Journal of Advanced Zoology

ISSN: 0253-7214
*Volume **44** Issue **S-1 Year 2023** Page **1059:1072***

Multifactorial Aspects Influencing Non-Alcoholic Fatty Liver Disease (Nafld)

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Article History

Received: 06 June 2023
Revised: 05 Sept 2023
Accepted: 31 Oct 2023

Abstract

Nonalcoholic fatty liver disease (NAFLD) is a growing public health concern, with a prevalence of up to 25% worldwide. While once considered a benign condition, NAFLD is now recognized as a major cause of chronic liver disease, liver failure, and hepatocellular carcinoma. The pathogenesis of NAFLD is multifactorial and involves a complex interplay between genetic, environmental, and metabolic factors. In this review, we provide an overview of the multifactorial aspects of NAFLD, including genetic predisposition, insulin resistance, dyslipidemia, gut microbiota, dietary factors, and physical inactivity. We also discuss the role of inflammation, oxidative stress, and hepatic steatosis in the progression of NAFLD to nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma. Finally, we review the current and emerging therapies for NAFLD and NASH, including lifestyle modifications, pharmacological interventions, and surgical approaches. The multifactorial nature of NAFLD requires a comprehensive approach to diagnosis, treatment, and prevention, with a focus on addressing the underlying metabolic and environmental factors that contribute to its development and progression.

Keywords: *Non-Alcoholic Fatty Liver Disease; metabolic associated fatty liver disease; Nonalcoholic steatohepatitis; diabetics; Genetic factors; Thyroid dysfunction*

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a term used to describe a prevalent clinicopathological illness in which patients do not have a history of drinking too much alcohol. The prevalence of NAFLD in the general population ranges from 10 to 39% [1]. According to Arab et al. [2], "NAFLD is defined as at least 5% steatosis observed in the hepatocytes on either histology or by imaging methods such as proton density fat fraction (PDFF)". Tarantino et al. [3] explained that, "NAFLD is an increasingly recognized condition, linked to metabolic syndrome (MS)". Green and Hodson [4] revealed that, "according to current theories, the NAFLD is a condition which is characterised by an excessive hepatic buildup of lipids by an enhanced input/output balance of fatty acids and because of high calorie intake, sedentarism, and MS, high energy diets cause the liver to absorb more free fatty acids, by lipolysis and de novo hepatic lipogenesis. Yet, the output mechanisms associated with fatty acid oxidation and the release of very low-density lipoproteins (VLDL) is still insufficient to prevent the accumulation of triglycerides".

Koek [5] observed that, "NAFLD, which includes benign steatosis and Non Alcoholic Steatohepatitis (NASH), can result in liver fibrosis, cirrhosis, and hepatocellular cancer. According to estimates, it affects 50–100% of patients who are overweight or obese, as well as 20% of the general population". NAFLD is a complex and multisystemic disease, and its pathogenesis involves many factors including genetic factors [6]. Diehl et al. [7] explained that, "environmental factors, and metabolic factors metabolism-related and anti-inflammatory factors to antifibrotic targets, almost covering all the key regulators in the pathogenesis of NAFLD". Kleiner and Makhlouf [8] denoted that, "NASH is a more progressive form of NAFLD and is characterized by steatosis, hepatocellular ballooning, lobular inflammation and almost always fibrosis". Matteoni et al. [9] reported that, "although simple steatosis has a lower rate of progression— only about 4% of patients develop cirrhosis and more than 20% of patients with NASH will develop cirrhosis in their lifetime". According to Matteoni et al. [9], "patients with NAFLD were divided into Type I (simple fatty liver), Type II (steatohepatitis), Type III (steatonecrosis), and Type IV (steatohepatitis and steatohepatitis) (steatonecrosis plus either Mallory hyaline or fibrosis)". Alberti et al. [10] found that, "Diabetes and non-alcoholic fatty liver disease (NAFLD) are both caused by the metabolic syndrome, formerly known as Syndrome X".

Cobbina et al. [11] observed that, "the diagnosis of NAFLD is challenging, as the current available routine techniques (serological tests and imaging techniques) are unable to distinguish between steatosis and NASH". Matteoni et al. [9] found that, "the *Matteoni's system* was based on fat accumulation, inflammation, ballooning degeneration, Mallory hyaline and fibrosis. NAFLD patients were put into four groups: Type I (simple fatty liver), Type II (steatohepatitis), Type III (steatonecrosis) and Type IV (steatonecrosis plus either Mallory hyaline or fibrosis)".

Sheth et al. [12] identified that, "risk factors associated with NAFLD include obesity, type II diabetes mellitus (Type II DM), hyperlipidemia, jejunoileal bypass, and medications". Younossi et al. [13] explained that, "the severity of NAFLD is expressed phenotypically and there is a clear variation in prevalence between populations. Many factors, including metabolic co-morbidities, the microbiome, environmental factors, and genetic and epigenetic factors, are responsible for these disparities". Matteoni et al. [9] pointed out that, "the gold standard for defining NAFLD is liver biopsy, which can distinguish between steatosis and NASH". Therefore, the aim of the present study was to identify the major factors influencing NAFLD and also effect of NAFLD on drug metabolism will be discussed in this article.

2. Materials And Methods

1. A ***Literature Search:*** We employed a systematic approach in which we searched renowned databases, including PubMed, Google Scholar, and pertinent medical journals. We conducted the search using specific keywords such as 'Non-Alcoholic Fatty Liver Disease,' 'metabolic associated fatty liver disease,' 'Nonalcoholic steatohepatitis,' 'diabetics,' 'Genetic factors,' and 'Thyroid dysfunction.

2. ***Review Method and Selection Criteria***: Our review methodology, aligned with our research objectives, involved meticulous definition of the scope. We established specific inclusion and exclusion criteria. Inclusion criteria covered research articles, clinical studies, reviews, and meta-analyses published in the last 10-15 years, with a primary focus on multifaceted aspects of NAFLD, including genetic predisposition, insulin resistance, dyslipidemia, gut microbiota, dietary factors, physical inactivity, inflammation, oxidative stress, hepatic steatosis, and their roles in NAFLD progression. Exclusion criteria filtered out unrelated studies and those published before 2010.

3. ***Data Extraction***: Within the context of our review article, and in alignment with our research objectives, we crafted a structured data extraction form to systematically gather essential information from the studies we selected. This form encompassed fields dedicated to the title, authors, publication year, study design, methodology, and key findings. Additionally, we diligently documented details pertaining to therapies, interventions, and preventive measures discussed within our review, which comprises introduction, methods, conclusion, epidemiology, pathophysiological characterization of NAFLD, histopathological diagnosis of NAFLD, and risk factors of NAFLD.

4. ***Data Synthesis:*** In accordance with our research objectives, we systematically synthesized the data obtained from the selected studies. We organized the findings into categories aligned with the multifactorial aspects of NAFLD, encompassing genetic factors, insulin resistance, dietary factors, and other pertinent domains. To enhance the effectiveness of our findings' presentation, we employed tables, figures, and narrative synthesis.

5. ***Manuscript Writing:*** In accordance with our research objectives, we meticulously composed the review article, upholding a well-structured and organized format. We prudently employed the extracted data to bolster the arguments articulated in the article.

Epidemology

Younossi et al. [14] explained that, "NAFLD has diverse manifestations described in all ethnicities all over the world and present in both sexes".Interestingly, we discovered that those with diabetes had a roughly threefold increased chance of dying from chronic liver disorders, primarily due to a non-virus and non-alcohol-related aetiology, which is largely linked to NAFLD [15]. Younossi et al. [16] described that, "in parallel with the obesity epidemic, there has been a rise in obesity-related complications, NAFLD notwithstanding. NAFLD is the most common liver disease worldwide".Lonardo et al. [17] pointed out that, "currently, it is estimated that the global prevalence of NAFLD is approximately 25%, with over 80 million individuals affected in the US alone.There are similar rates in Asia with an estimated pooled prevalence rate of 27.4% (95% CI 23.3–31.9%) observed". Powell et al. [18] observed that, "Although less than 10%17,18 of NAFLD patients experience cirrhotic sequelae and hepatocellular carcinoma in the 10–20 years of diagnosis". Roeb et al. [19] suggested that, "the NAFLD has grown to be a considerable clinical and financial burden in the absence of previously approved pharmacological therapy for this specific indication". Almost 40% of those with NAFLD/NASH-HCC lacked cirrhosis. Even without cirrhosis, NAFLD/NASH, the hepatic component of the metabolic syndrome, may be a risk factor for developing HCC [20].

A revolutionary idea called metabolic associated fatty liver disease (MAFLD) was put forth by a global consensus in 20206. When compared to earlier diagnostic standards for NAFLD7, MAFLD is notably different [21]. Adams et al. [22] concluded that, "according to epidemiological research, people with steatosis alone are more likely to experience the effects of cardiovascular diseases or non-hepatic cancer-related illnesses but are not at higher risk of dying from liver-related causes". Li et al. [23] denoted that, "the prevalence of obesity and NAFLD in Asia has not been thoroughly studied. Chinese adults aged 35 to 74 had an annual incidence rate of 0.70% obesity, which was greater in women (0.77%) than males (0.61%), northern China (0.93%) than southern China (0.51%), and rural areas (0.73%) than urban areas (0.65%). In Asia, the prevalence of obesity was very low previously and recently is increasing at an alarming rate, especially in China, Japan, and India [24].

Vernon et al. [25] added that, NASH, a form of NAFD with active hepatocellular necrosis, liver inflammation, and tissue destruction, and which is linked to more rapid fibrosis progression, would affect 23% of the people with NAFLD". The idea of the gut-liver axis has been offered as one of the treatment targets in this period of the NAFLD epidemic [26].

Pathophysiological Characterization of NAFLD

Byrne & Targher [27] estimated that "NAFLD occurs in at least 25%–30% of adults in high-income countries and in up to 70%–90% of individuals with obesity or type 2 diabetes mellitus (T2DM)". NAFLD patients are more likely to develop cardiovascular disease (CVD), type 2 diabetes, and kidney problems [28]. Furthermore, NAFLD is an independent risk factor for mortality from both liver-related and other causes, emphasizing the importance of slowing disease progression.

NAFLD development is a complicated process that is still not fully understood. Eslam & George [29] found that "the pathogenic pathways of NAFLD are influenced by multiple metabolic, genetic, and microbiome-related factors that are not completely understood". It has been proposed by Edmison & McCullough [30] that the development of NAFLD is a two-step process based on the body of evidence. This process begins with the liver accumulating fat, which will make insulin resistance worse. The second stage of this process is characterized by cellular and molecular alterations that result from oxidative stress and the oxidation of fatty acids in the liver as a result of a number of factors, including cytokine injury, hyperinsulinemia, hepatic iron and/or lipid peroxidation, variation in the extracellular matrix, altered energy homeostasis, and altered immune system function. Triglyceride (TG) buildup in hepatocyte cytoplasm is a defining feature of NAFLD [31]. Manne et al. [31] added that this results from an imbalance between the elimination of lipids and their intake (i.e., fatty acid uptake and de novo lipogenesis [DNL]) (i.e., mitochondrial fatty acid oxidation [FAO] and export as a component of very low-density lipoprotein [VLDL] particles) [31]. Common metabolic conditions such central obesity, type 2 diabetes, and hyperlipidemia are known risk factors for developing both benign liver steatosis and progressive NASH. Recent research has suggested that the etiology of NASH may be caused in part by the metabolic syndrome [32].

According to Sanyal [33], "overnutrition is the main cause of NAFLD, as it results in the growth of adipose depots and the buildup of ectopic fat". In this situation, the visceral adipose tissue compartment is invaded by macrophages, which results in an inflammatory state that encourages insulin resistance. Evidence suggests that altering unhealthy lifestyles can lower transaminase levels and improve NAFLD, which is often associated with an unhealthy lifestyle [34]. Moreover, improper lipolysis in the presence of insulin resistance causes the liver's metabolic capacity to be exceeded by increased de-novo lipogenesis and unchecked fatty acid supply to the organ [33]. The nucleus accumbens, a region of the brain involved in the emergence of cravings, has been connected with opioid and dopamine receptor activation as a result of excessive consumption of both high-fat foods and sugars [35].

Patients with NAFLD exhibit changes in the composition of their gut microbiota, and some findings imply that progressive fibrosis is connected with a fecal-microbiome signature **[**36**]**. The intestinal cells secrete several hormones—among these glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), oxyntomodulin and possibly glucagon—that are involved with pancreatic hormones insulin and glucagon and are important for the maintenance of glucose and lipid homeostasis [37]. Among these hormones, the most studied are the incretin hormones like GLP-1 and GIP that are secreted mainly by the intestine in response to a meal [38].

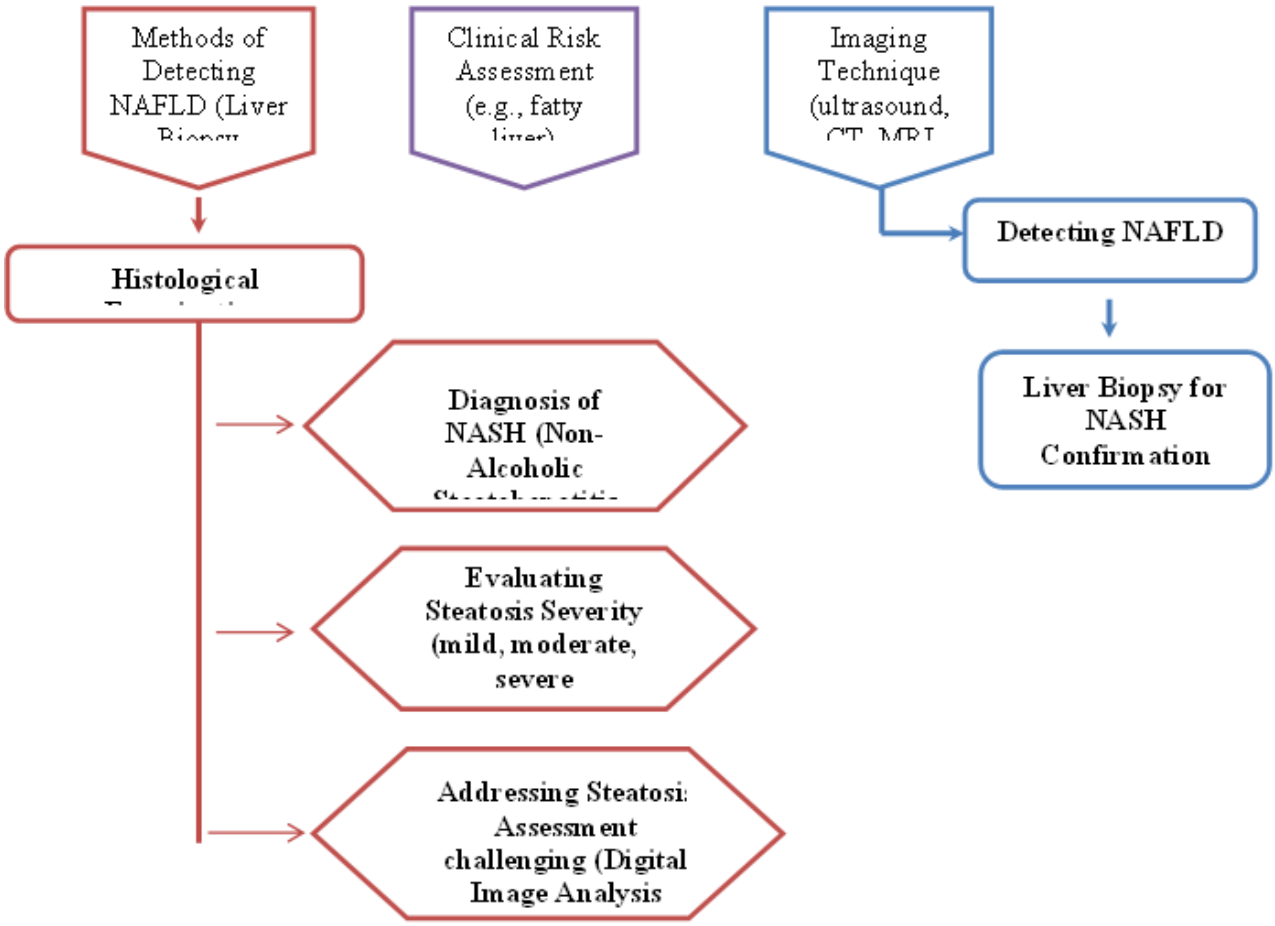
Steatosis, hepatic inflammation, and hepatocellular ballooning are features of Non-alcoholic steatohepatitis (NASH), the most severe version of the illness, which may also include variable degrees of fibrosis [39]. Friedman et al. [40] defined NAFLD as "a progressive disease whereby steatosis (the excessive accumulation of lipids in hepatocytes) constitutes the first disease stage, which can eventually evolve to the more complex stage of NASH". The clinical signs and course of the illness exhibit significant heterogeneity, with patients with NASH and advanced fibrosis (10–20% of NAFLD patients) possibly progressing to cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease, necessitating a liver transplant [41]. Hepatic steatosis, which affects more than 5% of hepatocytes, hepatocellular injury, which manifests as unique hepatocyte ballooning, inflammation, and variable degrees of fibrosis are all symptoms of NASH [40].

Histopathological Diagnosis of NAFLD

NAFLD can be detected histologically or inferred from clinical risk scores (such the fatty liver index) but is most frequently detected by imaging [42]. In order to determine the diagnosis of NASH, Buzzetti et al. [43] pointed out that "liver biopsy samples must undergo a histological examination". Imaging tests like ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) can be used to diagnose NAFLD, a liver biopsy is still necessary to determine the presence and location of NASH's characteristic features like inflammation, hepatocyte ballooning, Mallory-Denk bodies, and early fibrosis [44].

Burt et al. [45] stated that, "histological assessment of the extent of steatosis is usually semiquantitative and is based on the percentage of hepatocyte involvement". The damaged parenchyma is often separated into three sections: 5 to 33%, 33 to 66%, and > 66%. As a result, steatosis can be classified as mild, moderate, or severe, accordingly [46]. Hall et al. [47] observed that, "histopathologists have a tendency to overestimate the extent of steatosis, especially when it is severe; therefore, more accurate and objective methods for its quantitation have been devised mainly based on digital image analysis (DIA)".

Conventional noninvasive imaging techniques, like computed tomography, magnetic resonance imaging (MRI), and ultrasound, cannot detect very small levels of hepatic fat (involving 30% hepatocytes), which makes them potentially unreliable for diagnosing NAFLD [48]. According to the findings of several studies, NAFLD will progress benignly in patients with steatosis, with or without inflammatory acinar alterations, with a low likelihood of developing into NASH and/or fibrosis [49].



Flowchart: illustrating the Methods of NAFLD Diagnosis and Assessment

Risk Factorsof NAFLD

Perumpail et al. [50] revealed that, "based on our current knowledge, it appears that a combination of genetic, demographic, clinical and environmental factors may play a role in determining the likelihood of NAFLD in a given individual. Therefore, the pathogenesis of NAFLD is a multifactorial and multi-step process".

Metabolic risk factors- metabolic syndrome, obesity, diabetics

Angelico et al. [51] observed that, "NAFLD is the most common liver disease worldwide and has been long regarded as the hepatic manifestation of metabolic syndrome". Simmons et al. [52] estimated that, "the term MetS, also known as insulin resistance syndrome, refers to a cluster of metabolic abnormalities that are either causes or consequences of insulin resistance and that coexist particularly in obese sedentary patients". Marchesini et al. [53] pointed out that, "it is well known that NAFLD often occurs in the context of MS. The prevalence of MS in patients with NAFLD increases with higher body mass index (BMI), from 18% in nonobese NAFLD to 67% in obese NAFLD in a series of 304 patients". Nilsson et al. [54] suggested that, "MetS is comprised of multiple cardiovascular risk factors including elevated fasting blood glucose and waist circumference, dyslipidemia and elevated blood pressure". Reaven, [55] added that, "Met S is more common in obese people than in non-obese people, but some obese people are immune to the syndrome, and some non-obese people can get it".

Younossi et al. [56] revealed that, "obesity increases the risk of NAFLD". Tan [57] defined that, "the World Health Organization (WHO) defines obesity as having a body mass index (BMI) more than or equal to 30 and defines overweight as having a BMI larger than or equal to 25. The most helpful population-level indicator for defining overweight and obesity has been BMI". Finucane et al. [58] denoted that, "body mass index (BMI) > 30 kg/m2 designates obesity as a chronic condition, and BMI > 40 kg/m2 designates morbid obesity, one of the fastest-growing subsets of obesity. The World Health Organization has defined it as a global epidemic with an estimated 500 million obese adults and 1.5 billion overweight or obese people globally, with its prevalence rising in both adults and children". Williams et al. [59] suggested that, "NAFLD is significantly associated with obesity, with prevalence rates as high as 80% in patients who are obese and just 16% in those who have a normal BMI and no metabolic risk factors".

Zoppini et al. [60] suggested that, "diabetics NAFLD is largely to blame for the fact that diabetics have a roughly threefold increased chance of dying from chronic liver illnesses, which are primarily caused by non-viral and non-alcohol-related aetiologies. Although NAFLD is strongly associated with obesity, insulin resistance and T2DM, many people with NAFLD are not obese, and many people with NAFLD do not have T2DM. [61]. Mantovani et al. [62] pointed out that, "the prevalence of T2DM in patients with NAFLD depends on the severity of NAFLD starting from 9.8% in mild NAFLD to 17.8% in moderate to severe NAFLD". The diagnosis of NAFLD requires the presence of hepatic steatosis in the absence of excessive alcohol consumption (defined as average standard drinks per week >21 for men and > 14 for women) or other competing etiologies of liver disease [63]. In T2DM, there are numerous pathways implicated in insulin resistance, and these pathways are closely related to NAFLD. The relationship between lipid buildup in the liver and fat-induced hepatic insulin resistance is therefore of major interest. Following a meal, the pancreas' -cells detect elevated blood glucose levels, which triggers the release of insulin. Muscle, fat, and liver cells are the main tissues that contain insulin receptors. Insulin induces phosphorylation of insulin receptor substrates (IRS) and IRS2 by interacting to the insulin receptor tyrosine kinase (IRTK) [64].

Gut micro-biome composition

Augustyn et al. [65] explained that, "another theory suggest that gut microbiome alteration and dietary habits are another mechanism that induce and maintain T2DM and/or NAFLD". Loomba et al. [66] denoted that, "a surprising robust diagnostic accuracy (area under the curve 0.936) of a gut microbiota-derived signature for predicting the presence of advanced fibrosis F3 or F4 in 86 well-characterized people with biopsy-proven NAFLD is indicative of the growing body of evidence supporting an association between the gut microbiome and NAFLD". Aragonès et al. [67] added that, "when activated, inflammasome critical protein complexes cause the release of proinflammatory cells and cell apoptosis, which are crucial components of the host defence system. Through the gut microbiota, the NLRP3 inflammasome slows the advancement of NAFLD and obesity by upregulating the synthesis of leptin, suppressing the production of adiponectin, and encouraging fibrosis".

Genetic factors-irritability, gene loci

Browning et al. [68] mentioned that, "Patatin-like phospholipase domain-containing protein 3 (PNPLA3) was one of the first genes associated with increased hepatic steatosis". PNPLA3, which can act as a TG hydrolase or transacylase, is said to have both catabolic and anabolic enzymatic activities [69]. According to a genome-wide association analysis, persons with genotype rs641738 at the membrane bound O-acyltransferase domain-containing 7 gene and transmembrane channel-like 4 gene (MBOAT7- TMC4) locus had a higher risk of developing fibrosis, severe liver damage, and hepatic steatosis [70].

NAFLD has a heritable component, with genetic differences between individuals influencing disease risk estimates by 20–70% [71]. The PNPLA3 gene single nucleotide polymorphism is the genetic variation associated with NAFLD susceptibility that has been most thoroughly studied. This genetic variation is linked to an increased risk of liver fibrosis and the emergence of hepatocellular carcinoma as well as higher liver lipid content and more NASH activity [72]. Transmembrane 6 superfamily member 2 (TM6SF2) rs58542926 C > T, membrane bound O-acyltransferase domain-containing 7 (MBOAT7) rs641738 C > T, and glucokinase regulator (GCKR) P446L are three more genetic variations that have received much research. Moreover, they raise the severity of NAFLD and fibrosis risk (Mancina et al., 2016) [70].

Abdelmalek et al. [73] found that, "many genetic, nutritional, metabolic, immunological, and microbiological factors are thought to have contributed to its multifactorial nature. Studies indicate that genetic variables are significant in the pathophysiology and development of NAFLD. There is a familial cluster of NAFLD, according to epidemiological studies". Romeo et al. [74] mentioned that, recent large-scale genome-wide association studies provided more support for the significance of genetic variables. In one study, an allele in the PNPA3 gene was strongly linked to elevated hepatic flat content and hepatic inflammation". Loomba et al. [66] explained that, "NAFLD may be inherited to some extent, according to human genetic investigations, which may help to explain the wide variation in phenotypic and disease progression risk". The most commonly described genetic variants associated with NAFLD have been identified in the PNPLA3, transmembrane 6 superfamily member 2 (TM6SF2), and glucokinase regulatory protein (GCKR) genes [75].

Romeo et al. [76] pointed out that, "our ability to interpret the patient's propensity for disease and evaluate treatment alternatives is made possible by the inherent clarity of DNA sequencing.

Glucokinase regulator (GCKR), membrane-bound O-acyltransferase domain-containing protein 7 (MBOAT7), Patatin-like phospholipase domain-containing protein 3 (PNPLA3), transmembrane 6 superfamily member 2 (TM6SF2), and 17-hydroxysteroid dehydrogenase type 13 (HSD17B13) are among the genes whose genetic variations are known to affect the progression of NAFLD".

Epigenetic factors-DNA methylation,histone acetylation,miRNAs

It is undeniable that certain loci play a causal role in the pathogenesis of NAFLD, but it is also becoming evident that environmental and genetic factors cannot account for the entire rise in NAFLD prevalence. The study of epigenetics, which is the reversible and heritable modification of gene expression without altering the base nucleotide sequence, provides a mechanistic explanation for this occurrence. In fact, an increasing body of evidence suggests that epigenetics is a key player in the pathogenesis and development of NAFLD [77]. Ahrens et al. [78] observed that, "although the effect seen in NAFLD is hypomethylation, several interesting examples of hypermethylated genes with reduced expression can be found. Insulin-like growth factor-binding protein (IGFBP)-2 is often repressed in patients with NAFLD and NASH via methylation".

Sookoian et al. [79] pointed out that, "peroxisome Proliferator-Activated Receptor Gamma Coactivator (PGC)-1, a master regulator of numerous aspects of energy metabolism, particularly fatty acid oxidation and mitochondrial biogenesis, which are elements involved in the pathogenesis of fatty liver, is another well-known example of a hypermethylated gene in NAFLD. Promoter methylation in NAFLD patients reduces PGC1 expression, which is correlated with mitochondrial abnormalities and IR". Vienberg et al. [80] reported that, "numerous biological processes implicated in the pathogenesis of NAFLD, such as lipid uptake, de novo lipogenesis, lipid oxidation, and hepatic lipid export, as well as apoptosis, cell proliferation, or fibrosis, are known to be regulated by miRNAs. Horie et al. [81] identified that, "miR-33a and miR-33b, for example, negatively regulate the levels of ATP-binding cassette transporter 1 (ABCA1), which controls high-density lipoprotein biogenesis, thereby promoting high levels of circulating VLDL and triglycerides".

Demographic factor-age, gender

Williams et al. [59] explained that, "Generally, gender differences exist in NAFLD. Prevalence of NAFLD and NASH was higher in men Yang et al [82] suggested that, "when it comes to NAFLD, women are less susceptible to it than men are. However, after menopause, women lose this protective advantage and their frequency of NAFLD approaches that of men.

Environmental risk factor-diet, lifestyle, smoking, air pollution

Whitsel [83] identified that, "the government plays an important role in addressing lifestyle behaviors and population health, whose involvement comprises surveillance, research, programming, access to healthcare, and guidelines for diet and physical activity". Drummen et al. [84] found that, "protein diets in subjects with T2DM and NAFLD promotes loss of hepatic fat associated with better IR and decreased hepatic cytolytic profile". Alferink et al. [85] reported that, "the increase in knowledge-based employment has also aided in the rise in obesity rates. Economic globalisation has caused dietary changes, including an increase in the intake of animal proteins, refined sugars, and additives, all of which have a significant impact on the development of NAFLD.

Thyroid dysfuction

Mantovani et al. [86] mentioned that, "several epidemiological studies conducted across the globe have shown an inverse relationship between hypothyroidism and the incidence of NAFLD". Mansion, et al. [87] found that, "thyroid hormone (TH) effects on lipid metabolism have been known for over a century". Van der Spek, et al. [88] revealed that, "by impacting cholesterol synthesis, LDL clearance, and reverse cholesterol transport, TH lowers serum cholesterol levels. (RCT). In addition to the two main physiologically active THs, thyroxine (T4) and triiodothyronine (T3), additional TH metabolites are present in human serum and tissues at various quantities. These byproducts of deiodination, decarboxylation, deamination, N-acetylation, sulfation, and glucuronidation may also have biological action. Sinha and Yen [89] observed that, "when T3 is administered to NASH patients, it greatly reduces hepatosteatosis and inflammation while reestablishing mitochondrial function". Liu, et al. [90] estimated that, "there haven't been many research on the application of T4 treatment for NAFLD, similar to the T3 literature. According to reports, patients with subclinical hypothyroidism who used T4 supplements had a lower prevalence of NAFLD".

Vit D deficiency

Charoenngam and Holick [91] explained that, "as a pleiotropic hormone, vitamin D regulates more than just calcium homeostasis and bone mineralization. In the past few decades, experimental data has unambiguously demonstrated that vitamin D mediates a number of immune-inflammatory processes". Pacifico et al. [92] denoted that, "vitamin D is converted into its physiologically active metabolite, 1a, 25-dihydroxyvitamin D [1a, 25 (OH) 2D], through two important hydroxylation stages, whether it comes from the food or is generated by skin exposure to sunlight. The first process takes place in the liver to produce 25-hydroxyvitamin D [25 (OH) D], which is the most stable circulating form of vitamin D and its most popular status indicator. The second step, 1a -hydroxylation, takes place in the kidneys". NAFLD is frequently viewed as the hepatic symptom of the metabolic syndrome [93]. Li et al. [94] mentioned that, "vitamin D supplementation has been shown to improve insulin sensitivity and glycemic control in people with prediabetes and type 2 diabetes".

Reduction in LAL activity

Takaki et al. [95] observed that, "NAFLD is the result of many different pathogenic mechanisms which cause lipid accumulation into hepatocytes". Baratta et al. [96] suggesteds that, "LAL deficiency is a rare autosomal recessive genetic disease that is associated with a massive intra-lysosomal accumulation of cholesteryesters and triglycerides in many organs, such as the liver and spleen. Thus, in patients with Wolman and cholesteryl ester storage disease (CESD), the two genetic forms of LAL deficiency, splenomegaly is a typical feature". The hydrolase lysosomal acid lipase (LAL) is essential for the movement of cholesterol within cells. As seen in two recessive autosomal genetic diseases, Wolman disease and cholesterol ester storage disease, decreased LAL (LALD) activation supports increased lysosomal cholesterol ester storage (CESD). In CESD, LAL activity is significantly diminished (10%) and nonexistent in Wolman disease. The LIPA gene's E8SJM variation, a single mutation, is the most prevalent [96].

Muntoni et al. [97] denoted that, "only a small number of studies have been conducted to date to evaluate LAL activity in representative samples of healthy adult individuals or NAFLD patients. Additionally, no sizable study has been conducted on adults with NAFLD, and it is unclear how common the LIPA gene mutation is in this environment. Only one research examined the clinical phenotype of individuals who had heterozygous LIPA gene mutations. However, this study's attention was solely on the findings of the lipid panel and did not present information on the state of the liver or other biochemical values". Therefore, the identification of clinical and metabolic risk factors, especially those modifiable, which are able to modulate LAL activity, may have important clinical implications for the management of patients with NAFLD. Moreover, future research should also address epigenetic modulation of LAL activity and also take into consideration the effect of drug treatments. This would be particularly important to better understand the contribution of LAL in the complex scenario of NAFLD [96].

Baratta et al [96] showed that, "few studies have so far assessed the activity of LAL in patients with NAFLD, and the possible role of LAL as one of the multiple hits in NAFLD pathogenesis is under debate". The reduction of LAL activity, which is also a risk factor for the development of NAFLD, could be thought of as a further pathophysiological mechanism for progression to NASH and ultimately to cryptogenic cirrhosis, according to our results [98]. The inverse relationship between LAL activity and spleen size, which indicates that decreased LAL may be a factor in NAFLD-related spleen enlargement, is a novel finding. Only one small Japanese research has examined the relationship between spleen size and NAFLD, and it found that 32 NAFLD patients had a higher spleen volume measured by computed tomography than 34 patients with a normal liver [99].

Nuclear factor

Tanaka et al. [100] [revealed that, "NRs are a family of transcription factors, activated by a variety of ligands including hormones, lipids and bile acids". Nuclear receptors are, in general, ligand-dependent transcription factors that govern transcription by regulating cellular processes that influence or affect epigenetic changes. Specific members of the NR1 subfamily, which are typically kept in the nucleus and heterodimerize with the retinoid X receptor (RXR), including NR2B1, NR3B2, and NR2B3, are of special significance in NAFLD [7–12]. The peroxisome proliferator activated receptors (PPAR), NR1C1-3; the liver X receptors (LXR); the farnesoid X receptor (FXR); the constitutive androstane receptor (CAR); and the pregnane X receptor (PXR); NR1H2-3; and the NR1H4; are some examples of these transcription factors. To regulate nutrient homeostasis, these receptors typically bind hydrophobic dietary ligands with moderate affinity [101].

Ritz et al. [102] reported that, “the significance of NR, however, far exceeds its direct roles in hepatocytes because they also influence responses in populations of non-parenchymal liver cell types. Macrophages have become important actors in chronic liver diseases like NAFLD over the past few decades. The previous paradigms of "pro- and anti-inflammatory M1/M2 macrophages" were disproved by translational and clinical research, which also highlighted the functional plasticity of macrophage subsets”. NRs are transcription factors that directly control transcriptional processes and epigenetic changes to control the expression of numerous genes. Nuclear receptors work by joining with retinoid X receptor (RXR), and (NR2B1-3) to create heterodimers. The nuclear-permeable, lipophilic, endogenous substances produced from various nutrients [such as Fas, eicosanoids, oxysterols, and bile acids (Bas)] and other exogenous chemical substances are among the ligands of the NR subfamily. 48 NRs have been found in people so far [103].

Risk Factors for NAFLD	Findings	References
Metabolic risk factors	Metabolic syndrome, obesity, and diabetes are strongly linked to NAFLD. Obesity significantly elevates NAFLD risk, particularly in those with metabolic syndrome. Diabetics have a notably higher chance of developing non-viral, non-alcohol-related liver diseases, mainly NAFLD. A key diagnostic criterion for NAFLD is hepatic steatosis, often linked to insulin resistance. These factors intricately influence NAFLD risk.	[54, 56, 62, 63]
Gut microbiome composition	Changes in the gut microbiome and dietary choices are tied to both T2DM and NAFLD. A gut microbiota-based marker is highly accurate in diagnosing advanced fibrosis in NAFLD. The NLRP3 inflammasome, influenced by the gut microbiota, impacts the progression of NAFLD and obesity. These factors are interconnected in metabolic disorders like NAFLD and T2DM.	[67, 65, 66]
Genetic factors	Specific genes, such as PNPLA3 and the MBOAT7-TMC4 loci, heighten the risk of hepatic steatosis and fibrosis. Genetic disparities influence how we estimate the risk of NAFLD. Variants in genes like PNPLA3, TM6SF2, and GCKR are linked to more severe NAFLD and fibrosis risk. These genetic factors are pivotal in shaping the risk of severe NAFLD.	[76, 71]
Epigenetic factors	Epigenetic alterations, like DNA methylation and histone acetylation, impact NAFLD. Genes such as IGFBP-2 and PGC-1 experience hypermethylation in NAFLD. miRNAs control essential NAFLD processes, such as lipid metabolism and apoptosis. These epigenetic factors are pivotal in NAFLD's development.	[77, 80]
Demographic factor	NAFLD prevalence differs by gender, with men having a higher rate. Women are initially less prone to NAFLD than men, but this advantage wanes after menopause.	[82, 59]
Environmental risk factor	Government actions in public health encompass research and recommendations for diet and exercise. Dietary choices, lifestyles, and global economic shifts contribute to NAFLD development.	[85, 84, 83]
Thyroid dysfunction	Hypothyroidism is inversely related to NAFLD. Thyroid hormones affect lipid metabolism, and T3 treatment reduces hepatosteatosis and inflammation. T4 supplementation in subclinical hypothyroidism may lower NAFLD prevalence.	[86,88]
Vitamin D deficiency	Vitamin D controls immune responses and may boost insulin sensitivity and glycemic control in prediabetes and type 2 diabetes.	[91, 94]
Reduction in LAL activity	LAL deficiency leads to cholesteryl ester and triglyceride accumulation in the liver and spleen. Reduced LAL activity may be associated with spleen enlargement in NAFLD.	[98, 96, 95]
Nuclear factor	Nuclear receptors (NRs), like PPARs and FXR, are ligand-sensitive transcription factors that regulate genes involved in lipid metabolism and nutrient balance in NAFLD. NRs also influence non-parenchymal liver cells, including macrophages.	[102,100]

Regulation, Expression and Activity of Nafld on Major Drug Metabolism

Aitken et al. [104] suggested that, the influence of diseases on DMEs and transporters is complex due to the associated physiological and pathological changes”. It has been reported that inflammatory conditions can trigger the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. These cytokines act as signaling molecules that contribute to the down-regulation of drug metabolizing enzymes by suppressing transcription [105]. Hardwick et al. [106] described that, “oxidative stress in NAFLD and diabetes causes activation of Nrf2 (nuclear factor erythroid 2-related factor 2) in both

experimental and clinical studies". Fatty acids regulate gene expression by controlling the activity or expression of key nuclear receptors Jump, 2008.

Johnson et al. [107] found that, "changes in the architecture of the liver in hepatic cirrhosis have been reported to cause reduced liver blood flow, reduced functional hepatocytes and diminished functional capacity of the liver to synthesize serum proteins including albumin". Aitken et al. [104] revealed that, "the combined effects of surplus fatty acids, cytokines, oxidative stress, and other factors in NAFLD and diabetes can potentially impact the liver's ability to metabolize specific drugs. This may occur due to changes in the expression and function of DMEs and transporters, which could be influenced by various host defense mechanisms at the transcriptional, pre-translational, and post-translational levels.

Elens et al. [108] denoted that, "numerous elements have been identified as having an impact on DMEs and transporters. These factors consist of genetic polymorphisms, epigenetic influences, and non-genetic factors. Genetic polymorphisms cause changes in the DNA sequence of genes that control the activity of DMEs and transporters, resulting in variants that either reduce or enhance their function".

4. Conclusion

In conclusion, nonalcoholic fatty liver disease (NAFLD) is a complex and multifactorial disease that has become a significant health concern worldwide. The pathogenesis of NAFLD involves a range of factors, including genetic predisposition, insulin resistance, dyslipidemia, and environmental factors such as sedentary lifestyle and poor dietary habits. Additionally, emerging evidence suggests that the gut microbiome and the immune system play crucial roles in the development and progression of NAFLD.

Given the growing prevalence of NAFLD, it is essential to understand the various factors that contribute to the disease's pathogenesis to develop effective prevention and treatment strategies. Lifestyle modifications, including diet and exercise, remain the cornerstone of NAFLD management. However, recent advances in pharmacotherapy and targeted therapies that address specific mechanisms involved in NAFLD's pathogenesis offer new hope for patients with this condition.

Further research is needed to gain a better understanding of the complex interplay between various factors that contribute to NAFLD's development and progression. Multidisciplinary approaches that involve collaboration between hepatologists, endocrinologists, nutritionists, and other specialists may help develop more effective and personalized treatment strategies for NAFLD patients. Ultimately, a better understanding of NAFLD's multifactorial aspects is critical to reducing its burden on individuals and society.

Conflict Of Interest

The Authors declare that there is no conflict of interest.

Author's Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work

References:

1. Mulhall, B. P., Ong, J. P., & Younossi, Z. M. (2002). Non-alcoholic fatty liver disease: an overview. Journal of gastroenterology and hepatology, 17(11), 1136-1143.
2. Arab, J. P., Arrese, M., & Trauner, M. (2018). Recent insights into the pathogenesis of nonalcoholic fatty liver disease. Annual Review of Pathology: Mechanisms of Disease, 13, 321-350.
3. Tarantino, G., Saldalamacchia, G., Conca, P., & Arena, A. (2007). Non-alcoholic fatty liver disease: further expression of the metabolic syndrome. Journal of gastroenterology and hepatology, 22(3), 293-303.
4. Green, C. J., & Hodson, L. (2014). The influence of dietary fat on liver fat accumulation. Nutrients, 6(11), 5018-5033.
5. Koek G. H. (2011). Behandeling van niet-alcoholische vetleverziekte [Treatment of non-alcoholic fatty liver disease]. Nederlands tijdschrift voor geneeskunde, 155, A3181.
6. Anstee, Q.M., Seth, D. and Day, C.P., 2016. Genetic factors that affect risk of alcoholic and nonalcoholic fatty liver disease. Gastroenterology, 150(8), pp.1728-1744.
7. Diehl, A. M., & Day, C. (2017). Cause, Pathogenesis, and Treatment of Nonalcoholic Steatohepatitis. The New England journal of medicine, 377(21), 2063–2072.
8. Kleiner, D. E., & Makhlouf, H. R. (2016). Histology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in adults and children. Clinics in liver disease, 20(2), 293-312.
9. Matteoni, C. A., Younossi, Z. M., Gramlich, T., Boparai, N., Liu, Y. C., & McCullough, A. J. (1999). Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology, 116(6), 1413-1419.

10. Alberti, K. G., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., ... & Smith Jr, S. C. (2009). Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation, 120(16), 1640-1645.
11. Cobbina, E., & Akhlaghi, F. (2017). Non-alcoholic fatty liver disease (NAFLD)–pathogenesis, classification, and effect on drug metabolizing enzymes and transporters. Drug metabolism reviews, 49(2), 197-211.
12. Sheth, S. G., Gordon, F. D., & Chopra, S. (1997). Nonalcoholic steatohepatitis. Annals of internal medicine, 126(2), 137-145.
13. Younossi, Z., Tacke, F., Arrese, M., Sharma, B. C., Mostafa, I., Bugianesi, E., ... & Vos, M. B. (2019). Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology, 69(6), 2672-2682.
14. Younossi, Z. M., Koenig, A. B., Abdelatif, D., Fazel, Y., Henry, L., & Wymer, M. (2016). Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology, 64(1), 73-84.
15. Zoppini, G., Fedeli, U., Gennaro, N., Saugo, M., Targher, G., & Bonora, E. (2014). Mortality from chronic liver diseases in diabetes. Official journal of the American College of Gastroenterology| ACG, 109(7), 1020-1025.
16. Younossi, Z. M., Stepanova, M., Younossi, Y., Golabi, P., Mishra, A., Rafiq, N., & Henry, L. (2020). Epidemiology of chronic liver diseases in the USA in the past three decades. Gut, 69(3), 564-568.
17. Lonardo, A., Byrne, C. D., Caldwell, S. H., Cortez-Pinto, H., & Targher, G. (2016). Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology, 64(4), 1388-1389.
18. Powell, E. E., Jonsson, J. R., & Clouston, A. D. (2005). Steatosis: co-factor in other liver diseases. Hepatology, 42(1), 5-13.
19. Roeb, E., Steffen, H. M., Bantel, H., Baumann, U., Canbay, A., Demir, M., ... & Bojunga, J. (2015). S2k Guideline non-alcoholic fatty liver disease. Zeitschrift fur Gastroenterologie, 53(7), 668-723.
20. Ertle, J., Dechêne, A., Sowa, J. P., Penndorf, V., Herzer, K., Kaiser, G., ... & Canbay, A. (2011). Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. International journal of cancer, 128(10), 2436-2443.
21. Valenti, L., & Pelusi, S. (2020). Redefining fatty liver disease classification in 2020. Liver International, 40(5), 1016-1017.
22. Adams, R. B., & Mehran, H. (2005, August). Corporate performance, board structure and its determinants in the banking industry. In EFA 2005 Moscow meetings.
23. Li, Z., Xue, J., Chen, P., Chen, L., Yan, S., & Liu, L. (2014). Prevalence of nonalcoholic fatty liver disease in mainland of C hina: A meta-analysis of published studies. Journal of gastroenterology and hepatology, 29(1), 42-51.
24. Chakraborty, J., & Das, S. (2016). Molecular perspectives and recent advances in microbial remediation of persistent organic pollutants. Environmental Science and Pollution Research, 23, 16883-16903.
25. Vernon, G., Baranova, A., & Younossi, Z. M. (2011). Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Alimentary pharmacology & therapeutics, 34(3), 274-285.
26. Kirpich, I. A., Marsano, L. S., & McClain, C. J. (2015). Gut–liver axis, nutrition, and non-alcoholic fatty liver disease. Clinical biochemistry, 48(13-14), 923-930.
27. Byrne, C. D., & Targher, G. (2015). NAFLD: a multisystem disease. Journal of hepatology, 62(1), S47-S64.
28. Baumeister, S. E., Völzke, H., Marschall, P., John, U., Schmidt, C. O., Flessa, S., & Alte, D. (2008). Impact of fatty liver disease on health care utilization and costs in a general population: a 5-year observation. Gastroenterology, 134(1), 85-94.
29. Eslam, M., & George, J. (2020). Genetic contributions to NAFLD: leveraging shared genetics to uncover systems biology. Nature reviews Gastroenterology & hepatology, 17(1), 40-52.
30. Edmison, J., & McCullough, A. J. (2007). Pathogenesis of non-alcoholic steatohepatitis: human data. Clinics in liver disease, 11(1), 75-104.
31. Manne, V., Handa, P., & Kowdley, K. V. (2018). Pathophysiology of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. Clinics in liver disease, 22(1), 23-37.
32. Aichler, M., Luber, B., Lordick, F., & Walch, A. (2014). Proteomic and metabolic prediction of response to therapy in gastric cancer. World journal of gastroenterology: WJG, 20(38), 13648.
33. Sanyal, A. J., Harrison, S. A., Ratziu, V., Abdelmalek, M. F., Diehl, A. M., Caldwell, S., ... & Goodman, Z. (2019). The natural history of advanced fibrosis due to nonalcoholic steatohepatitis: data from the simtuzumab trials. Hepatology, 70(6), 1913-1927.
34. Ou, H., Fu, Y., Liao, W., Zheng, C., & Wu, X. (2019). Association between smoking and liver fibrosis among patients with nonalcoholic fatty liver disease. Canadian Journal of Gastroenterology and Hepatology, 2019.
35. Pelchat, M. L., Johnson, A., Chan, R., Valdez, J., & Ragland, J. D. (2004). Images of desire: food-craving activation during fMRI. Neuroimage, 23(4), 1486-1493.

36. Loomba, R., Seguritan, V., Li, W., Long, T., Klitgord, N., Bhatt, A., ... & Nelson, K. E. (2017). Gut microbiome-based metagenomic signature for non-invasive detection of advanced fibrosis in human nonalcoholic fatty liver disease. Cell metabolism, 25(5), 1054-1062.
37. Sun, E. W., Martin, A. M., Young, R. L., & Keating, D. J. (2019). The regulation of peripheral metabolism by gut-derived hormones. Frontiers in endocrinology, 9, 754.
38. Herrmann, W. A., Elison, M., Fischer, J., Köcher, C., & Artus, G. R. (1995). Metal complexes of N-heterocyclic carbenes—a new structural principle for catalysts in homogeneous catalysis. Angewandte Chemie International Edition in English, 34(21), 2371-2374.
39. Cohen, J. C., Horton, J. D., & Hobbs, H. H. (2011). Human fatty liver disease: old questions and new insights. Science, 332(6037), 1519-1523.
40. Friedman, S. L., Neuschwander-Tetri, B. A., Rinella, M., & Sanyal, A. J. (2018). Mechanisms of NAFLD development and therapeutic strategies. Nature medicine, 24(7), 908-922.
41. Angulo, P., Kleiner, D. E., Dam-Larsen, S., Adams, L. A., Bjornsson, E. S., Charatcharoenwitthaya, P., ... & Bendtsen, F. (2015). Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology, 149(2), 389-397.
42. Powell, E. E., Wong, V. W. S., & Rinella, M. (2021). Non-alcoholic fatty liver disease. The Lancet, 397(10290), 2212-2224.
43. Buzzetti, E., Pinzani, M., & Tsochatzis, E. A. (2016). The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism, 65(8), 1038-1048.
44. European Association for the Study of The Liver, & European Association for the Study of Diabetes (EASD. (2016). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Obesity facts, 9(2), 65-90.
45. Burt, A. D., Lackner, C., & Tiniakos, D. G. (2015, August). Diagnosis and assessment of NAFLD: definitions and histopathological classification. In Seminars in liver disease (Vol. 35, No. 03, pp. 207-220). Thieme Medical Publishers.
46. Kleiner, D. E., Brunt, E. M., Van Natta, M., Behling, C., Contos, M. J., Cummings, O. W., ... & Nonalcoholic Steatohepatitis Clinical Research Network. (2005). Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology, 41(6), 1313-1321.
47. Hall, A. R., Green, A. C., Luong, T. V., Burroughs, A. K., Wyatt, J., & Dhillon, A. P. (2014). The use of guideline images to improve histological estimation of hepatic steatosis. Liver International, 34(9), 1414-1427.
48. Karlas, T., Petroff, D., Garnov, N., Böhm, S., Tenckhoff, H., Wittekind, C., ... & Wiegand, J. (2014). Non-invasive assessment of hepatic steatosis in patients with NAFLD using controlled attenuation parameter and 1H-MR spectroscopy. PloS one, 9(3), e91987.
49. Pais, R., Pascale, A., Fedchuck, L., Charlotte, F., Poynard, T., & Ratziu, V. (2011). Progression from isolated steatosis to steatohepatitis and fibrosis in nonalcoholic fatty liver disease. Clinics and research in hepatology and gastroenterology, 35(1), 23-28.
50. Perumpail, B. J., Khan, M. A., Yoo, E. R., Cholankeril, G., Kim, D., & Ahmed, A. (2017). Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. World journal of gastroenterology, 23(47), 8263.
51. Angelico, F., Del Ben, M., Conti, R., Francioso, S., Feole, K., Maccioni, D., ... & Alessandri, C. (2003). Non-alcoholic fatty liver syndrome: a hepatic consequence of common metabolic diseases. Journal of gastroenterology and hepatology, 18(5), 588-594.
52. Simmons, N. B., Seymour, K. L., Habersetzer, J., & Gunnell, G. F. (2010). Inferring echolocation in ancient bats. Nature, 466(7309), E8–E9.
53. Marchesini, G., Bugianesi, E., Forlani, G., Cerrelli, F., Lenzi, M., Manini, R., ... & Rizzetto, M. (2003). Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology, 37(4), 917-923.
54. Nilsson, A., Santoro, A., Franceschi, C., & Kadi, F. (2019). Detrimental links between physical inactivity, metabolic risk and N-glycomic biomarkers of aging. Experimental gerontology, 124, 110626.
55. Reaven, G., Abbasi, F., & McLaughlin, T. (2004). Obesity, insulin resistance, and cardiovascular disease. Recent progress in hormone research, 59, 207-224.
56. Gurmeet, K., & Mohammadi, A. . (2023). Understanding the Social Determinants of Health: Implications for Health Sociology. *Jurnal Perilaku Kesehatan Terpadu*, *2*(1), 12–17. Retrieved from https://hasmed.org/index.php/Jupiter/article/view/37
57. Younossi, Z. M., Loomba, R., Anstee, Q. M., Rinella, M. E., Bugianesi, E., Marchesini, G., ... & Lindor, K. (2018). Diagnostic modalities for nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and associated fibrosis. Hepatology, 68(1), 349-360.
58. Tan, K. C. B. (2004). Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. The lancet.
59. Finucane, F. M., Sharp, S. J., Hatunic, M., Sleigh, A., De Lucia Rolfe, E., Aihie Sayer, A., ... & Wareham, N. J. (2014). Liver fat accumulation is associated with reduced hepatic insulin extraction and beta cell dysfunction in healthy older individuals. Diabetology & metabolic syndrome, 6(1), 1-8.
60. Williams, C. D., Stengel, J., Asike, M. I., Torres, D. M., Shaw, J., Contreras, M., ... & Harrison, S. A. (2011). Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-

aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology, 140(1), 124-131.
61. Zoppini, G., Fedeli, U., Gennaro, N., Saugo, M., Targher, G., & Bonora, E. (2014). Mortality from chronic liver diseases in diabetes. Official journal of the American College of Gastroenterology| ACG, 109(7), 1020-1025.
62. Sung, K. C., Ryu, S., Lee, J. Y., Kim, J. Y., Wild, S. H., & Byrne, C. D. (2016). Effect of exercise on the development of new fatty liver and the resolution of existing fatty liver. Journal of hepatology, 65(4), 791-797.
63. Mantovani, A., Byrne, C. D., Bonora, E., & Targher, G. (2018). Nonalcoholic fatty liver disease and risk of incident type 2 diabetes: a meta-analysis. Diabetes care, 41(2), 372-382.
64. Chalasani, N., Younossi, Z., Lavine, J. E., Charlton, M., Cusi, K., Rinella, M., ... & Sanyal, A. J. (2018). The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology, 67(1), 328-357.
65. Copps, K. D., & White, M. F. (2012). Regulation of insulin sensitivity by serine/threonine phosphorylation of insulin receptor substrate proteins IRS1 and IRS2. Diabetologia, 55, 2565-2582.
66. Augustyn, M., Grys, I., & Kukla, M. (2019). Small intestinal bacterial overgrowth and nonalcoholic fatty liver disease. Clinical and experimental hepatology, 5(1), 1-10.
67. Loomba, R., Seguritan, V., Li, W., Long, T., Klitgord, N., Bhatt, A., ... & Nelson, K. E. (2017). Gut microbiome-based metagenomic signature for non-invasive detection of advanced fibrosis in human nonalcoholic fatty liver disease. Cell metabolism, 25(5), 1054-1062.
68. Aragonès, G., Colom-Pellicer, M., Aguilar, C., Guiu-Jurado, E., Martínez, S., Sabench, F., ... & Auguet, T. (2020). Circulating microbiota-derived metabolites: a "liquid biopsy?. International journal of obesity, 44(4), 875-885.
69. Browning, J. D., Cohen, J. C., & Hobbs, H. H. (2010). PNPLA3 and the pathogenesis and progression of pediatric NAFLD. Hepatology (Baltimore, Md.), 52(4), 1189.
70. Jenkins, D. J., Josse, A. R., Labelle, R., Marchie, A., Augustin, L. S., & Kendall, C. W. (2006). Nonalcoholic fatty liver, nonalcoholic steatohepatitis, ectopic fat, and the glycemic index. The American journal of clinical nutrition, 84(1), 3-4.
71. Mancina, R. M., Dongiovanni, P., Petta, S., Pingitore, P., Meroni, M., Rametta, R., ... & Romeo, S. (2016). The MBOAT7-TMC4 variant rs641738 increases risk of nonalcoholic fatty liver disease in individuals of European descent. Gastroenterology, 150(5), 1219-1230.
72. Eslam, M., & George, J. (2020). Reply to: correspondence regarding "A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement": Bringing evidence to the NAFLD-MAFLD debate. Journal of Hepatology, 73(6), 1575.
73. Singal, A. K., Salameh, H., Kuo, Y. F., & Wiesner, R. H. (2014). Evolving frequency and outcomes of simultaneous liver kidney transplants based on liver disease etiology. Transplantation, 98(2), 216-221.
74. Abdelmalek, M. F., Liu, C., Shuster, J., Nelson, D. R., & Asal, N. R. (2006). Familial aggregation of insulin resistance in first-degree relatives of patients with nonalcoholic fatty liver disease. Clinical Gastroenterology and Hepatology, 4(9), 1162-1169.
75. Romeo, S., Kozlitina, J., Xing, C., Pertsemlidis, A., Cox, D., Pennacchio, L. A., ... & Hobbs, H. H. (2008). Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nature genetics, 40(12), 1461-1465.
76. Donati, M., Menozzi, D., Zighetti, C., Rosi, A., Zinetti, A., & Scazzina, F. (2016). Towards a sustainable diet combining economic, environmental and nutritional objectives. Appetite, 106, 48-57.
77. Romeo, S., Sanyal, A., & Valenti, L. (2020). Leveraging human genetics to identify potential new treatments for fatty liver disease. Cell metabolism, 31(1), 35-45.
78. Jonas, W., & Schürmann, A. (2021). Genetic and epigenetic factors determining NAFLD risk. Molecular Metabolism, 50, 101111.
79. Ahrens, M., Ammerpohl, O., von Schönfels, W., Kolarova, J., Bens, S., Itzel, T., ... & Hampe, J. (2013). DNA methylation analysis in nonalcoholic fatty liver disease suggests distinct disease-specific and remodeling signatures after bariatric surgery. Cell metabolism, 18(2), 296-302.
80. Sookoian, S., Rosselli, M. S., Gemma, C., Burgueño, A. L., Fernández Gianotti, T., Castaño, G. O., & Pirola, C. J. (2010). Epigenetic regulation of insulin resistance in nonalcoholic fatty liver disease: Impact of liver methylation of the peroxisome proliferator–activated receptor γ coactivator 1α promoter. Hepatology, 52(6), 1992-2000.
81. Vienberg, S., Geiger, J., Madsen, S., & Dalgaard, L. T. (2017). Micro RNA s in metabolism. Acta physiologica, 219(2), 346-361.
82. Horie, T., Ono, K., Horiguchi, M., Nishi, H., Nakamura, T., Nagao, K., ... & Kita, T. (2010). MicroRNA-33 encoded by an intron of sterol regulatory element-binding protein 2 (Srebp2) regulates HDL in vivo. Proceedings of the National Academy of Sciences, 107(40), 17321-17326.
83. Yang, M., Gong, S., Ye, S. Q., Lyman, B., Geng, L., Chen, P., & Li, D. Y. (2014). Non-alcoholic fatty liver disease in children: focus on nutritional interventions. Nutrients, 6(11), 4691-4705.
84. Whitsel, L. P. (2017). Government's role in promoting healthy living. Progress in Cardiovascular Diseases, 59(5), 492-497.

85. Drummen, M., Tischmann, L., Gatta-Cherifi, B., Adam, T., & Westerterp-Plantenga, M. (2018). Dietary protein and energy balance in relation to obesity and co-morbidities. Frontiers in endocrinology, 9, 443.
86. Alferink, L. J., Kiefte-de Jong, J. C., Erler, N. S., Veldt, B. J., Schoufour, J. D., de Knegt, R. J., ... & Murad, S. D. (2019). Association of dietary macronutrient composition and non-alcoholic fatty liver disease in an ageing population: the Rotterdam Study. Gut, 68(6), 1088-1098.
87. Mantovani, A., Nascimbeni, F., Lonardo, A., Zoppini, G., Bonora, E., Mantzoros, C. S., & Targher, G. (2018). Association between primary hypothyroidism and nonalcoholic fatty liver disease: a systematic review and meta-analysis. Thyroid, 28(10), 1270-1284.
88. MASON, R. L., Hunt, H. M., & Hurxthal, L. (1930). Blood cholesterol values in hyperthyroidism and hypothyroidism—their significance. New England Journal of Medicine, 203(26), 1273-1278.
89. van der Spek, D. P. C., Katwaroe, W. K., van Kleef, L. A., Brakenhoff, S., de Man, R. A., de Knegt, R. J., ... & Sonneveld, M. J. (2023). Time-trends in disease characteristics and comorbidities in patients with chronic hepatitis B in the period 1980–2020. European Journal of Internal Medicine, 107, 86-92.
90. Sinha, R. A., & Yen, P. M. (2016). Thyroid hormone-mediated autophagy and mitochondrial turnover in NAFLD. Cell & bioscience, 6(1), 1-6.
91. Liu, Z., Zhang, Y., Graham, S., Wang, X., Cai, D., Huang, M., ... & Liu, W. (2020). Causal relationships between NAFLD, T2D and obesity have implications for disease subphenotyping. Journal of hepatology, 73(2), 263-276.
92. Charoenngam, N., Shirvani, A., & Holick, M. F. (2019). Vitamin D for skeletal and non-skeletal health: What we should know. Journal of clinical orthopaedics and trauma, 10(6), 1082-1093.
93. Pacifico, L., Osborn, J. F., Bonci, E., Pierimarchi, P., & Chiesa, C. (2019). Association between vitamin D levels and nonalcoholic fatty liver disease: potential confounding variables. Mini Reviews in Medicinal Chemistry, 19(4), 310-332.
94. Jayakumar, S., Middleton, M. S., Lawitz, E. J., Mantry, P. S., Caldwell, S. H., Arnold, H., ... & Loomba, R. (2019). Longitudinal correlations between MRE, MRI-PDFF, and liver histology in patients with non-alcoholic steatohepatitis: analysis of data from a phase II trial of selonsertib. Journal of hepatology, 70(1), 133-141.
95. Li, J., Chen, N., Wang, D., Zhang, J., & Gong, X. (2018). Efficacy of vitamin D in treatment of inflammatory bowel disease: A meta-analysis. Medicine, 97(46).
96. Takaki, A., Kawai, D., & Yamamoto, K. (2013). Multiple hits, including oxidative stress, as pathogenesis and treatment target in non-alcoholic steatohepatitis (NASH). International journal of molecular sciences, 14(10), 20704-20728.
97. Baratta, F., Pastori, D., Del Ben, M., Polimeni, L., Labbadia, G., Di Santo, S., ... & Angelico, F. (2015). Reduced lysosomal acid lipase activity in adult patients with non-alcoholic fatty liver disease. EBioMedicine, 2(7), 750-754.
98. Muntoni, S., Wiebusch, H., Jansen-Rust, M., Rust, S., Schulte, H., Berger, K., ... & Assmann, G. (2013). Heterozygosity for lysosomal acid lipase E8SJM mutation and serum lipid concentrations. Nutrition, Metabolism and Cardiovascular Diseases, 23(8), 732-736.
99. Ramirez, S., Liu, X., MacDonald, C. J., Moffa, A., Zhou, J., Redondo, R. L., & Tonegawa, S. (2015). Activating positive memory engrams suppresses depression-like behaviour. Nature, 522(7556), 335-339.
100. Tsushima, Y., & Endo, K. (2000). Spleen enlargement in patients with nonalcoholic fatty liver. Digestive diseases and sciences, 45, 196-200.
101. Tanaka, N., Aoyama, T., Kimura, S., & Gonzalez, F. J. (2017). Targeting nuclear receptors for the treatment of fatty liver disease. Pharmacology & therapeutics, 179, 142–157.
102. Evans, R. M., & Mangelsdorf, D. J. (2014). Nuclear receptors, RXR, and the big bang. Cell, 157(1), 255-266.
103. Ritz, T., Krenkel, O., & Tacke, F. (2018). Dynamic plasticity of macrophage functions in diseased liver. Cellular Immunology, 330, 175-182.
104. Evans, R. M., & Mangelsdorf, D. J. (2014). Nuclear receptors, RXR, and the big bang. Cell, 157(1), 255-266.
105. Aitken, A. E., Richardson, T. A., & Morgan, E. T. (2006). Regulation of drug-metabolizing enzymes and transporters in inflammation. Annu. Rev. Pharmacol. Toxicol., 46, 123-149.
106. Aitken, A. E., & Morgan, E. T. (2007). Gene-specific effects of inflammatory cytokines on cytochrome P450 2C, 2B6 and 3A4 mRNA levels in human hepatocytes. Drug Metabolism and Disposition, 35(9), 1687-1693.
107. Hardwick Jones, R., Westra, S., & Sharma, A. (2010). Observed relationships between extreme sub-daily precipitation, surface temperature, and relative humidity. Geophysical Research Letters, 37(22).
108. Johnson, T. N., Boussery, K., Rowland-Yeo, K., Tucker, G. T., & Rostami-Hodjegan, A. (2010). A semi-mechanistic model to predict the effects of liver cirrhosis on drug clearance. Clinical pharmacokinetics, 49, 189-206.
109. Elens, L., Vandercam, B., Yombi, J. C., Lison, D., Wallemacq, P., & Haufroid, V. (2010). Influence of host genetic factors on efavirenz plasma and intracellular pharmacokinetics in HIV-1-infected patients. Pharmacogenomics, 11(9), 1223-1234.