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Non-Alcoholic Fatty Liver Disease: Epidemiology, Mechanisms, and Management Strategies

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Abstract. **General Background:** Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of hepatic pathologies ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), potentially progressing to cirrhosis and hepatocellular carcinoma, affecting approximately 25% of the global population. **Specific Background:** The escalating prevalence of NAFLD parallels the worldwide epidemics of obesity, type 2 diabetes mellitus, and metabolic syndrome, positioning NAFLD as the hepatic manifestation of metabolic dysfunction with significant cardiovascular and extrahepatic complications. **Knowledge Gap:** Despite its substantial health burden, NAFLD frequently remains asymptomatic in early stages, and the complex interplay of genetic, metabolic, environmental, and gut microbiota factors in disease progression remains incompletely characterized. **Aims:** This comprehensive review examines the epidemiology, pathophysiology, risk factors, diagnostic modalities, and management strategies of NAFLD to elucidate current understanding and therapeutic approaches. **Results:** The review synthesizes evidence on multifactorial disease mechanisms, evaluates non-invasive diagnostic techniques including advanced imaging and serum biomarkers, and assesses lifestyle modifications alongside emerging pharmacological interventions. **Novelty:** This work provides an integrated analysis of NAFLD's systemic nature, emphasizing the gut-liver axis and novel therapeutic targets. **Implications:** Understanding these multidimensional aspects is essential for developing effective prevention and treatment strategies to address this escalating global health challenge.

Keywords: Non-Alcoholic Fatty Liver Disease, NASH, Metabolic Syndrome, Insulin Resistance, Liver Fibrosis

Highlights:

1. Global burden rising to ~25% population linked to obesity, diabetes, metabolic syndrome.
2. Pathogenesis driven by insulin resistance, genetic variants, gut microbiota and metabolic dysfunction.
3. Weight loss 7–10% via lifestyle changes improves steatosis, inflammation, and fibrosis outcomes.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver disease that is defined by excessive hepatic accumulation of fat with no notable alcohol intake, viral hepatitis, and other secondary factors that cause hepatic steatosis (1). The disease is classified into isolated hepatic steatosis, which is the non-alcoholic accumulation of triglycerides over 5 per cent of hepatocytes with minimal inflammation and fibrosis, and non-alcoholic steatohepatitis (NASH), a disease that is associated with the hepatocellular injury of the liver, inflammation, and a range of fibrosis (2). NASH is capable of developing into cirrhosis, end stage liver disease and hepatocellular carcinoma, a leading cause of liver related morbidity and mortality in the global world.

NAFLD is becoming significantly more prevalent in the world in the last 30 years, which is also correlated with the global epidemics of obesity, type 2 diabetes mellitus, and metabolic syndrome (3). The recent estimates show that NAFLD is estimated to be affecting about 25 percent of the world population with the prevalence of NAFLD found to be higher in the western world and in those areas where there are rapid economic growth and changes in lifestyle (4). The disease is seen in all ages such as children and adolescents and is more prevalent among older individuals and peaks in middle-aged and elderly individuals. The healthcare costs between the disease management and complications are large as well as the indirect cost of low productivity and early death are all items that NAFLD inflicts on the economy.

Nowadays NAFLD is identified as the liver manifestation of the metabolic syndrome, which is closely linked with insulin resistance, central obesity, dyslipidemia, and hypertension (5). The two-way connection of NAFLD and these metabolic disorders underscores the systemic complexity of the disease and its impact on the cardiovascular health, chronic kidney disease, and extrahepatic malignancies (6). Although NAFLD is very common and has great health-related impacts, it is frequently asymptomatic in its early phases and many patients are not even aware of the condition. The creation of efficient screening systems, non-invasive diagnostic techniques, and therapeutic treatment is one of the key concerns and issues of hepatology and community health.

Epidemiology and Risk Factors.

A. Global Prevalence

The worldwide incidence of NAFLD is regarded to be around 25 percent, even though the incidence greatly differs among the geographical areas and populations (7). Its prevalence is the highest in South America and Middle East, where the rates are more than 30, and low prevalence is present in Africa (8). In the Western world, NAFLD is found in one out of five to ten individuals and is prevalent in the obese and type 2 diabetes mellitus patients with 70-90 and 60-75 percent respectively (9). Such differences are manifestations of genetic variations, dietary differences, variability of physical activities, and the presence of predisposing risk factors in different populations.

NASH, the more serious instance of NAFLD, is deemed to be prevalent at 1.5-6.5 per

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cent in the general population and 37 per cent in NAFLD patients (10). Development of NASH after the simple steatosis depends on various factors such as metabolic dysfunction severity, genetic tendency and environmental exposures. The critical predictor of liver-related outcomes in NAFLD is fibrosis which is found in up to 20-30% of NASH patients at the time of diagnosis with a high degree of fibrosis in 10-25% (11). Increasing cases of NAFLD have made it become a leading indication of liver transplantation in most countries and is expected to become the leading cause of an end-stage liver disease which needs a transplant in the next few decades (12).

B. Risk Factors

There are several risk factors that cause NAFLD. Obesity, especially central or visceral adiposity is the biggest risk factor and the prevalence of NAFLD is over 90% in the morbidly obese (13). The obesity-NAFLD association is mediated by various processes such as insulin resistance, dysfunction of adipose tissues, disturbed adipokines release, and low-grade inflammatory processes. One predisposing and outcome factor of NAFLD is type 2 diabetes mellitus and they have bidirectional relationships, where each condition predisposes the other (14). Insulin resistance, which is the leading diabetes problem of metabolic syndrome, is at the center of NAFLD pathogenesis with or without obesity.

Dyslipidemia is a disorder with high triglyceride, low HDL cholesterol, and high small dense LDL that tends to develop in NAFLD patients and enhance disease progression (15). Food components especially excess intake of fructose, saturated fats, and processed foods enhance the hepatic fat build-up and metabolic impairments (16). Unadjusted physical inactivity and sedentary lifestyle are risk factors of NAFLD that persist despite body weight control. They also have strong genetic effects, and genetic variants such as PNPLA3, TM6SF2, GCKR, and MBOA7 are related to the risk of NAFLD development and progression (17). Adult age, male sex, and some ethnic groups, especially Hispanic and Asian, also put a person at greater risk of NAFLD (18).

Naturally, the natural history and prognosis of this disease vary according to the site affected.<|human|>Natural History and Prognosis.--Naturally, the natural history and prognosis of this disease differ, depending on the affected site.

Natural history of NAFLD is not consistent as some patients have simple steatosis throughout their decades, whereas others develop NASH, fibrosis, and cirrhosis (19). Around 20-30 percent of NAFLD patients progress to NASH and of NASH patients, 10-20 percent advance to cirrhosis within a period of 10-15 years (20). The hepatic fibrosis, the existence and severity are the best predictors of liver and general death in NAFLD patients. Persons of advanced fibrosis or cirrhosis are at a significantly increased risk of hepatic decompensation, hepatocellular carcinoma and death due to liver causes (21).

Noteworthy, NAFLD patients die not only due to liver-related conditions but cardiovascular disease, extrahepatic malignancies, and chronic kidney diseases (22). The most common cause of death amongst NAFLD patients is the cardiovascular disease which kills a larger number of patients compared to liver-related diseases despite these deaths occurring in patients with advanced fibrosis (23). This highlights the systemic character of NAFLD and the relevance of cardiovascular risk evaluation and management

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in the individuals with NAFLD. Some of the factors linked to the disease progression are old age, diabetes mellitus, obesity, metabolic syndrome, and certain genetic polymorphisms (24).

Pathophysiology

A. Hepatic steatosis is a pathology in which the liver fatty tissue grows progressively heavier (Sorbiere, 1967).<|human|>3.1 Mechanisms of Hepatic Steatosis.

Hepatic steatosis is a condition caused by a disproportion between lipid uptake and disposition with greater hepatic lipid accumulation developed by an amplified de novo lipogenesis, augmented dietary fat intake and liver delivery, and exemption in hepatic lipid export and oxidation (25). Insulin resistance assumes a key role in enhancing hepatic steatosis in a series of ways. During the insulin resistant condition, the adipose tissue lipolysis is enhanced leading to the rise of free fatty acids in the bloodstream which are absorbed by the liver (26). At the same time, hepatic de novo lipogenesis is counterintuitive because insulin stimulates lipogenic pathways by keeping sterol regulatory element-binding protein-1c (SREBP-1c), but does not inhibit hepatic glucose formation.

Food intakes, especially the high intake of fructose, favor hepatic lipogenesis and triglyceride buildup (27). In contrast to glucose, the metabolism of fructose does not involve the rate limiting step of phosphofructokinase and therefore the substrate is freely available to the process of de novo lipogenesis. High fructose diets also cause insulin resistance, which further leads to metabolic malfunction. The liver products impaired lipid export via very low-density lipoprotein (VLDL) release and decreased fatty acid oxidation that contributes to the accretion of triglycerides in the liver (28). Genetic variations, especially in PNPLA3, have an influence in both lipid droplet remodeling and VLDL secretion, which explains their close association with the susceptibility of NAFLD.

B. Progression to NASH

Simple steatosis leads to the development of NASH, which is associated with multiple parallel hits such as oxidative stress, lipotoxicity, mitochondrial dysfunction, endoplasmic reticulum stress, and immune activation (29). Hepatocyte injury and apoptosis are caused by lipotoxicity, which is caused by the deposition of toxic lipid species such as free fatty acids, diacylglycerols, and ceramides (30). These lipid species activate the inflammatory signaling pathways, produce reactive oxygen species, and disrupt insulin signaling, forming a vicious cycle of metabolic malfunction and cell damage.

The pathogenesis of NASH focuses on the mitochondrial dysfunction, which is characterized by the inability to oxidize fatty acids, the excess production of reactive oxygen species, and the decrease of ATP production (31). Mitochondrial dysfunction leads to oxidative stress that causes cellular damage by damaging cellular macromolecules such as lipids, proteins and DNA, which induces inflammatory reactions and the death of hepatocytes. Stress in the endoplasmic reticulum caused by too much lipid and metabolic data disturbances triggers the unfolded protein response and facilitates inflammation and apoptosis (32). Activation of inflammasome cytokine

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production, especially NLRP3, in the hepatocytes and immune cells promotes the production of IL-1b and IL-18, which increases the inflammatory reactions, and draw more immune cells toward the liver (33).

C. Fibrosis Development

Hepatic fibrosis is the wound healing process response to prolonged liver damage and inflammation, and the hepatic stellate cells (HSCs) activation is the key marker in fibrogenesis (34). When hepatocyte injury, inflammatory mediators and oxidative stress arise, quiescent HSCs are converted to myofibroblast like cells that secrete an excessive amount of extracellular matrix proteins such as collagen type I and III (35). Several cell types and pathways are involved in the activation of HSC, they are Kupffer cells, hepatocytes, sinuoidal endothelial cells and infiltrating immune cells.

Transforming growth factor-b (TGF-b) is the ultimate controller of fibrogenesis, which induces the activation of HSCs, expansion, and collagen synthesis and suppresses the destruction of the matrix (36). The process of platelet-derived growth factor (PDGF) stimulates the proliferation and chemotaxis of HSC, whereas connective tissue growth factor (CTGF) mediates the TGF-b profibrotic activities. Fibrosis accumulation depends on the balance between matrix synthesis and degradation that are controlled by the presence of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) (37). In NAFLD, this ratio is reversed and the matrix is deposited more and degraded less which results in progressive fibrosis. Developed fibrosis and cirrhosis leads to the architectural distortion, loss of hepatic functionality and the development of hepatocellular carcinoma.

D. Role of Gut Microbiota

The gut microbiota is relevant to NAFLD pathogenesis via various ways such as energy harvest when it is modulated, lipid and glucose metabolism regulation and intestinal barrier functional effects (38). The patients of NAFLD show changes in the gut microbiota composition, which is a reduction in diversity of bacteria, a reduction in abundance of beneficial bacteria with the capacity to produce short-chain fatty acid, and an increase in abundance of bacteria linked to metabolic malfunction (39). Such alterations of microbes help in NAFLD because of increasing dietary energy extraction, heightened intestinal permeability, and more portal delivery of bacterial products such as lipopolysaccharide (LPS).

Bacterial products can be translocated to the portal circulation with altered intestinal barrier dysfunction and increased permeability to activate hepatic innate immune receptors, such as the tolerance-like receptors (TLRs) (40). This activates inflammatory cascades, facilitates hepatic inflammation and fibrosis and worsens insulin resistance. The production of ethanol by some bacteria in the gut could be a contributing factor to fat in the liver and liver damage. On the other hand, positive gut flora generate short-chain fatty acids that enhance the levels of insulin sensitivity, suppress inflammation, and counteract NAFLD progression (41). The knowledge of gut-liver axis interactions has created new treatment options such as probiotics, prebiotics, and fecal microbiota.

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Diagnosis and Assessment

A. Clinical Presentation

NAFLD is generally asymptomatic during the onset and majority of the cases are associated with incidental findings due to the presence of high liver enzymes in the body or the use of imaging that has been done due to other reasons (42). The symptoms are not specific and tend to be fatigue, malaise, and right upper quadrant pain when they do come on. The results of physical examination are typically not remarkable during the early stages of the disease, although hepatomegaly could be observed. Portal hypertension and hepatic decompensation, ascites, splenomegaly, spider angiomata, and hepatic encephalopathy are possible in more severe fibrosis or cirrhosis (43).

In the majority of NAFLD patients laboratory assessment will show a high level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), yet the liver enzymes could be normal in up to 50% of the patients (44). The extent of enzyme increment is not well correlated with the severity of the disease and it does not always differentiate simple steatosis and NASH. Other biochemical abnormalities can be a high level of gamma-glutamyl transferase (GGT), alkaline phosphatase, ferritin, and presents of metabolic syndrome such as impaired glucose tolerance, dyslipidemia, and increased waist circumference. The assessment must involve the rule out of other causes of chronic liver disease such as viral hepatitis, alcoholic liver disease, hemochromatosis, autoimmune hepatitis and liver damage due to medication (45).

B. Imaging Modalities

The most common imaging modality that is used to detect hepatic steatosis is ultrasonography, which shows specific results such as greater echogenicity, hepatorenal contrast and attenuation of the ultrasound beam (46). Nevertheless, ultrasound is less sensitive to steatosis involving less than 20-30 percent of hepatocytes and is not reliable in distinguishing NASH and simple steatosis or evaluating fibrosis. Computed tomography (CT) is able to identify moderate to severe steatosis depending on reduced liver attenuation as compared to the spleen, but it subjects patients to ionizing radiation and has low sensitivity to mild steatosis (47).

The most effective and non-invasive technique of measuring hepatic steatosis has proven to be magnetic resonance imaging (MRI) and specifically MRI-based proton density fat fraction (MRI-PDFF) (48). MRI-PDFF has high correlation rate with histological grade of steatosis and is capable of identifying steatosis with as few as 5 percent of hepatocytes. MRE equally offers a reliable measurement of liver stiffness that is associated with the stage of fibrosis and has been found to be better than ultrasound elastography techniques in staging fibrosis in NAFLD (49). MRI-PDFF in combination with MRE enables a complete analysis of steatosis and fibrosis using non-invasive methods, but it is expensive and unavailable to many.

The evaluation of non-invasive fibrosis will be made using the following methodology:

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C. Non-Invasive Fibrosis Assessment The non-invasive fibrosis assessment will be conducted as per the following methodology:

Since fibrosis stage is prognostically important, it is important to non-invasively measure fibrosis to facilitate risk stratification and management. A number of serum biomarker assays have been created, among them NAFLD Fibrosis Score (NFS), Fibrosis-4 (FIB-4) index, and Enhanced Liver Fibrosis (ELF) (50). These scores are a combination of easily available clinical and laboratory parameters used to determine the likelihood of fibrosis. The NFS includes age, BMI, hyperglycemia, platelet count, albumin, and AST/ALT ratio whereas FIB-4 includes age, AST, ALT, and platelet count (51). These scores indicate a good performance at the exclusion level of advanced fibrosis but a low accuracy at intermediate levels.

Transient elastography (FibroScan) is a method of measuring the stiffness of the liver as a surrogate of fibrosis, where controlled attenuation parameter (CAP) also offers an evaluation of hepatic steatosis simultaneously (52). Research indicates that transient elastography is good in identifying advanced fibrosis and cirrhosis, but low in the case of early fibrosis and can be influenced by obesity, inflammation, and hepatic congestion. According to the current guidelines, combinations of non-invasive tests should be used, with liver biopsy being used in cases of non-invasive assessment being inconclusive, or competing etiologies are to be evaluated (53).

D. Liver Biopsy

The gold standard of the definitive diagnosis of NASH and the grading of necroinflammatory activity, as well as the staging of fibrosis, are liver biopsy, but its invasive property, sampling error, and interobserver variability are obstacles to its routine application (54). Semi-quantitative measures are known as NAFLD Activity Score (NAS), which consists of measures of steatosis, lobular inflammation, and hepatocellular ballooning, which, nevertheless, does not conclusively identify NASH. More often than not, fibrosis staging is done using systems that classify progressive scarring level starting with stage 0 (no fibrosis) and into stage 4 (cirrhosis) (55).

Liver biopsy indications in NAFLD are unclear diagnosis when other liver diseases are not ruled, non-invasive tests discordant, disease severity assessment when these would be of pertinence in management decisions (56). Some of the possible complications are pain, bleeding, infection, and death, but these are rare with experienced operators. A significant weakness is sampling variability because hepatic steatosis and fibrosis may be heterogeneously distributed. Sample Adequate assessment requires a minimum sample size of at least 15-20 mm in length, 10-11 portal tracts. The need to have biopsy in most patients might be minimized through the development of more precise non-invasive biomarkers and imaging techniques.

Management Strategies

A. Lifestyle Modifications

The cornerstone of NAFLD management is lifestyle intervention, including dietary change and physical exercise, and the existing evidence indicates that lifestyle intervention is effective towards enhancing hepatic steatosis, inflammatory, and fibrotic changes (57).

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A reduction in weight by 3-5% leads to improvement in hepatic steatosis whereas weight loss of at least 7-10 weight loss is necessary to enhance necroinflammation and potentially decrease fibrosis (58). An increased amount of weight loss provides increased success rates of NASH resolving, which is accompanied by regression of fibrosis. Notably, the positive outcomes of weight loss are diminished when weight is regained, hence the necessity of making life-long changes.

The dietary interventions are supposed to be based on caloric restriction, decreased consumption of saturated fats and refined carbohydrates, decreased intake of fructose, and increased intake of fiber (59). The type of Mediterranean diets, high in fruits, vegetables, whole grains, legumes, nuts, and olive oil and moderate intake of fish, shows specific advantage in NAFLD (60). Physical exercise enhances hepatic steatosis and hepatic metabolic parameters despite a lack of substantial weight loss both with aerobic exercise and resistance training being effective. It is recommended to at least maintain 150-200 minutes of moderate exercise per week but any increase in physical activity is beneficial (61).

B. Pharmacological Interventions

As of now, no drugs are directly targeted to treat NAFLD, although a number of different agents appear promising during trials and can be administered off-label in some patients (62). The 800 IU daily of vitamin E can be used to improve the liver histology of non-diabetic individuals with biopsy-proven NASH, although its application is limited by the risk of negative effects, such as the increased all-cause mortality and the development of prostate cancer in certain studies (63). A thiazolidinedione insulin sensitizer, pioglitazone, has been shown to enhance steatosis, inflammation, and hepatocyte ballooning in patients with NASH with or without diabetes, but enthusiasm about the routine use of the product has been dampened by weight gain, fluid retention, bone loss, and cardiovascular issues (64).

GLP-1 receptor agonists such as liraglutide and semaglutide are weight-reducing, glycemic control, and hepatic that shows benefits in NASH patients (65). These agents decrease hepatic steatosis as well as could enhance histological characteristics of NASH, with fewer studies on fibrosis outcomes. SGLT2 inhibitors enhance the metabolic parameters and have a potential to benefit hepatologically, yet there is no actual histological evidence. Statins are safe in patients with NAFLD, lower cardiovascular risk, and have hepatoprotective properties, although they are not NASH-specific treatment (66). Comorbid conditions such as diabetes, hypertension, and dyslipidemia should be managed in order to treat NAFLD patients in a comprehensive manner.

C. Emerging Therapies

There are many new therapeutic agents that are specific pathways involved in the pathogenesis of NA which are currently being studied in clinical trials. Obeticholic acid is a farnesoid X receptor (FXR)-agonist that enhanced fibrosis in a phase 3 trial but issues of pruritus and unfavorable lipid effects have postponed regulatory approval (67). Agonists of thyroid hormone receptor-beta lower hepatic fat and enhance lipid profile, and resmetirom demonstrates promising results in phase 3 studies. The inhibitors of

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acetyl-CoA carboxylase (ACC) prevent de novo lipogenesis and steatosis but have no effect on inflammation and fibrosis (68).

Analogs of fibroblast growth factor 21 (FGF21) have the benefit of improving metabolic parameters and fat reduction in the liver, and current trials measure histological outcomes. ASK1 inhibitors, caspase inhibitors and galactoseregulin-3 inhibitors are antifibrotic and anti-inflammatory agents that inhibit distinct pathways leading to hepatocyte injury and fibrosis (69). Combination therapies investigating several pathogenic pathways simultaneously are promising and can be more effective compared to single-agent therapies. The discovery of efficient pharmacological intervention is a high priority since there is a big number of affected individuals and minimal existing treatment interventions.

D. Bariatric Surgery

Bariatric surgery results in significant and sustained weight reduction in severely obese patients and shows positive results on NAFLD histology (70). Research indicates that bariatric surgery reduces or corrects steatosis in most patients and can reduce necroinflammation and fibrosis but the outcomes differ by the type of surgery and individual characteristics of patients. Roux- en-Y gastric bypass and sleeve gastrectomy are similar in their ability to ameliorate NAFLD. Hepatic benefits are due to the metabolic efficiencies that accompany bariatric surgery such as elevated insulin sensitivity, weight reduction, and positive gut hormone and microbiota modifications (71).

The existing evidence supports the treatment of obese NAFLD patients with the use of bariatric surgery when they meet the standard requirements of a metabolic surgery, but NAFLD is not the reason to undergo surgery (72). The risk associated with perioperative should be properly balanced with the possible benefits and deep preoperative evaluation should be performed to detect patients with advanced liver disease who might encounter a greater risk and encounter surgery. Follow-ups have to be done over long periods to check whether weight has been regained and whether the metabolic and hepatic gains have been maintained. New endoscopic bariatric surgeries have the potential to offer alternative yet less invasive options to some patients but the impact of these surgeries on NAFLD needs additional examination.

Conclusion

There has been the emergence of non-alcoholic fatty liver disease as a critical worldwide health issue with around one quarter of the global population being affected as the hepatic form of the epidemic of the metabolic syndrome. The disease also has a wide range of simple steatosis to NASH with progressive fibrosis, cirrhosis, and hepatocellular carcinoma. Not only liver-related morbidity and mortality are linked to NAFLD, but cardiovascular disease, chronic kidney disease, and extrahepatic malignancies increase, highlighting the overall nature of NAFLD and potential health-wide effects. The increasing prevalence of NAFLD especially among children and young adults is an indication of increasing disease burden in the decades to come.

Significant headway has been achieved in the pathogenesis of NAFLD with the

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acknowledgement of the intricate interaction of genetic predisposition, metabolic impairments, environmental influences, and microbiota composition of the gut that have a role in the disease development and progression. This mechanistic knowledge has been used to shape the creation of new therapeutic approaches to activating particular pathogenic pathways. Non-invasive diagnostic techniques, especially MRI-based procedures and blood biomarkers, have enhanced the diagnostic capabilities of NAFLD, and nowadays, many patients do not need liver biopsy to diagnose the condition and stage it. Nevertheless, there are still serious issues regarding the creation of the effective tools to identify the patients who are at high risks of the disease progression.

Today, diet and physical exercise as a lifestyle immodiation method is still the foundation of NAFLD treatment, and many patients have a hard time losing significant weight and keeping it at a low level. Lack of approved pharmacological treatments specifically targeting NAFLD is a significant unmet clinical requirement although a number of promising agents are undergoing advanced clinical trials. The research priorities in the future involve identification of biomarkers to forecast disease progression and response to treatment, establishment of effective pharmacological interventions, population based approach to screening of the high risk and management of the larger metabolic and cardiovascular complications linked with NAFLD. An interdisciplinary team that includes hepatology, endocrinology, nutrition, and primary care will be the key to the successful management of this disease that is becoming more and more common. The role of promoting NAFLD prevention and reducing its worldwide prevalence will be played by the public health programs concerning obesity, the encouragement of healthy eating habits, and physical exercises.

References

[1] N. Chalasani, Z. Younossi, J. E. Lavine, M. Charlton, K. Cusi, M. Rinella, S. A. Harrison, E. M. Brunt, and A. J. Sanyal, "The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance from the American Association for the Study of Liver Diseases," Hepatology, vol. 67, no. 1, pp. 328-357, Jan. 2018, doi: 10.1002/hep.29367.

[2] E. M. Brunt, V. W. Wong, V. Nobili, C. P. Day, S. Sookoian, J. J. Maher, E. Bugianesi, C. B. Sirlin, B. A. Neuschwander-Tetri, and M. E. Rinella, "Nonalcoholic Fatty Liver Disease," Nature Reviews Disease Primers, vol. 1, no. 1, p. 15080, Dec. 2015, doi: 10.1038/nrdp.2015.80.

[3] Z. M. Younossi, A. B. Koenig, D. Abdelatif, Y. Fazel, L. Henry, and M. Wymer, "Global Epidemiology of Nonalcoholic Fatty Liver Disease-Meta-Analytic Assessment of Prevalence, Incidence, and Outcomes," Hepatology, vol. 64, no. 1, pp. 73-84, Jul. 2016, doi: 10.1002/hep.28431.

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i3.337

[4] Z. Younossi, Q. M. Anstee, M. Marietti, T. Hardy, L. Henry, M. Eslam, J. George, and E. Bugianesi, "Global Burden of NAFLD and NASH: Trends, Predictions, Risk Factors and Prevention," Nature Reviews Gastroenterology & Hepatology, vol. 15, no. 1, pp. 11-20, Jan. 2018, doi: 10.1038/nrgastro.2017.109.

[5] C. D. Byrne and G. Targher, "NAFLD: A Multisystem Disease," Journal of Hepatology, vol. 62, no. 1 Suppl, pp. S47-64, Apr. 2015, doi: 10.1016/j.jhep.2014.12.012.

[6] G. Targher, C. D. Byrne, and H. Tilg, "NAFLD and Increased Risk of Cardiovascular Disease: Clinical Associations, Pathophysiological Mechanisms and Pharmacological Implications," Gut, vol. 69, no. 9, pp. 1691-1705, Sep. 2020, doi: 10.1136/gutjnl-2020-320622.

[7] Z. M. Younossi, P. Golabi, L. de Avila, J. M. Paik, M. Srishord, N. Fukui, Y. Qiu, L. Burns, A. Afendy, and F. N. Nader, "The Global Epidemiology of NAFLD and NASH in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis," Journal of Hepatology, vol. 71, no. 4, pp. 793-801, Oct. 2019, doi: 10.1016/j.jhep.2019.06.021.

[8] G. Vernon, A. Baranova, and Z. M. Younossi, "Systematic Review: The Epidemiology and Natural History of Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis in Adults," Alimentary Pharmacology & Therapeutics, vol. 34, no. 3, pp. 274-285, Aug. 2011, doi: 10.1111/j.1365-2036.2011.04724.x.

[9] S. Bellentani, F. Scaglioni, M. Marino, and G. Bedogni, "Epidemiology of Non-Alcoholic Fatty Liver Disease," Digestive Diseases, vol. 28, no. 1, pp. 155-161, 2010, doi: 10.1159/000282080.

[10] Z. M. Younossi, M. Stepanova, M. Afendy, Y. Fang, Y. Younossi, H. Mir, and M. Srishord, "Changes in the Prevalence of the Most Common Causes of Chronic Liver Diseases in the United States from 1988 to 2008," Clinical Gastroenterology and Hepatology, vol. 9, no. 6, pp. 524-530, Jun. 2011, doi: 10.1016/j.cgh.2011.03.020.

[11] S. Singh, A. M. Allen, Z. Wang, L. J. Prokop, M. H. Murad, and R. Loomba, "Fibrosis Progression in Nonalcoholic Fatty Liver vs Nonalcoholic Steatohepatitis: A Systematic Review and Meta-Analysis of Paired-Biopsy Studies," Clinical Gastroenterology and Hepatology, vol. 13, no. 4, pp. 643-654, Apr. 2015, doi: 10.1016/j.cgh.2014.04.014.

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i3.337

[12] R. J. Wong, M. Aguilar, R. Cheung, R. B. Perumpail, S. A. Harrison, Z. M. Younossi, and A. Ahmed, "Nonalcoholic Steatohepatitis is the Second Leading Etiology of Liver Disease Among Adults Awaiting Liver Transplantation in the United States," Gastroenterology, vol. 148, no. 3, pp. 547-555, Mar. 2015, doi: 10.1053/j.gastro.2014.11.039.

[13] R. Loomba and A. J. Sanyal, "The Global NAFLD Epidemic," Nature Reviews Gastroenterology & Hepatology, vol. 10, no. 11, pp. 686-690, Nov. 2013, doi: 10.1038/nrgastro.2013.171.

[14] A. Mantovani, C. D. Byrne, E. Bonora, and G. Targher, "Nonalcoholic Fatty Liver Disease and Risk of Incident Type 2 Diabetes: A Meta-Analysis," Diabetes Care, vol. 41, no. 2, pp. 372-382, Feb. 2018, doi: 10.2337/dc17-1902.

[15] R. Sarwar, N. Pierce, and S. Koppe, "Obesity and Nonalcoholic Fatty Liver Disease: Current Perspectives," Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, vol. 11, pp. 533-542, Sep. 2018, doi: 10.2147/DMSO.S146339.

[16] T. Jensen, M. F. Abdelmalek, S. Sullivan, K. J. Nadeau, M. Green, C. Roncal, T. Nakagawa, M. Kuwabara, Y. Sato, E. Kang, L. Tolan, G. G. Sanchez-Lozada, H. R. Rosen, M. A. Lanaspa, A. M. Diehl, and R. J. Johnson, "Fructose and Sugar: A Major Mediator of Non-Alcoholic Fatty Liver Disease," Journal of Hepatology, vol. 68, no. 5, pp. 1063-1075, May 2018, doi: 10.1016/j.jhep.2018.01.019.

[17] S. Romeo, J. Kozlitina, C. Xing, A. Pertsemlidis, D. Cox, L. A. Pennacchio, E. Boerwinkle, J. C. Cohen, and H. H. Hobbs, "Genetic Variation in PNPLA3 Confers Susceptibility to Nonalcoholic Fatty Liver Disease," Nature Genetics, vol. 40, no. 12, pp. 1461-1465, Dec. 2008, doi: 10.1038/ng.257.

[18] N. E. Rich, S. Oji, A. R. Mufti, J. D. Browning, N. D. Parikh, M. Odewole, H. Mayo, and A. G. Singal, "Racial and Ethnic Disparities in Nonalcoholic Fatty Liver Disease Prevalence, Severity, and Outcomes in the United States: A Systematic Review and Meta-Analysis," Clinical Gastroenterology and Hepatology, vol. 16, no. 2, pp. 198-210, Feb. 2018, doi: 10.1016/j.cgh.2017.09.041.

[19] S. McPherson, T. Hardy, E. Henderson, A. D. Burt, C. P. Day, and Q. M. Anstee, "Evidence of NAFLD Progression from Steatosis to Fibrosing-Steatohepatitis Using Paired Biopsies: Implications for Prognosis and Clinical Management," Journal of Hepatology, vol. 62, no. 5, pp. 1148-1155, May 2015, doi: 10.1016/j.jhep.2014.11.034.

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i3.337

[20] P. Angulo, D. E. Kleiner, S. Dam-Larsen, L. A. Adams, E. S. Bjornsson, P. Charatcharoenwitthaya, P. R. Mills, J. C. Keach, H. D. Lafferty, A. Stahler, S. Haflidadottir, and F. Bendtsen, "Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease," Gastroenterology, vol. 149, no. 2, pp. 389-397, Aug. 2015, doi: 10.1053/j.gastro.2015.04.043.

[21] P. S. Dulai, S. Singh, J. Patel, M. Soni, L. J. Prokop, Z. Younossi, G. Sebastiani, E. Ekstedt, M. Hagstrom, P. Nasr, S. Stal, V. W. Wong, R. Kechagias, N. Hultcrantz, and R. Loomba, "Increased Risk of Mortality by Fibrosis Stage in Nonalcoholic Fatty Liver Disease: Systematic Review and Meta-Analysis," Hepatology, vol. 65, no. 5, pp. 1557-1565, May 2017, doi: 10.1002/hep.29085.

[22] L. A. Adams, Q. M. Anstee, H. Tilg, and G. Targher, "Non-Alcoholic Fatty Liver Disease and its Relationship with Cardiovascular Disease and Other Extrahepatic Diseases," Gut, vol. 66, no. 6, pp. 1138-1153, Jun. 2017, doi: 10.1136/gutjnl-2017-313884.

[23] G. Targher, C. D. Byrne, A. Lonardo, G. Zoppini, and C. Barbui, "Non-Alcoholic Fatty Liver Disease and Risk of Incident Cardiovascular Disease: A Meta-Analysis," Journal of Hepatology, vol. 65, no. 3, pp. 589-600, Sep. 2016, doi: 10.1016/j.jhep.2016.05.013.

[24] R. Pais, F. Charlotte, L. Fedchuk, C. Bedossa, E. Lebray, T. Poynard, and V. Ratziu, "A Systematic Review of Follow-up Biopsies Reveals Disease Progression in Patients with Non-Alcoholic Fatty Liver Disease," Journal of Hepatology, vol. 59, no. 3, pp. 550-556, Sep. 2013, doi: 10.1016/j.jhep.2013.04.027.

[25] K. L. Donnelly, C. I. Smith, S. J. Schwarzenberg, J. Jessurun, M. D. Boldt, and E. J. Parks, "Sources of Fatty Acids Stored in Liver and Secreted via Lipoproteins in Patients with Nonalcoholic Fatty Liver Disease," Journal of Clinical Investigation, vol. 115, no. 5, pp. 1343-1351, May 2005, doi: 10.1172/JCI23621.

[26] V. T. Samuel and G. I. Shulman, "Nonalcoholic Fatty Liver Disease as a Nexus of Metabolic and Hepatic Diseases," Cell Metabolism, vol. 27, no. 1, pp. 22-41, Jan. 2018, doi: 10.1016/j.cmet.2017.08.002.

[27] S. Softic, D. E. Cohen, and C. R. Kahn, "Role of Dietary Fructose and Hepatic De Novo Lipogenesis in Fatty Liver Disease," Digestive Diseases and Sciences, vol. 61, no. 5, pp. 1282-1293, May 2016, doi: 10.1007/s10620-016-4054-0.

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i3.337

[28] Y. Kawano and D. E. Cohen, "Mechanisms of Hepatic Triglyceride Accumulation in Non-Alcoholic Fatty Liver Disease," Journal of Gastroenterology, vol. 48, no. 4, pp. 434-441, Apr. 2013, doi: 10.1007/s00535-013-0758-5.

[29] H. Tilg and A. R. Moschen, "Evolution of Inflammation in Nonalcoholic Fatty Liver Disease: The Multiple Parallel Hits Hypothesis," Hepatology, vol. 52, no. 5, pp. 1836-1846, Nov. 2010, doi: 10.1002/hep.24001.

[30] N. Alkhouri, L. J. Dixon, and A. E. Feldstein, "Lipotoxicity in Nonalcoholic Fatty Liver Disease: Not All Lipids Are Created Equal," Expert Review of Gastroenterology & Hepatology, vol. 3, no. 4, pp. 445-451, Aug. 2009, doi: 10.1586/egh.09.32.

[31] N. E. Sunny, A. L. Brill, and E. J. Parks, "Mitochondrial Dysfunction in Nonalcoholic Fatty Liver Disease and Insulin Resistance: Cause or Consequence?," Clinical Science, vol. 131, no. 14, pp. 1591-1606, Jul. 2017, doi: 10.1042/CS20160426.

[32] C. Lebeaupin, D. Vallee, Y. Hazari, C. Hetz, E. Chevet, and B. Bailly-Maitre, "Endoplasmic Reticulum Stress Signalling and the Pathogenesis of Non-Alcoholic Fatty Liver Disease," Journal of Hepatology, vol. 69, no. 4, pp. 927-947, Oct. 2018, doi: 10.1016/j.jhep.2018.06.008.

[33] A. R. Mridha, A. Wree, A. A. Robertson, M. M. Yeh, C. D. Johnson, D. M. Van Rooyen, R. N. Haczeyni, N. C. Teoh, C. Savard, M. M. Ioannou, K. A. Masters, N. Miyata, J. K. Hamdorf, B. A. Naguib, S. Hui, D. P. Holt, S. Haynes, G. W. McCaughan, M. A. Cooper, and G. C. Farrell, "NLRP3 Inflammasome Blockade Reduces Liver Inflammation and Fibrosis in Experimental NASH in Mice," Journal of Hepatology, vol. 66, no. 5, pp. 1037-1046, May 2017, doi: 10.1016/j.jhep.2017.01.022.

[34] S. L. Friedman, B. A. Neuschwander-Tetri, M. Rinella, and A. J. Sanyal, "Mechanisms of NAFLD Development and Therapeutic Strategies," Nature Medicine, vol. 24, no. 7, pp. 908-922, Jul. 2018, doi: 10.1038/s41591-018-0104-9.

[35] T. Tsuchida and S. L. Friedman, "Mechanisms of Hepatic Stellate Cell Activation," Nature Reviews Gastroenterology & Hepatology, vol. 14, no. 7, pp. 397-411, Jul. 2017, doi: 10.1038/nrgastro.2017.38.

[36] S. Dooley and P. ten Dijke, "TGF-beta in Progression of Liver Disease," Cell and Tissue Research, vol. 347, no. 1, pp. 245-256, Jan. 2012, doi: 10.1007/s00441-011-1246-y.

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i3.337

[37] V. Arpino, M. Brock, and S. E. Gill, "The Role of TIMPs in Regulation of Extracellular Matrix Proteolysis," Matrix Biology, vols. 44-46, pp. 247-254, May-Jul. 2015, doi: 10.1016/j.matbio.2015.03.005.

[38] H. Tilg, T. E. Adolph, and A. R. Moschen, "Multiple Parallel Hits Hypothesis in Nonalcoholic Fatty Liver Disease: Revisited After a Decade," Hepatology, vol. 73, no. 2, pp. 833-842, Feb. 2021, doi: 10.1002/hep.31518.

[39] J. Boursier, O. Mueller, M. Barret, M. Machado, L. Fizanne, F. Araujo-Perez, C. D. Guy, C. E. Seed, R. L. Rawls, L. A. David, C. Hunault, J. F. Oberti, P. Cales, and A. M. Diehl, "The Severity of Nonalcoholic Fatty Liver Disease is Associated with Gut Dysbiosis and Shift in the Metabolic Function of the Gut Microbiota," Hepatology, vol. 63, no. 3, pp. 764-775, Mar. 2016, doi: 10.1002/hep.28356.

[40] K. Miura and H. Ohnishi, "Role of Gut Microbiota and Toll-like Receptors in Nonalcoholic Fatty Liver Disease," World Journal of Gastroenterology, vol. 20, no. 23, pp. 7381-7391, Jun. 2014, doi: 10.3748/wjg.v20.i23.7381.

[41] E. E. Canfora, R. C. Meex, K. Venema, and E. E. Blaak, "Gut Microbial Metabolites in Obesity, NAFLD and T2DM," Nature Reviews Endocrinology, vol. 15, no. 5, pp. 261-273, May 2019, doi: 10.1038/s41574-019-0156-z.

[42] M. E. Rinella, "Nonalcoholic Fatty Liver Disease: A Systematic Review," JAMA, vol. 313, no. 22, pp. 2263-2273, Jun. 2015, doi: 10.1001/jama.2015.5370.

[43] A. Wieckowska and A. E. Feldstein, "Diagnosis of Nonalcoholic Fatty Liver Disease: Invasive versus Noninvasive," Seminars in Liver Disease, vol. 28, no. 4, pp. 386-395, Nov. 2008, doi: 10.1055/s-0028-1091983.

[44] P. Mofrad, M. J. Contos, M. Haque, C. Sargeant, R. A. Fisher, V. A. Luketic, M. L. Sterling, M. J. Shiffman, R. T. Stravitz, and A. J. Sanyal, "Clinical and Histologic Spectrum of Nonalcoholic Fatty Liver Disease Associated with Normal ALT Values," Hepatology, vol. 37, no. 6, pp. 1286-1292, Jun. 2003, doi: 10.1053/jhep.2003.50229.

[45] European Association for the Study of the Liver, European Association for the Study of Diabetes, and European Association for the Study of Obesity, "EASL-EASD-EASO Clinical Practice Guidelines for the Management of Non-Alcoholic Fatty Liver Disease," Journal of Hepatology, vol. 64, no. 6, pp. 1388-1402, Jun. 2016, doi: 10.1016/j.jhep.2015.11.004.

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i3.337

[46] S. Dasarathy, J. Dasarathy, A. Khiyami, R. Joseph, R. Lopez, and A. J. McCullough, "Validity of Real Time Ultrasound in the Diagnosis of Hepatic Steatosis: A Prospective Study," Journal of Hepatology, vol. 51, no. 6, pp. 1061-1067, Dec. 2009, doi: 10.1016/j.jhep.2009.09.001.

[47] P. J. Pickhardt, S. H. Park, L. Hahn, J. G. Lee, M. Baus, and S. G. Lee, "Specificity of Unenhanced CT for Non-Invasive Diagnosis of Hepatic Steatosis: Implications for the Investigation of the Natural History of Incidental Steatosis," European Radiology, vol. 22, no. 5, pp. 1075-1082, May 2012, doi: 10.1007/s00330-011-2349-2.

[48] S. B. Reeder, I. Cruite, G. Hamilton, and C. B. Sirlin, "Quantitative Assessment of Liver Fat with Magnetic Resonance Imaging and Spectroscopy," Journal of Magnetic Resonance Imaging, vol. 34, no. 4, pp. 729-749, Oct. 2011, doi: 10.1002/jmri.22580.

[49] S. Singh, S. K. Venkatesh, R. Loomba, Z. Wang, C. Sirlin, M. H. Chen, S. K. Yin, M. Talwalkar, J. K. Muddu, R. Ehman, and A. M. Yin, "Magnetic Resonance Elastography for Staging Liver Fibrosis in Non-Alcoholic Fatty Liver Disease: A Diagnostic Accuracy Systematic Review and Individual Participant Data Pooled Analysis," European Radiology, vol. 26, no. 5, pp. 1431-1440, May 2016, doi: 10.1007/s00330-015-3949-z.

[50] G. Musso, R. Gambino, M. Cassader, and G. Pagano, "Meta-Analysis: Natural History of Non-Alcoholic Fatty Liver Disease (NAFLD) and Diagnostic Accuracy of Non-Invasive Tests for Liver Disease Severity," Annals of Medicine, vol. 43, no. 8, pp. 617-649, Dec. 2011, doi: 10.3109/07853890.2010.518623.

[51] S. McPherson, S. F. Stewart, E. Henderson, A. D. Burt, and C. P. Day, "Simple Non-Invasive Fibrosis Scoring Systems Can Reliably Exclude Advanced Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease," Gut, vol. 59, no. 9, pp. 1265-1269, Sep. 2010, doi: 10.1136/gut.2010.216077.

[52] L. Castera, M. Friedrich-Rust, and R. Loomba, "Noninvasive Assessment of Liver Disease in Patients With Nonalcoholic Fatty Liver Disease," Gastroenterology, vol. 156, no. 5, pp. 1264-1281, Apr. 2019, doi: 10.1053/j.gastro.2018.12.036.

[53] V. W. Wong, J. Vergniol, G. L. Wong, J. Foucher, H. L. Chan, B. Le Bail, P. C. Choi, M. Kowo, A. W. Chan, R. Merrouche, C. H. Sung, and V. de Ledinghen, "Diagnosis of Fibrosis and Cirrhosis Using Liver Stiffness Measurement in Nonalcoholic Fatty Liver Disease," Hepatology, vol. 51, no. 2, pp. 454-462, Feb. 2010, doi:

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i3.337

10.1002/hep.23312.

[54] V. Ratziu, F. Charlotte, A. Heurtier, S. Gombert, P. Giral, E. Bruckert, A. Grimaldi, F. Capron, and T. Poynard, "Sampling Variability of Liver Biopsy in Nonalcoholic Fatty Liver Disease," Gastroenterology, vol. 128, no. 7, pp. 1898-1906, Jun. 2005, doi: 10.1053/j.gastro.2005.03.084.

[55] D. E. Kleiner, E. M. Brunt, M. Van Natta, C. Behling, M. J. Contos, O. W. Cummings, L. D. Ferrell, Y. C. Liu, M. S. Torbenson, A. Unalp-Arida, M. Yeh, A. J. McCullough, and A. J. Sanyal, "Design and Validation of a Histological Scoring System for Nonalcoholic Fatty Liver Disease," Hepatology, vol. 41, no. 6, pp. 1313-1321, Jun. 2005, doi: 10.1002/hep.20701.

[56] D. C. Rockey, S. H. Caldwell, Z. D. Goodman, R. C. Nelson, A. D. Smith, and American Association for the Study of Liver Diseases, "Liver Biopsy," Hepatology, vol. 49, no. 3, pp. 1017-1044, Mar. 2009, doi: 10.1002/hep.22742.

[57] M. Romero-Gomez, S. Zelber-Sagi, and M. Trenell, "Treatment of NAFLD with Diet, Physical Activity and Exercise," Journal of Hepatology, vol. 67, no. 4, pp. 829-846, Oct. 2017, doi: 10.1016/j.jhep.2017.05.016.

[58] E. Vilar-Gomez, Y. Martinez-Perez, L. Calzadilla-Bertot, A. Torres-Gonzalez, B. Gra-Oramas, L. Gonzalez-Fabian, S. L. Friedman, A. M. Diehl, and L. A. Romero-Gomez, "Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis," Gastroenterology, vol. 149, no. 2, pp. 367-378, Aug. 2015, doi: 10.1053/j.gastro.2015.04.005.

[59] F. M. Sacks, G. A. Bray, V. J. Carey, S. R. Smith, D. H. Ryan, S. D. Anton, K. McManus, C. M. Champagne, L. M. Bishop, N. Laranjo, M. S. Leboff, J. C. Rood, L. de Jonge, F. L. Greenway, C. M. Loria, E. Obarzanek, and D. A. Williamson, "Comparison of Weight-Loss Diets with Different Compositions of Fat, Protein, and Carbohydrates," New England Journal of Medicine, vol. 360, no. 9, pp. 859-873, Feb. 2009, doi: 10.1056/NEJMoa0804748.

[60] M. C. Ryan, C. Itsiopoulos, T. Thodis, G. Ward, N. Trost, S. Hofferberth, K. O'Dea, P. W. Desmond, N. G. Johnson, and A. M. Wilson, "The Mediterranean Diet Improves Hepatic Steatosis and Insulin Sensitivity in Individuals with Non-Alcoholic Fatty Liver Disease," Journal of Hepatology, vol. 59, no. 1, pp. 138-143, Jul. 2013, doi: 10.1016/j.jhep.2013.02.012.

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i3.337

[61] K. Hallsworth, G. Fattakhova, K. G. Hollingsworth, C. Thoma, S. Moore, R. Taylor, C. P. Day, and M. I. Trenell, "Resistance Exercise Reduces Liver Fat and its Mediators in Non-Alcoholic Fatty Liver Disease Independent of Weight Loss," Gut, vol. 60, no. 9, pp. 1278-1283, Sep. 2011, doi: 10.1136/gut.2011.242073.

[62] Y. Sumida and M. Yoneda, "Current and Future Pharmacological Therapies for NAFLD/NASH," Journal of Gastroenterology, vol. 53, no. 3, pp. 362-376, Mar. 2018, doi: 10.1007/s00535-017-1415-1.

[63] A. J. Sanyal, N. Chalasani, K. V. Kowdley, A. McCullough, A. M. Diehl, N. M. Bass, B. A. Neuschwander-Tetri, J. E. Lavine, J. Tonascia, A. Unalp, M. Van Natta, J. Clark, E. M. Brunt, D. E. Kleiner, J. H. Hoofnagle, and P. R. Robuck, "Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis," New England Journal of Medicine, vol. 362, no. 18, pp. 1675-1685, May 2010, doi: 10.1056/NEJMoa0907929.

[64] K. Cusi, B. Orsak, F. Bril, R. Lomonaco, J. Hecht, C. Ortiz-Lopez, T. M. Tio, E. Hardies, C. Darland, N. Musi, S. Webb, and J. Portillo-Sanchez, "Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Trial," Annals of Internal Medicine, vol. 165, no. 5, pp. 305-315, Sep. 2016, doi: 10.7326/M15-1774.

[65] M. J. Armstrong, P. Gaunt, G. P. Aithal, D. Barton, D. Hull, R.