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Systematically Decoding NASH Step by Step

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Abstract
NAFLD encompasses a wide spectrum of disease including hepatic steatosis, inflammation and fibrosis. NASH is a progressive form of NAFLD. The prevalence of NAFLD and NASH correlates with the global rise in obesity and metabolic syndrome, affecting both adults and children. NAFLD is rising to be one of the major causes of liver disease worldwide with an approximate global incidence of 24%. The association between NAFLD and Type 2 Diabetes has been well documented, but other endocrine disorders like PCOS, hypothyroidism, are known in clinical practice to be associated with NAFLD. The 20% rule says that 20% of individuals with NASH with advanced NFS (F3) proceed to have cirrhosis over a 2-year time frame. The most effective intervention to manage NAFLD remains to be lifestyle modifications, with sustained weight loss. Bariatric surgery is mostly indicated for morbidly obese patients, as it helps reduce the weight of the patient. Metformin and Litaglutide are pharmacological options to control diabetes, Obeticholic acid has anti-fibrotic effects, while Gemfibrozil and Clofibrate control the level of triglycerides and cholesterol in the blood thereby controlling the development of NASH. Thiazolidinediones (TZD) is an insulin sensitiser and Resmetriom helps by reducing the formation of fat in liver, which is helpful in treating NASH. Treatment with berry juice decreased apoptosis rates in NASH models. Inspite of several challenges, liver transplantation is the standard treatment option for NASH. The risk of developing steatosis reaches 100% at 5 years after liver transplantation.

Keywords: Non-alcoholic Steatohepatitis: A Comprehensive Review of Pathogenesis, Diagnosis, and Treatment Approaches

1. Introduction

Non-alcoholic Steatohepatitis (NASH) is an advanced stage of Non-alcoholic Fatty Liver Disease (NAFLD), characterised by hepatic steatosis, inflammation and cellular damage, occurring in patients who consume little to no alcohol [1]. While fatty liver disease has been recognized for centuries, the specific condition of NASH, where fat accumulation in the liver is accompanied by inflammation and cell damage, was not clearly defined until the mid-20th century. It has become a major global health issue, affecting both adults and children and a primary contributor to liver disease. The prevalence of NASH is correlated with the global increase in metabolic disorder in the late 20th century [2].

Currently, lifestyle modifications remain the most effective intervention for managing NAFLD before the onset of fibrosis. However, there is an urgent need for effective pharmacological therapies to be widely available. The problem is further compounded by the challenges of diagnosing NASH, which often requires invasive liver biopsies, leading to high screen-failure rates in clinical trials [3].

Recent advances in understanding the pathogenesis of NASH have identified potential therapeutic targets, including insulin sensitizers, antioxidants, and modulators of the gut-liver axis [3].

In light of these developments, it is crucial for healthcare providers and policymakers to prioritize NAFLD and NASH management, as the growing patient population may impose significant burdens on healthcare systems. This systematic review discusses the recent advances in elucidating the pathological mechanism of NASH, diagnostic methods and highlights emerging therapeutic strategies including aimed at addressing this escalating health crisis.

2. Epidemiology

NAFLD is becoming one of the leading causes of liver disease globally, with an average incidence rate of 24%. In actuality, reports of NAFLD prevalence indicate that it is highest in South America and the Middle East and lowest in Africa [4-6]. Individuals with type 2 diabetes are particularly vulnerable to NASH and NAFLD. According to a recent meta-analysis, the

prevalence of NAFLD worldwide among T2DM patients is 57.80%, while the prevalence of NASH is 65.26% among T2DM patients who have had a biopsy [7].

There has been a lot of interest in the higher risk of NASH and associated fibrosis in Hispanic Americans. Indeed, the estimated prevalence rate of NAFLD among Hispanics of Mexican descent is 33%, whereas it is only 18% among Hispanics of Dominican or Puerto Rican descent [8]. These data suggest a complex interplay between environmental and inheritable factors.

There have been reports of adult NAFLD prevalence in India ranging from 6.7% to 55.1%. NAFLD may be the cause of an asymptomatic rise in liver enzymes in nearly one-third of cases. Furthermore, two-thirds of patients with "cryptogenic" cirrhosis had NAFLD, according to specimen histology data from liver transplant institutes [9, 10]. The prevalence of NAFLD in the paediatric age group in India varies from 7.3% to 22.4% [11, 12]. It is seen that the prevalence of NAFLD increases with age [13].

An estimated 168 million children in India alone suffer from non-alcoholic fatty liver disease (NAFLD) [14]. In both high- and low-income socioeconomic groups, the number of children and adolescents who are overweight is increasing, at about 20% [14]. Potential obesity-related concerns are concerning since weight growth in school, rather than adulthood, increases the risk of NAFLD. Given that NAFLD is more prevalent in older adults, the overall percentage of adults in India who have the condition may continue to rise over the coming decades [15]. From a public health standpoint, these estimates are crucial.

3. Pathophysiology

NAFLD is a spectrum of disease which occurs in the liver that can begin as simple steatosis to fibrosis and finally convert into cirrhosis, including NASH. NASH is characterized by steatosis, injury in the hepatocyte cell and inflammation, with or without the presence of fibrosis. The major associating factors of this disease are type 2 diabetes and insulin resistance [16-18].

3.1 General pathophysiology

The "*multiple parallel hits*" hypothesis model, which depicts the process of NAFLD formation and progression in people with genetic predisposition, has superseded the conventional "*two hits theory*" [19, 20, 21]. It posits that a variety of variables act in parallel and synergistically. The premise behind this multiple hit theory is that it is caused by a multitude of conditions, like obesity, poor diet, and insulin resistance.

Intra-hepatic fatty acid buildup results in mitochondrial dysfunction [22]. Reactive oxygen species (ROS) generation, oxidative stress, and endoplasmic reticulum stress all are increased. The change of the gut microbiome triggers the formation of cytokines, including Interleukin-6 and Tumor Necrosing Factor-α [22]. These result in a persistent inflammatory condition of the liver, which facilitates the onset and advancement of NAFLD and NASH.

3.2 Causes of NASH

3.2.1 Type 2 diabetes

Glucotoxicity and lipotoxicity along with individual genetic susceptibility appear to be the reason for a higher prevalence of steatohepatitis in patients of T2DM [23]. Conversely, a high correlation of NAFLD with hepatic insulin resistance makes it one of the major presumptive causes for the development of type 2 diabetes [24]. Ectopic fat accumulation in the liver results in increased generation of ROS pro-inflammatory cytokines and decreased insulin signalling [25].

3.2.2 PCOS

According to a meta-analysis of 17 studies, women with PCOS have a markedly increased risk of NAFLD, with the risk being higher in obese and patients of hyperandrogenism [26]. In the UK, a retrospective longitudinal cohort research revealed that women suffering with PCOS had a greater prevalence of NAFLD [27].

3.2.3 Hypothyroidism

Hypothyroidism is a prevalent endocrine condition defined by thyroid hormone deficiency [28]. Possible pathophysiological mechanisms for this epidemiological relationship include increased oxidative stress, elevated lipid peroxidation, and the common development of insulin resistance in hypothyroidism, which may be brought on by elevated levels of different cytokines such as TNF-α, interleukin-1, or leptin [29, 30].

3.2.4 Growth Hormone Imbalance

Growth hormone (GH) is thought to have the liver as one of its primary organ targets. GH increases glycogenolysis and gluconeogenesis, which decreases glucose metabolism because free fatty acids and glucose compete for substrate status, causing insulin resistance and the favored discharge of free fatty acids from visceral adipose tissue [31].

Excess GH secretion stimulates gluconeogenesis and glycogenolysis, which has detrimental effects on insulin signalling and glucose metabolism at hepatic and extrahepatic locations. It has been proposed that increased local glucocorticoid clearance caused by 5α-reductase activation serves as a protective mechanism that stops the advancement of metabolic abnormalities in the liver [32].

3.2.5 Others

In individuals with normal aminotransferase (AST/ALT) levels, vitamin D insufficiency has been linked in a number of observational studies to the onset and severity of NAFLD [33, 34]. Moreover, patients with NAFLD are 25% more likely to have vitamin D deficiency than those without the disease [35]. Prolactin receptors may be involved in the control of hepatic metabolism because they are found in the liver. Observational studies have shown a negative connection between prolactin plasma levels and the development of NAFLD, insulin resistance, and body weight [36, 37].

4. Disease progression in NASH

The 20% rule: Approximately 20% of subjects with NASH and advanced NFS fibrosis or compensated cirrhosis advance to cirrhosis or decompensation within 2 years [38].

According to Sanyal *et al*., 1 out of 5 NASH patients with severe fibrosis or cirrhosis will eventually have decompensation or cirrhosis. A higher risk of cirrhosis is associated with elevated hepatic fibrogenesis, which can assist individuals to be prioritized for more rigorous lifestyle control, monitoring. This is demonstrated by elevated activation of hepatic stellate cell, collagen deposition on biopsy, and elevated serum fibrosis markers. However, non-invasive serum markers only guide clinical management decisions with limited accuracy, and the best combination of measures to reflect changes in disease state or reliably predict outcomes is still to be found [39].

5. Histopathological changes in NASH

On liver biopsy it is observed that more than 5% fat

accumulation in hepatocytes is an important characteristic of NAFLD.

According to the oxygen supply, the liver is functionally separated into three zones:

- Zone 1: Maximum oxygenation, surrounding portal tracts.
- Zone 2: In between Zone 1 and Zone 3
- Zone 3: Minimal oxygenation, surrounding central veins.

For diagnosing NASH, the American Association for the Study of Liver Diseases (AASLD) has identified the following key histopathological features [40]:

1. Steatosis: Predominantly macrovesicular.
2. Lobular Inflammation.
3. Hepatocellular swelling: Maximum evident in zone 3.

Fibrosis often accompanies NASH, starting in zone 3 and resembling a "chicken wire" pattern due to collagen and extracellular matrix deposition along sinusoids. NASH-related cirrhosis can be macronodular or mixed, and its development may obscure other histological features.

6. Grading

NASH is graded based on the degree of inflammation, ballooning, and steatosis [40, 41, 42]:

- Grade 1: Steatosis up to 66%,
- Grade 2: Any level of steatosis, evident swelling in zone 3, and moderate portal inflammation.
- Grade 3: Pan-acinar steatosis, swelling and clear chaos in zone 3.

7. Staging

The stages of NASH are determined by the location and degree of fibrosis [40, 41, 42]:

- Stage 0: No fibrosis
- Stage 1: Zone 3 pericellular fibrosis only.
- Stage 2: Periportal Fibrosis along with stage 1.
- Stage 3: Bridging fibrosis along with stage 2.
- Stage 4: Cirrhosis

Macrovesicular steatosis, ballooning hepatocyte degeneration, distributed inflammation, apoptotic cells, and Mallory-Denk bodies (MDBs) are further histological characteristics of NASH.

NASH can result in cirrhosis and severe fibrosis, which can lead to hepatocellular carcinoma (HCC). Patients with defective metabolism and either cirrhotic or noncirrhotic NAFLD are more likely to develop the Steatohepatitic type of HCC (SH-HCC), which shares several histologic characteristics with NASH [43]. Extensive fatty changes can limit the effectiveness of these diagnostic markers. NASH and alcoholic steatosis (ASH) may also show reticulin loss, presenting a diagnostic pitfall when evaluating SH-HCC. It is still unknown where the steatotic phenotype in SH-HCC originates, whether it is due to an independent mechanism or the tumor's reaction to a fatty environment.

8. Signs and symptoms

In most of the cases of NAFLD patients do not present with any symptoms or show any sign except in a few cases where fatigue, hepatomegaly, lipoma, and abdominal discomfort are reported. NASH can be asymptomatic in approximately 48-100% of cases. It is often discovered during medical evaluations for unrelated reasons.

9. Methodology

We conducted an electronic search using databases like Medline through Ovid, PubMed, Embase, Cochrane& Google Scholar. The goal was to find articles related to keywords 'Non-alcoholic steatohepatitis (NASH)', 'Non-alcoholic fatty liver disease (NAFLD)', 'Cirrhosis' in conjunction with 'Pathophysiology', 'Prevalence', 'diagnosis', 'Histopathology' & 'Therapeutic measures'. This search focused solely on studies involving humans, without any language restrictions. Moreover, we manually checked reference lists from relevant studies to see how the information applied to our research. To prevent overlap in patient groups, if authors wrote about the same cohorts in multiple publications, we only included the most recent or detailed study in our analysis. For a study to be eligible for inclusion, it had to meet specific criteria: addressing NASH, elaborating pathophysiology, discussing treatment modalities, and being published after January 2000.

9.1 Data Extraction and Methodological Assessment

The reports we retrieved contained information such as authorship, publication year, journal name, sample size, methodologies used, histological information, diagnostic techniques & therapeutic strategies employed. To minimize bias during data abstraction, four reviewers independently gathered the required data.

9.2 Diagnostic techniques

The three criteria that determine if NASH is present are not being an alcoholic, identifying steatosis through imaging or histology, and properly ruling out other liver conditions [44-49].

10. Imaging techniques

10.1 Ultrasound

The most popular technique for qualitative evaluation of hepatic steatosis at the moment is abdominal ultrasonography (USG) due to its non-invasive nature, accessibility, affordability, and informational value. Ultrasound diagnosis has a number of drawbacks, including being subjective, operator-dependent, and having low sensitivity for identifying mild steatosis.

While magnetic resonance imaging (MRI) is currently far more expensive and less accessible than computed tomography (CT), both seem to be more objective and sensitive methods for quantifying steatosis. On the other hand, magnetic resonance spectroscopy (MRS) offers even higher sensitivity in detecting these pathological processes, though it is less commonly available [50].

In addition to these imaging modalities, laboratory investigation (AST, ALT), omic based biomarkers, RNA biomarkers, liver biopsy can be used [50].

11. Treatment

NAFLD, per se, is considered as a benign condition and does not generally require any drugs or surgical treatment. However, co-morbidities like diabetes mellitus, dyslipidemia, and obesity need to be looked into and treated accordingly [49, 51].

11.1 Lifestyle Modifications

First line management is focussed mainly on bringing about

a sustained loss in weight [49]. In many situations, dietary and activity changes may not be enough to improve behavior since smoking and other factors may also be linked to advanced liver fibrosis. [52, 53]. Remarkably, moderate alcohol use has been related to a decreased risk of NASH onset and progression in cohort studies [54, 55]. Most of NAFLD patients do not exercise, and hence, the prevalence is negatively correlated with fitness levels [56].

11.2 Thiazolidinediones (TZDs)

TZDs improve steatosis, hepatocellular ballooning, inflammation and reduce the risk of fibrosis progression [57]. A meta-analysis of 8 RCTs found that pioglitazone reversed the advanced stages of NASH, irrespective of the diabetic status of the patient [58]. Another TZD, rosiglitazone, was taken off European markets by the European Medicines Agency in 2010 [59].

11.3 Metformin

Metformin, one of the first anti-diabetic medications used to treat NASH, improves liver function tests, helps people lose weight, and helps some people with fibrosis and necroinflammation [60]. Evidence seems to suggest that it reduces the chance of hepatocellular carcinoma (HCC) [61].

11.4 Liraglutide

Glucagon-like peptide-1 (GLP-1) analogues like liraglutide improve glycemic control and promote weight loss [62]. Liraglutide is one of the leading drugs available for NASH as the safety profile of this drug is known and has benefit over a number of metabolic diseases.

11.5 Statins

Statins are a cornerstone in the pharmacological therapy of dyslipidemias. Statins modulate NASH by inhibiting small GTPases, improves hepatic fatty acid oxidation via PPARα, increases antioxidant paraoxonase 1 (PON) activity, exerting anti fibrogenic and anti-inflammatory effect [63]. Pravastatin has been shown to reduce inflammation and steatosis with no effect on the extent of fibrosis [64]. Post hoc data from clinical trials show that mainly, atorvastatin, improves NASH and reduces cardiovascular events with rosuvastatin showing significant histological improvement [65]. Statins usage may decrease the serum transferase levels toward normal range and ultrasound findings may improve but further long term trials are needed to address clinically important outcomes [66].

11.6 Farnesoid X receptor (FXR) agonists

FXR, cognate sensor for bile acid, is involved in controlling enzymes like the sterol regulatory element-binding transcription factor 1 (SREBP-1) and reducing endogenous bile acid production, thereby regulating glucose and lipid metabolism [67, 68, 69]. Novel roles include promoting liver regeneration and protecting against hepatocarcinogenesis [70].

A partly-synthetic derivative of the major bile acid chenodeoxycholic acid, obeticholic acid (6α-ethyl-chenodeoxycholic acid) is a natural FXR agonist that is 100 times more powerful [71, 72]. With improvements in indicators like ALT, AST, and GGT, treatment with obeticholic acid has been demonstrated to stop the course of fibrotic illness [73]. Activation of FXRs present in hepatic stellate cells reduces expression of the extracellular matrix and protects against fibrosis [74, 75, 76]. The anti-fibrotic effect has been well demonstrated by liver histology and non-invasive tests [77]. Other such agents under investigation and clinical trials include Cilofexor, Tropifexor, Nidufexor and Fexaramine [78].

11.7 Apical Na+ dependent bile acid transporter (ASBT) inhibition

Increased hepatic free cholesterol has been linked to severity of NASH [79]. Hepatic cholesterol will be diverted for further de novo bile acid synthesis if bile acid resorption in the final ileum is blocked [80]. In light of this, it is predicted that intestinal bile salt reabsorption restriction will ameliorate NASH [81]. Volixibat is an oral, potent, competitive inhibitor of ASBT that is minimally absorbed [82].

A Phase 2 interventional clinical trial, however, failed to show any liver-related therapeutic benefit of volixibat, only increasing C4 and decreasing serum cholesterol levels [83].

11.8 Orlistat

Orlistat helps in overcoming fat accumulation and liver fibrosis in obese NASH patients [84]. As of right now, evidence only supports its usage as a palliative therapy approach to improve liver damage markers [85].

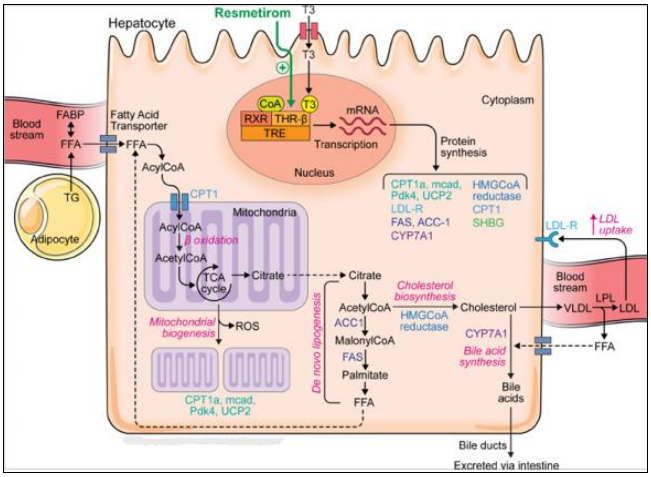

Fig 1: Mechanism of action of Resmetirom

11.9 Resmetirom

Resmetirom is an orally acting selective agonist of thyroid hormone receptor beta (THR-ß) [86] (Figure 1). The U.S. FDA authorized it as the first therapeutic medication for NASH on March 14, 2024 [87]. Recommended dosage is 80 mg once daily, which needs to be reduced to 60 mg, when used concomitantly with moderate CYP2C8 inhibitors like clopidogrel [88].

11.10 Vaccinium

Both leaves and fruits of *Vaccinium myrtillus* (bilberry) were recognized in the Middle Ages for their medicinal value [90]. Multiple pharmacological effects have been documented from in vitro and preclinical studies, including ophthalmic activity, wound-healing, anti-ulcer, anti-atherosclerotic, anti-diabetic, antibacterial, antiviral, anti-carcinogenic, anti-inflammatory and vasoprotective properties [91, 92]. Bilberry has been called a “liver-friendly food supplement” as it has been shown to reduce oxidative injury, steatosis and improved hepatocyte survival [93]. Histochemical staining and biochemical analysis of hepatic

collagen (marker of fibrosis) was found to be significantly lower in Mirtoselect (anthocyanin rich billbery extract) treated mice [94]. Blueberry juice, via PPAR-α, modulates the SREBP-1c/PNPLA-3 pathway, and thereby inhibits the progression of NASH [95]. Cranberry (*Vaccinium macrocarpon*) has been shown to significantly reduce the markers of fibrosis like TGF–β, α-SMA expression and collagen deposition [96]. Analysis using flow cytometry showed that berry juice administration reduced the rates of apoptosis in NASH models [97].

11.11 Vitamin E

In NASH patients, the thought that vitamin E which is an antioxidant can improve liver histology over time has been explored on a regular basis. A clinical trial done between Pioglitazone and Vitamin E indicated that Vit E had a greater percentage of NAS (NAFLD Activity Score) improvement in liver biochemistry [98].

11.12 Bariatric surgery

Procedures like bilio-intestinal bypass, laparoscopic gastric banding, Roux-en-Y, sleeve gastrectomy, and Biliopancreatic division are mostly indicated in morbidly obese patients. Jejunoileal bypass is obsolete now due to vast liver complications that arose after surgery. Though not recognized by recommendations, weight loss improves insulin sensitivity and contributes to the reduction of visceral fat [99].

11.13 Liver Transplantation (LT)

For severe liver pathology and NASH, LT is the usual course of therapy. The survival of patients with NASH after liver transplantation is found to be the same as in the patients of other etiologies with 1-, 3-, 5-year survival rate of 88%, 82% and 77% respectively [104]. However, in individuals who have received a transplant, NASH following LT may either develop de novo or recur [105]. The person having increased triglyceride and high BMI post LT is highly associated with post LT recurrence of NAFLD [106]. Several challenges are present for post LT care of patients with NASH. Calcineurin inhibitors and antimetabolites are recommended at its lowest effective dose. Since corticosteroids can induce and worsen the disorder, they should not be used after the initial postoperative phase [107]. The optimal time for getting a biopsy after transplantation for NASH or cryptogenic cirrhosis is, however, not known. A sizable percentage of NASH patients may have normal liver enzymes. The widespread use of magnetic resonance elastography (MRE) and transient elastography (TE) can lessen the requirement for biopsy. Weight management is very much important to overcome the post LT metabolic syndrome [108,109].

11.14 Vaccination

The Centers for Disease Control and Prevention (CDC) advises individuals with liver disease to stay up-to-date with pneumococcal, hepatitis B, and hepatitis A immunisations [110, 111]. Nonetheless, vaccination rates—even for hepatitis A and B—have been demonstrated to be below ideal for individuals with chronic liver disease under hepatologist care [112]. A vaccination schedule should be maintained by physicians.

12. Conclusion

Advancement in the medical field has paved the way to properly understand the pathophysiology & predict the upcoming secular trend of NASH. It is recommended to develop a more sensitive and specific diagnostic method, which is cost effective and can provide noninvasive tools for mass screening. Collaboration of different specialities is needed to tackle the high prevalence of NASH in society. An international response is needed to unify the guidelines for treatment [113]. As the global trend for NASH is peaking, lifestyle modification & proper control of blood sugar will be the mainstay approach to prevent & reduce the burden for NASH. However, NASH can only be tackled by day-to-day changes like increasing physical activity and rejecting a sedentary lifestyle. Epidemic of NASH is imminent, so the health system should accordingly, increase their modalities & services to tackle the burden.

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