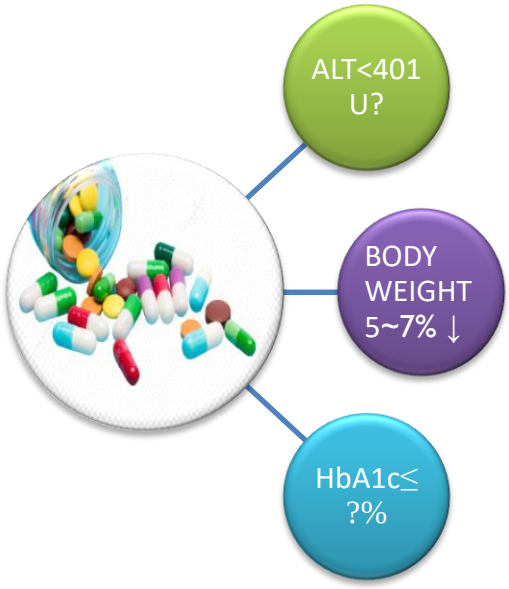

Figure 7: Milestones in the treatment of NASH

Liver histology has been the gold standard for evaluating the efficacy of treatment in nonalcoholic steatohepatitis (NASH). However, risk, sample error, observers' variety in pathological interpretation, and cost make repeated liver biopsies almost impossible to perform in NASH patients. To track the illness and assess the effectiveness of treatment, it is important to set up measures that are simple, reliable, and economical.

ALT, **body weight**, and **HbAIc** are the three parameters that have been considered as the milestones in the treatment of NASH [142] (Figure.7).

ALT: The sub-analysis of the PIVENS trial found that ALT response, defined as a drop of > 30% from baseline or ALT levels below 40 IU/l, indicates histological improvement [154]. In 2015 [155], we found that ALT response was the most effective predictor of NAS or fibrosis regression in 52 Japanese patients with NASH who underwent repeated biopsies.

Body weight: Weight loss is thought to be correlated with improvements in liver histology in NAFLD/NASH patients. A study of 261 NASH patients with recurrent liver biopsies found that weight loss, diabetes absence, ALT normalization, and baseline NAS less than 5 were independent predictors of NASH resolution without fibrosis worsening following a year of lifestyle management [156].

HbA1c: In 39 Japanese patients with diabetes and NAFLD who had sequential liver biopsies, lower HbA1c levels [157] were significantly related with improved fibrosis. We believe that these three clinical measures, ALT, body weight, and HbA1c, can serve as milestones in treating NASH (Fig.7). However, each parameter's goal to improve hepatic fibrosis will be determined.

2.3 Who ought to give care?

A diabetes specialist should consider liver function. According to three fibroscan investigations, 12–18% of diabetes patients

are thought to have severe liver fibrosis based on various cutoffs [158-160]. However, cardiovascular illnesses are the main cause of death for people with nonalcoholic fatty liver disease (NAFLD), followed by extra hepatic malignancy and disorders related to the liver [161]. Treatment for NASH/NAFLD involves a wide range of stakeholders (Fig.8), including patients, hepatologists, cardiologists, endocrinologists, and dieticians. Pharmacotherapies and lifestyle modification interventions ought to be administered in collaboration with multidisciplinary medical personnel [162].

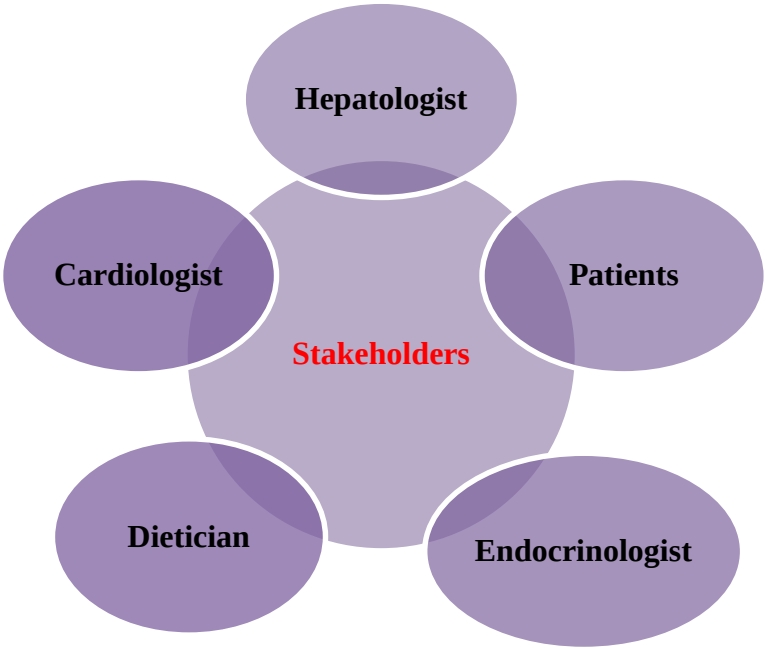

Figure 8: Variety of stakeholders in the treatment of NASH/NAFLD

CONCLUSION:

The liver is essential for lipid metabolism, as it manages the intake, production, oxidation, and distribution of lipids to various organs. The majority of the liver's cell population is made up of parenchymal cells, with hepatocytes comprising approximately 78%. Research indicates that NAFLD primarily involves hepatocyte inflammation and fat accumulation in its early stages, progressing to fibrosis and/or cirrhosis in the later stages. Moreover, the development and progression of NAFLD are influenced by mitochondrial dysfunction, lifestyle factors, and both genetic and epigenetic variables. Making lifestyle changes can greatly enhance metabolic imbalances, reduce hepatic steatosis, and alleviate inflammation linked to NAFLD.

Genetic variations, especially single nucleotide polymorphisms, can influence

various processes such as the liver's uptake of FFAs, oxidative stress, endotoxin response, and the synthesis and activity of cytokines. Thus, they seem to play a crucial role in the initiation and development of NAFLD. Insulin resistance, obesity, and elevated TNF-α levels are closely associated with mitochondrial dysfunction. Moreover, reactive oxygen species (ROS) and oxidized LDL particles can stimulate hepatic stellate cells and Kupffer cells, resulting in increased collagen production and subsequent liver fibrosis.

This present article discusses the pathophysiology of NAFLD, the impact of nutrition in NAFLD, and the involvement of genetic variables and mitochondrial disorders in raising the prevalence of NAFLD condition. This page also discusses NAFLD treatment techniques, which mostly include weight loss and the use of various pharmaceuticals such as pioglitazone, rosiglitazone, metformin, atorvastatins, and vitamin E.

CONFLICT OF INTEREST:

There is no such conflict of interest related to this investigation.

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