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FELIPE SANCHES EDAES

Universidade de São Paulo, USP, São Paulo, SP, Brasil.

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UNLOCKING THE SECRETS OF NAFLD: NAVIGATING THE COMPLEX INTERSECTION OF DIET, HORMONES, AND METABOLIC SYNDROME

ABSTRACT

Amidst rising obesity and type 2 diabetes rates, non-alcoholic fatty liver disease (NAFLD) stands as a major global health challenge. Using a narrative approach, this review navigates major databases up to April 2023, delving into NAFLD's complex pathophysiology and highlighting the interplay of genetic, environmental, and behavioral factors. We spotlight pronounced regional and ethnic disparities and the critical roles of diet, hormones, and metabolic syndrome. We also address the estrogen receptor alpha (ERα) in postmenopausal women. While pinpointing current treatment shortfalls, we push for advanced diagnostic tools and highlight emerging therapies that target hepatic steatosis and insulin resistance. Ultimately, personalized medicine, combining genetic, epigenetic, and lifestyle factors, positions itself as a key strategy for NAFLD prevention and management.

Palavras-Chave: nafld. erα. metabolic syndrome.

DESVENDANDO OS SEGREDOS DA DHGNA: NAVEGANDO A COMPLEXA INTERSEÇÃO DE DIETA, HORMÔNIOS E SÍNDROME METABÓLICA

RESUMO

Com o aumento das taxas de obesidade e diabetes tipo 2, a doença hepática gordurosa não alcoólica (NAFLD) torna-se um desafio de saúde global. Usando uma abordagem narrativa, esta revisão analisa bancos de dados até abril de 2023, explorando a fisiopatologia da NAFLD e enfatizando a interação entre fatores genéticos, ambientais e comportamentais. Salientamos as disparidades regionais e étnicas e o impacto da dieta, hormônios e síndrome metabólica. O papel do receptor de estrogênio alfa (ERα) em mulheres pós-menopausa também é discutido. Identificamos lacunas nos tratamentos atuais, defendendo ferramentas diagnósticas aprimoradas e destacando terapias emergentes para esteatose hepática e resistência à insulina. Concluímos que a medicina personalizada, integrando genética, epigenética e estilo de vida, é essencial para a prevenção e gestão da NAFLD.

Keywords: dhgna, erα, síndrome metabólica.

Revista UNILUS Ensino e Pesquisa
Rua Dr. Armando de Salles Oliveira, 150
Boqueirão - Santos - São Paulo
11050-071

http://revista.lusiada.br/index.php/ruep
revista.unilus@lusiada.br

Fone: +55 (13) 3202-4100

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), alternatively known as metabolic associated fatty liver disease (MAFLD), presents a pressing global health issue intimately tied to surging obesity and type 2 diabetes rates. Characterized by abnormal hepatocyte fat accumulation, this progressive metabolic disorder extends from simple steatosis to cirrhosis (HADIZADEH et al., 2017; QI et al., 2017; FONTES-CAL et al., 2021; YOUNOSSI et al., 2023), necessitating improved diagnostic tools and novel therapeutic strategies in light of its complexity and alarming progression. Such complexity arises from an elaborate interplay of genetic, environmental, and behavioral factors, further compounded by impactful lifestyle choices and significant regional and ethnic disparities (HAN et al., 2014; OATES et al., 2019).

We aim to unravel the pathophysiology of NAFLD in this review, primarily delving into the intricate intersections of diet, hormones, and metabolic syndrome, with a special focus on the estrogen receptor alpha (ERα). Beyond assessing the prevalence, risk factors, and demographics of NAFLD, we emphasize the economic repercussions of the disease, identify existing diagnostic hurdles, and spotlight promising research directions (DUELL et al., 2022).

The broad spectrum of NAFLD, extending from simple steatosis to severe non-alcoholic steatohepatitis (NASH), underscores its inherent complexity, illustrated by the diverse roles of liver and immune cells in inflammation, fibrosis, and hepatocellular damage. Despite their widespread prevalence, these conditions often go undetected, emphasizing the urgent need for better diagnostic methodologies (ALISI et al., 2017; GREFHORST et al., 2021).

The clinical parallels between NAFLD and metabolic syndrome, such as abdominal obesity, hypertension, dyslipidemia, and insulin resistance/dysglycemia, assert a convincing link. This association becomes particularly pertinent in postmenopausal women, where hormonal changes potentially exacerbate NAFLD risk via increased abdominal fat accumulation (LONARDO et al., 2019; GUO et al., 2022).

Lifestyle elements such as high-fat, high-calorie diets, and sedentary behavior significantly drive NAFLD's onset and progression. Potential amplifiers of obesity-induced lipotoxicity and hepatic triglyceride accumulation include high-fructose corn syrup consumption and insulin resistance (COHEN et al., 2011; BESSONE et al., 2018). Hormonally, post-menopausal reductions in 17β-estradiol (E2) correlate with heightened NAFLD susceptibility (LONARDO et al., 2019; DISTEFANO, 2020).

The ERα receptor, responsive to E2, plays a central role in NAFLD pathophysiology. Gene polymorphisms related to ERα's metabolic functions could impact NAFLD susceptibility and progression (DUELL et al., 2022). Additional pathogenic elements in NAFLD include ER stress, lipotoxicity, and fibrosis, with the interplay between ERα and fibroblast growth factor 21 (FGF21) earning increasing recognition (DEMIR et al., 2021).

NAFLD management presently centers on lifestyle modifications. However, the future holds promise for novel therapies that target hepatic steatosis, insulin sensitivity, and obesity-associated metabolic imbalances (MUOIO et al., 2008; DUELL et al., 2022). The advent of personalized medicine, integrating genetic, epigenetic, and lifestyle factors, could lay the groundwork for custom treatment protocols (BOTELLO-MANILLA et al., 2020; PIROLA et al., 2020).

The immense economic burden of NAFLD, with estimated annual costs amounting to billions in regions such as the United States and Europe, underscores the urgency for early diagnosis and intervention. The current diagnostic limitations and the invasive nature of liver biopsies accentuate the need for non-invasive approaches and advancements in gene expression profiling for diagnostic biomarker discovery and drug

development (DING et al., 2020; DUELL et al., 2022). By synthesizing existing knowledge and exploring future research avenues, this review seeks to deepen our understanding of NAFLD and facilitate the development of effective prevention and management strategies.

Search Strategy

This review necessitated a meticulous and comprehensive approach to underscore the subtle connections between diet, hormones, and metabolic syndrome within the frame of nonalcoholic fatty liver disease (NAFLD).

We conducted an exhaustive search through several databases—PubMed, Scopus, and Web of Science—to cover publications from their inception until April 2023. Our search strategy employed a combination of specific keywords and Medical Subject Headings (MeSH) terms, such as "Nonalcoholic fatty liver disease", "NAFLD", “high-fat diet", "hormones", "metabolic syndrome", and "ERα", among others, while restricting the search to articles published in English.

During the selection phase, we initially excluded articles based on their titles and abstracts, focusing on those that aligned with our central themes. We subsequently reviewed the full texts of the remaining articles, selecting those that specifically examined the role of diet, hormones, and metabolic syndrome in NAFLD, reported original research, and presented significant findings relevant to our main themes. We dismissed studies that did not focus primarily on NAFLD or for which full texts were not accessible.

Upon curating a robust collection of articles, we extracted pertinent data and classified each study based on its type, the population examined, key findings, and contributions to our research themes. Our analysis pivoted around the interplay of diet, hormones, and metabolic syndrome in the initiation, diagnosis, and treatment of NAFLD. To ensure the credibility of our findings, we performed a quality assessment of each study using the Newcastle-Ottawa Scale for observational studies and the Cochrane risk-of-bias tool for randomized trials. We incorporated only those studies that exhibited high quality and minimal bias.

The culmination of our methodology involved a qualitative synthesis of data, threading together pivotal findings from various studies. Given the heterogeneity of the included studies, we refrained from conducting a meta-analysis. Instead, we sought to deliver a unified perspective on the current understanding of NAFLD and delineate potential trajectories for future research.

Establishing the Context: The Global Health Dilemma of NAFLD and the Goals of Our Review

Unveiling the Clinical Ramifications and Implications of NAFLD

NAFLD, characterized by abnormal hepatocyte fat accumulation not attributable to alcohol, stands as a pervasive metabolic disorder (FONTES-CAL et al., 2021). The breadth of NAFLD ranges from simple steatosis to NASH, with the extreme manifestation being cirrhosis (HADIZADEH; FAGHIHIMANI; ADIBI, 2017; FANG et al., 2020; YE et al., 2023). A matrix of lifestyle influences and genetic factors underlie NAFLD, the hallmark of which is hepatic steatosis - fat content that exceeds 5% in liver cells (HAN et al., 2014; GREFHORST et al., 2021).

The intricate web that connects NAFLD with metabolic syndrome amplifies the threat of consequent metabolic disorders. This correlation exists due to the frequent overlap of obesity, type 2 diabetes, hyperlipidemia, and hypertension (HEINE et al., 2000; CAMPOREZ et al., 2013a; LEE et al., 2017; BOTELLO-MANILLA et al., 2020; ZOU et al., 2020; HUBY; GAUTIER, 2021; DUAN et al., 2022; GUO et al., 2022). High-calorie diets and sedentary behavior exacerbate lipotoxicity and hepatic lipid accumulation (PERLA et al., 2017; DING et al., 2020; TANASE et al., 2020; GREFHORST et al., 2021; DUELL et

al., 2022). Hence, it is critical to conduct in-depth molecular research into NAFLD's prognosis and severity, given its vast impact on patient health and healthcare expenditure (BOTELLO-MANILLA et al., 2020).

Positioning NAFLD as an Unseen yet Escalating Global Health Crisis

NAFLD, in conjunction with its metabolic counterpart—MAFLD, poses a significant public health challenge, tightly bound with the concurrent epidemics of obesity and type 2 diabetes (QI et al., 2017; JEYAKUMAR; VAJRESWARI, 2022; YOUNOSSI et al., 2023). Constituting 25% of adult liver diseases globally, NAFLD carries a substantial economic toll, evident in the surge of hospitalizations and liver transplantations, particularly in regions like the Middle East and South America (ALISI et al., 2017; AHMED et al., 2022; DUAN et al., 2022; EL-KASSAS et al., 2022; JEYAKUMAR; VAJRESWARI, 2022; CHO; KWON; HWANG, 2023; YE et al., 2023).

As the second leading cause for liver transplantation in the US, NAFLD's ubiquity emphasizes the urgent need for enhanced diagnostic measures and innovative therapies (COHEN; HORTON; HOBBS, 2011; CAO et al., 2020). Although specific genetic mutations may induce severe steatosis, the global NAFLD surge primarily results from unhealthy dietary habits and physical inactivity (COHEN; HORTON; HOBBS, 2011; GOEDEKE et al., 2018; ZOU et al., 2020; GREFHORST et al., 2021; DUAN et al., 2022; DUELL et al., 2022; JEYAKUMAR; VAJRESWARI, 2022; YE et al., 2023). The economic impact of NAFLD, set against rising obesity rates, is predicted to skyrocket dramatically by 2025 (DING et al., 2020). Hence, it calls for a unified response from global health organizations to curb its rise and associated health consequences (GUO et al., 2022; YOUNOSSI et al., 2023).

Charting the Objectives and Scope of Our Review

Our review delves into the intricate pathophysiology of NAFLD, laying emphasis on the convergence of diet, hormones, and metabolic syndrome, with a special focus on the role of ERα. We aim to fuse current knowledge on NAFLD prevalence, demographics, risk factors, and therapeutic strategies while addressing its economic implications. We further aspire to underscore the diagnostic and treatment-related challenges that precede symptomatic cirrhosis (QI et al., 2017; DUELL et al., 2022).

Throughout our discourse, we highlight the progression of NAFLD, spotlighting pathophysiological transformations such as liver inflammation and fibrosis, which may escalate to more severe hepatic conditions. We also stress the need for a comprehensive understanding of NAFLD etiology and pathophysiology, considering the high rates of underdiagnosis or misdiagnosis (DUELL et al., 2022; DING et al., 2020).

Ultimately, by offering a detailed overview of current NAFLD management strategies and identifying potential areas for future investigation, our aim is to impart meaningful insights into this rapidly evolving field with far-reaching global health implications.

Dissecting NAFLD: An In-depth Exploration of its Epidemiology, Pathophysiology, and Crossroads with Metabolic Syndrome

Unveiling the Pathophysiology and Diagnostic Challenges of NAFLD and NASH

NAFLD's pathophysiology cascades from mere steatosis, or non-alcoholic fatty liver (NAFL), towards the more severe state of NASH. This shift engenders inflammation, varying degrees of fibrosis, and hepatocellular injury, largely incited by complex interactions among hepatocytes, hepatic stellate cells (HSCs), sinusoidal endothelial

cells, and immune cells. Such interplay precipitates liver fibrosis onset, consequently heightening the risk of cirrhosis and hepatocellular carcinoma (ALISI et al., 2017; GREFHORST et al., 2021; YE et al., 2023). Notwithstanding the serious health implications of these conditions, their diagnosis frequently slips under the radar, underscoring an urgent need for more sophisticated diagnostic methods (DUELL et al., 2022).

Decoding the Epidemiology and Risk Factors of NAFLD

NAFLD's prevalence, defined by excessive non-alcoholic liver fat accumulation, shows marked regional and ethnic disparities, molded by an interplay of genetic, environmental, and behavioral influences. While conspicuously prevalent in obese individuals (~35%), NAFLD also afflicts populations with a BMI < 23 kg/m², as exemplified in India (OATES et al., 2019). Obesity, insulin resistance, accumulation of toxic lipid free radicals, oxidative stress, and a sedentary lifestyle serve as critical risk factors, driving NAFLD's systemic progression and potentially spawning comorbidities like type 2 diabetes, atherosclerosis, and liver cancer (HAN et al., 2014; EL-KASSAS et al., 2022). The ALT/AST index, a promising non-invasive biomarker, aligns with insulin resistance and NAFLD, offering diagnostic, prognostic, and risk stratification opportunities (ZOU et al., 2020).

Probing the Intersection between NAFLD and Metabolic Syndrome

NAFLD and metabolic syndrome often coexist, reflecting shared clinical features such as abdominal obesity, hypertension, atherogenic dyslipidemia, and insulin resistance/dysglycemia (GUO et al., 2022). The tight coupling of obesity, type 2 diabetes, metabolic syndrome, and NAFLD suggests a unified origin. Hormonal fluctuations, like those seen in postmenopausal women, may escalate risk due to increased abdominal fat accumulation (LONARDO et al., 2019; EL-KASSAS et al., 2022). Given the profound interplay between NAFLD and metabolic syndrome constituents, in-depth research, preventive measures, and tailored therapeutic development are of utmost significance (PATERNOSTRO; TRAUNER, 2022). The c-Jun N-terminal kinase (JNK) pathway, instigated by obesity-induced elevation of free fatty acids (FFA), emerges as a pivotal link, engendering insulin resistance and facilitating the nexus between NAFLD and metabolic syndrome (CAELLES et al., 2016).

Unraveling the Pathophysiology of NAFLD: At the Crossroads of Diet, Hormones, and Metabolic Syndrome

Surveying the Role of Diet and Lifestyle in NAFLD Manifestation

Sedentary behaviors and diets high in fat and calories primarily instigate NAFLD, leading to significant hepatic triglyceride accumulation and insulin resistance (COHEN; HORTON; HOBBS, 2011; BESSONE; RAZORI; ROMA, 2018; DUELL et al., 2022; HASSEN et al., 2022). Obesity-induced lipotoxicity escalates NAFLD progression by promoting hepatic lipid accumulation, necroinflammation, fibrogenesis, and cell apoptosis (DING et al., 2020; TANASE et al., 2020; GREFHORST et al., 2021). Insulin resistance and obesity also boost NAFLD development by amplifying the hepatic fatty acid supply (PERLA et al., 2017; CHO; KWON; HWANG, 2023). The Western lifestyle, marked by imbalanced nutrition and restricted physical activity, advances NAFLD progression, notably with frequent high-fructose corn syrup (HFCS) consumption stimulating hepatic lipogenesis (PERLA et al., 2017; DISTEFANO, 2020; ESLAM et al., 2020; DUELL et al., 2022; JEYAKUMAR; VAJRESWARI, 2022). While lifestyle modifications remain the cornerstone of NAFLD treatment, emerging therapies like ERα modulation and epigenetic strategies show

promise (DISTEFANO, 2020; ESLAM et al., 2020; DUELL et al., 2022; PATERNOSTRO; TRAUNER, 2022).

Assessing the Influence of Hormonal Shifts on NAFLD Progression

The effects of sex hormones on NAFLD demonstrate variability, dictated by gender and hormonal status (LONARDO et al., 2019; DISTEFANO, 2020; FONTES-CAL et al., 2021; YE et al., 2023). Hepatic-derived Sex Hormone Binding Globulin (SHBG) contributes to insulin resistance and inflammation, promising potential therapeutic and biomarker uses (QI et al., 2017). Post-menopausal women, due to the waning protective impact of E2 against visceral adiposity and insulin resistance, face heightened susceptibility to central adiposity, increased cardiovascular disease risk, and NAFLD (CAMPOREZ et al., 2011; HAN et al., 2014; LIAO et al., 2015; HAMILTON et al., 2016; DISTEFANO, 2020; DUELL et al., 2022). Thus, E2 administration aimed at ERα has emerged as a potential therapeutic strategy.

Revealing the Complex Interface between NAFLD and Metabolic Syndrome

Shared attributes such as abdominal obesity, hypertension, atherogenic dyslipidemia, and insulin resistance/dysglycemia establish the connection between metabolic syndrome and NAFLD (HASSEN et al., 2022). In insulin-resistant states, the liver is constantly subjected to FFAs, promoting NAFLD, with obesity amplifying systemic FFA levels and exacerbating insulin resistance (CAELLES et al., 2016; GREFHORST et al., 2021). A comprehensive grasp of the intricate interactions among NAFLD, metabolic syndrome, and risk factors like obesity and type 2 diabetes is pivotal for refining prevention and treatment strategies (YANG et al., 2013; BRIL; CUSI, 2016; DING et al., 2020; DISTEFANO, 2020; TANASE et al., 2020; WANG et al., 2020; HASSEN et al., 2022). Current research emphasizes FGF21 as a potential target given its capacity to mitigate hyperglycemia and counteract endoplasmic reticulum stress, thereby improving cellular glucose uptake (DEMIR et al., 2021). Therefore, illuminating the molecular mechanisms entwining NAFLD, metabolic syndrome, and gut microbiota is critical for devising effective therapeutic strategies (YANG et al., 2013; KITADE et al., 2017; GUO et al., 2022).

Emphasizing ERα and Hormonal Signaling's Crucial Influence on NAFLD Pathogenesis

Deciphering the Impact of ERα, Hormonal Variations, and Metabolic Aberrations on NAFLD

ERα, a sensor for E2, exerts influence on NAFLD's pathophysiology by modulating key metabolic functions, including energy metabolism, glucose tolerance, and insulin resistance (CAMPOREZ et al., 2013a; DUELL et al., 2022). Fascinatingly, polymorphisms in genes associated with these metabolic functions could modify NAFLD susceptibility and progression (DUELL et al., 2022).

The genesis of NAFLD involves intricate hormonal cross-talk, specifically between estrogen and thyroid hormones. Estradiol fosters insulin sensitivity via ERα-mediated energy metabolism, thereby defending against NAFLD (DUELL et al., 2022). Conversely, hypothyroidism destabilizes hepatic lipid metabolism, affecting serum lipid levels (DING et al., 2020). Transitioning into menopause escalates NAFLD risk due to hormonal imbalances and diminished energy expenditure, encouraging exploration into interventions like hormone replacement therapy (CAMPOREZ et al., 2013a).

The upregulation of FGF21, triggered by ER stress and capable of modulating insulin signaling via lipogenesis inhibition and glucose uptake enhancement, also features in NAFLD pathophysiology (DEMIR et al., 2021). Concurrently, free cholesterol

accumulation in the liver often parallels NAFLD progression, stemming from imbalances in cholesterol homeostasis and intracellular transport, which ignites insulin resistance and mitochondrial dysfunction (PERLA et al., 2017).

Clarifying ER Stress, Lipotoxicity, and Fibrosis Interplay in NAFLD Progression

ER stress, lipotoxicity, and fibrosis interweave in NAFLD pathogenesis, attributing significant roles to ERα and FGF21 (JIANG et al., 2021; DUELL et al., 2022). High-fat diets can incite ER stress and liver injury, prompting progression to NASH and hepatocellular carcinoma (HCC) (HUBY; GAUTIER, 2021).
Within the realm of obesity, excessive fatty acids augment lipolysis, culminating in ectopic fat accumulation and the generation of detrimental metabolites that precede hepatic steatosis (LIAO et al., 2015; DING et al., 2020). Lipid oxidation products further amplify hepatic inflammation and fibrosis, exacerbating liver damage (DING et al., 2020).

ERα defends against severe hepatic steatosis and insulin resistance during NAFLD progression (GUILLAUME et al., 2019). The regulation of ER stress by ERα proves pivotal, considering how this condition escalates inflammation, insulin resistance, and hepatocyte apoptosis (DISTEFANO, 2020; WANG et al., 2020; DUAN et al., 2022).

The intricacy of NAFLD pathogenesis is further complicated by hyperammonemia, a progression marker from steatosis to cirrhosis and HCC (THOMSEN et al., 2023). Lipotoxicity, characterized by escalated free fatty acids and lipid metabolites, intensifies hepatic fat accumulation, mitochondrial dysfunction, and oxidative stress (PERLA et al., 2017).

Promising therapeutic strategies are emerging, such as FASN and ACC inhibition, that reduce fibrogenic activity and enhance insulin sensitivity (GOEDEKE et al., 2018; O'FARRELL et al., 2022). Delving deeper into the molecular mechanisms underpinning NAFLD, including lipotoxicity, inflammation, and ER stress, is vital for crafting effective treatments (HONMA et al., 2018; GREFHORST et al., 2021; DUELL et al., 2022; JEYAKUMAR; VAJRESWARI, 2022).

Navigating NAFLD Management: From Lifestyle Overhauls to the Dawn of Personalized Medicine

Reevaluating Traditional Lifestyle Modifications and Appraising Progress in Pharmacological Interventions for NAFLD

With FDA-approved medications yet to emerge, lifestyle alterations, encompassing physical activity and dietary amendments, remain the bedrock of NAFLD management. These measures ameliorate liver steatosis, boost insulin sensitivity, and rectify obesity-related metabolic imbalances (MUOIO; NEWGARD, 2008; ROCHLANI et al., 2017; DUELL et al., 2022). Complementary strategies, including blood pressure control and alcohol consumption regulation, dovetail with these interventions, yielding both preventive and therapeutic benefits in NAFLD (COHEN; HORTON; HOBBS, 2011; COTTER; RINELLA, 2020; ESLAM et al., 2020; HASSEN et al., 2022).

Pharmacological advances have spotlighted potential therapeutic targets such as vitamin E, pioglitazone, GLP-1 agonists, FXR ligands, PPAR, and FGF21, while scrupulously examining experimental therapies (DING et al., 2020; HAN et al., 2020; TANASE et al., 2020; PATERNOSTRO; TRAUNER, 2022). Established treatments for metabolic syndrome, namely metformin, thiazolidinediones, and liraglutide, exhibit promise in NAFLD (ESLAM et al., 2020; POUWELS et al., 2022). Current research assesses the efficacy of carotenoids, particularly β-cryptoxanthin and astaxanthin, in diminishing hepatic steatosis and fibrosis (KITADE et al., 2017).

NAFLD's intricate pathogenesis and the lack of FDA-approved treatments highlight the imperative for ongoing research, expansive clinical trials, and advancements in non-invasive diagnostic markers (OATES et al., 2019; CHEN; WU; WU, 2020). Thus, an unwavering commitment to lifestyle interventions and probing pharmacological targets persists as essential for NAFLD management.

Revealing the Promising Influence of Personalized Medicine in NAFLD Management

Personalized medicine, amalgamating genetic, epigenetic, and lifestyle factors, ushers in a revolutionary approach to NAFLD management (BOTELLO-MANILLA et al., 2020; PIROLA; SOOKOIAN, 2020). This approach necessitates a thorough comprehension of genetic variants and epigenetic modifications associated with NAFLD. Numerous gene variants predisposing individuals to NAFLD and hepatic fibrosis have been identified (COHEN; HORTON; HOBBS, 2011; ANSTEE et al., 2016), while bioinformatics analyses aid in pinpointing potential biomarkers differentiating NAFLD from NASH (QI et al., 2017; HUANG et al., 2018; PELLICANO et al., 2021).

Epigenetic regulators such as DNA methylation, histone modifications, and microRNAs (miRs) play critical roles in lipid metabolism and homeostasis (LEE et al., 2017; PIROLA; SOOKOIAN, 2020). Abnormal expressions of specific miRs can potentially worsen NAFLD, thereby providing promising therapeutic targets.

Manipulating ERα and the transcription factor FOXO1, along with natural compounds like polyphenols, flavonoids, alkaloids, terpenoids, and anthocyanins that affect FOXO1, are surfacing as potential NAFLD treatments (DUELL et al., 2022; SABIR et al., 2022). The integration of genetic and epigenetic insights might reveal potential targets for personalized NAFLD therapies, such as FGF21, PPAR agonists, miR modulation, and the inhibition of hepatic p300 activity (CAMPOREZ et al., 2013b; LEE et al., 2017; POUWELS et al., 2022). In-depth understanding of these targets, bolstered by continuous research into epigenetic and miR expressions, may enable the development of potent personalized treatments for NAFLD.

Charting the Course Ahead: Shaping Economic and Clinical Strategies for NAFLD Management

Gauging the Economic Burden of NAFLD

NAFLD imposes a considerable economic burden, with developed regions such as the United States and Europe registering annual expenditures of $103 billion and €35 billion respectively (DING et al., 2020). Obesity and other comorbid conditions exacerbate this financial strain, contributing to an estimated 300,000 annual deaths in the US alone (HEINE et al., 2000). In the context of NASH, a severe variant of NAFLD, costs escalate further, with the US allocating an estimated $222.6 billion to patient treatment in 2017, nearly half of which was attributed to advanced NASH cases (DING et al., 2020). As the demand for NASH treatments continues to increase, the economic burden of NAFLD intensifies, underscoring the need for effective management strategies.

Prioritizing Early Detection and Overcoming Diagnostic Challenges in NAFLD

NAFLD often progresses without symptoms until severe liver damage occurs, making early diagnosis and intervention paramount (DUELL et al., 2022; HASSEN et al., 2022). The scarcity of reliable circulating markers and the limitations of liver biopsy, the current gold standard, present obstacles to accurate and timely detection (HADIZADEH et al., 2017). As a result, research is pivoting towards non-invasive strategies. Emerging alternatives such as the fatty liver index (FLI), hepatic steatosis index (HSI), lipid accumulation product (LAP), NASH index, and NAFLD fat score offer cost-

effective options (HASSEN et al., 2022). Parallel advancements in gene expression profiling show promise for diagnostic biomarker discovery and drug development (QI et al., 2017). The association of NAFLD with increased cardiovascular risk further emphasizes the need for diagnostic methods with balanced sensitivity and specificity and early lifestyle interventions to hinder disease progression (HASSEN et al., 2022).

Delving into Innovative Therapeutic Interventions: Spotlighting Inflammatory Cytokines and Insulin Signaling

Connections between NAFLD pathogenesis, inflammatory cytokines, and insulin signaling position these as potential therapeutic targets (YANG et al., 2013; HADIZADEH et al., 2017; FONTES-CAL et al., 2021). Research has singled out adipokines, secretory proteins that modulate insulin signaling and inflammation, with adiponectin emerging as a potential biomarker for NAFLD due to its protective role against inflammation and fibrosis (HADIZADEH et al., 2017; GREFHORST et al., 2021). Therapeutic strategies that explore molecules such as ERα, FGF21, and FOXO1 show promise in managing obesity-associated NAFLD (DONG, 2017; HADIZADEH et al., 2017; PAN et al., 2017; GUO et al., 2022; SABIR et al., 2022). These investigations, paired with advancements in gene expression profiling and bioinformatics, shed light on the roles of specific genes and pathways, like JNK, in contributing to insulin resistance, thereby directing the design of targeted therapeutic strategies (SHOELSON, 2006; CAELLES et al., 2016; SOLINAS et al., 2017).

Mapping the Territory of Evolving Pharmacological Strategies: Current Investigations and Future Prospects

As the call for effective NAFLD management grows louder, research vigorously explores innovative pharmacological strategies. Investigations include those targeting the RhoA/PI3K/AKT pathway and studies unraveling the molecular mechanisms linking NAFLD with cardiovascular risks (LEE et al., 2017; HASSEN et al., 2022; THOMSEN et al., 2023; YE et al., 2023). Concurrently, studies probing new therapeutic targets, such as the ghrelin system and TGF-β pathway, show potential for reversing hepatic lipogenesis and improving insulin resistance (QUIÑONES et al., 2019; AHMED et al., 2022; JEYAKUMAR et al., 2022). Additionally, the exploration of miRs as biomarkers for NAFLD severity necessitates wider standardization and validation (LEE et al., 2017). This multifaceted drive towards more powerful pharmacological interventions in NAFLD underscores the need for sustained research across multiple fronts.

Closing Remarks

This review accentuates the intricate landscape of NAFLD, an ailment intricately intertwined with a maze of metabolic and genetic pathways, lifestyle habits, hormonal dynamics, and environmental factors. With a progression from simple steatosis to cirrhosis, NAFLD emerges as an urgent global health predicament necessitating immediate attention due to its significant economic ramifications. Despite the widening understanding of NAFLD's multifaceted pathophysiology, the pursuit of accurate diagnostic tools and potent treatments remains paramount.

Our scrutiny reveals numerous research voids, including the limited availability of trustworthy non-invasive diagnostic markers, the absence of disease-specific pharmacological interventions, and the intricate role of hormonal factors—specifically ERα—in the progression of NAFLD. Despite noteworthy advancements, the task of refining our collective grasp of the implicated genetic and epigenetic factors remains ongoing. The delicate molecular interplay among dietary and lifestyle factors,

lipotoxicity, ER stress, and fibrosis demands deeper exploration, emphasizing the central roles of FGF21, JNK, and the gut microbiota.

To attain an integrated understanding of NAFLD, ensuing research must adopt an individualized medicine approach, accommodating genetic, epigenetic, and lifestyle influencers. Therapeutic interventions show promise in addressing lipotoxicity, inflammation, ER stress, and insulin resistance. Simultaneously, genetic and epigenetic alterations could serve as effective preventive strategies. Furthermore, investigating hormonal influences, particularly the effect of post-menopausal reductions in E2 on ER α, presents a promising trajectory for future exploration.

The advancement of non-invasive diagnostic tools and strides in gene expression profiling carry potential to revolutionize NAFLD diagnosis and monitoring. Considering the economic burden that NAFLD imposes, such innovations necessitate rapid advancement, as they could notably reduce healthcare costs by facilitating early interventions.

Functioning as a distillation of our current understanding of NAFLD, this review emphasizes the necessity for continued investigation into the disease's complex nature. The future of NAFLD research and clinical practice hinges on our ability to weave together the diverse aspects of this condition into a unified comprehension. With this comprehensive grasp at our disposal, we will be well-equipped to make significant headway in tackling this escalating global health concern.

Take Home Message

a) NAFLD's prevalence is escalating due to rising rates of obesity and type 2 diabetes.
b) The disease poses significant economic challenges globally.
c) Current research highlights pivotal knowledge gaps, notably in hormonal dynamics and genetic contributions.
d) The horizon shows promise with advancements in personalized medicine and innovative diagnostics.
e) Persistent and focused research is the cornerstone for devising effective interventions and management strategies.

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Initials List

ACC	Acetyl-CoA Carboxylase
AKT	Protein Kinase B
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BMI	Body Mass Index
E2	Estradiol-17β
ER	Endoplasmic Reticulum
ERα	Estrogen Receptor Alpha
FASN	Fatty Acid Synthase
FDA	U.S. Food and Drug Administration
FFA	Free Fatty Acids
FGF21	Fibroblast Growth Factor 21
FLI	Fatty Liver Index
FOXO1	Forkhead Box Protein O1
FXR	Farnesoid X Receptor
GLP-1	Glucagon-like Peptide-1
HCC	Hepatocellular Carcinoma
HFCS	High-fructose Corn Syrup
HSCs	Hepatic Stellate Cells
HSI	Hepatic Steatosis Index
JNK	c-Jun N-terminal Kinase
LAP	Lipid Accumulation Product
MAFLD	Metabolic Associated Fatty Liver Disease
miRs	MicroRNAs
NAFL	Non-alcoholic Fatty Liver
NAFLD	Non-alcoholic Fatty Liver Disease
NASH	Non-alcoholic Steatohepatitis
PI3K	Phosphatidylinositol 3-kinase
PPAR	Peroxisome Proliferator-activated Receptor
RhoA	Ras Homolog Family Member A
SHBG	Sex Hormone Binding Globulin
TGF-β	Transforming Growth Factor Beta
US	United States

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