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THE ROLE OF STATINS IN NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) MANAGEMENT: A MINI REVIEW

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) commonly results in elevated transaminase levels with underlying issues such as diabetes, obesity, or both. Patients with NAFLD often face a high risk of experiencing cardiovascular events globally, which is a leading cause of death. Therefore, this research aims to review current evidence regarding the use of statins in NAFLD patients and discuss their effects on liver histology and cardiovascular disease. We comprehensively reviewed current evidence on the safety of statins in NAFLD patients and their effects on cardiovascular events or liver histology. Findings indicate that statins are safe for administration to NAFLD patients, including those with elevated transaminase levels (<3 times the upper limit of normal). Reviewed studies suggest that statins can reduce cardiovascular risk. Some controversial data also emerged from the literature regarding the effects of statins on liver histology in NAFLD patients. Treatment with statins is safe and can also reduce cardiovascular events in patients with NAFLD. Future and ongoing research will elucidate whether statins play a role in NAFLD treatment. Despite doctors often hesitating to prescribe statins for NAFLD patients, this medication is used to reduce cardiovascular mortality and morbidity, as well as lower liver enzymes.

Keywords: Statin, Liver Enzymes, HMG Co-A, Steatosis, Fibrosis, Hepatocellular Carcinoma, Non-alcoholic steatohepatitis, Steatohepatitis.

1. INTRODUCTION

Non-Alcoholic Liver Diseases

The recent studies have shown that non-alcoholic fatty liver disease (NAFLD) is a significant health concern that affects a quarter of the general population [1]. A recent study has predicted a significant increase in the global burden of end-stage liver disease linked to NAFLD, with a projected rise from 64% to 156% by 2030 [2]. The leading cause of liver transplantation in the next decade will be liver complications arising from NAFLD [3]. The link between NAFLD and liver-related morbidity and mortality extends to CVD and cancer-related fatalities [4].

Based on multidimensional studies, it is proven that NAFLD is closely related to components of metabolic syndrome such as obesity, dyslipidemia, hypertension, and type 2 diabetes [4]. While there are currently no approved pharmacological therapies for treating NAFLD, effective lifestyle modifications are recommended as a treatment option [5]. Statin therapy is suggested by a recent study to be effective in reducing the risk of NAFLD development and significantly improving liver fibrosis [6]. Statins are recognized as a viable treatment option due to their highly effective lipid-lowering properties, given the close association between NAFLD and dyslipidemia, as stated by various studies [7]. It is important to note that study findings suggest that statin treatment may be necessary for individuals with NAFLD, regardless of dyslipidemia, to reduce the risk of advanced liver disease [8].

There is a significant increase in non-alcoholic liver disease in Western countries every day [9]. Chronic liver disease is a complication that affects 25% of the population in the United States. Research has been done on non-alcoholic liver disease (NAFLD), which is a symptom of liver problems that are associated with metabolic syndrome such as obesity, type 2 diabetes, hypertension, and elevated fat levels (dyslipidemia) [10]. Non-alcoholic steatohepatitis (NASH) is characterized by liver inflammation. Patients with severe scarring such as cirrhosis and liver failure can still experience this condition [11]. The long-term use of statins is supported by the results of numerous well-conducted large-scale studies and randomized clinical trials. According to these studies,

statins reduce the risk of significant damage to coronary and vascular diseases in patients. In both primary and secondary prevention, this can lead to average levels of good lipids [12]. Statins are now prescribed for individuals with a NAFLD diagnosis in multiple regions worldwide.

Studies show that statins have a significant therapeutic effect on NAFLD. Furthermore, this research indicates that the use of statins can reduce the liver fibrosis index. However, this study has some limitations, such as unclear details on randomization, randomization concealment, or blinding methods. Long-term follow-up is needed to evaluate the effects of statins on NAFLD management. Statins have the potential to significantly reduce liver biochemical indicators in patients with NAFLD. Statin usage has the potential to affect liver histology in NAFLD, but it is still unclear [13-16]. The pathogenesis of NAFLD is still not fully comprehended [17].

The identification of NAFLD can be done by detecting asymptomatic increases in liver enzymes. NAFLD can be compared to non-alcoholic hypertransaminasemia as a crucial surrogate measure. Currently, physicians are being consulted by gastric and liver specialists about the usage of statins in patients with elevated serum transaminases. Clinical history or serum markers are not sufficient to explain liver biochemical abnormalities. The liver enzymes can rise by up to 90% in patients with NAFLD[18].

Symptoms

The majority of people with non-alcoholic fatty liver disease (NAFLD) usually do not show any symptoms; however, a few may experience fatigue, discomfort in the upper right abdomen, acanthosis nigricans, hepatomegaly, and lipomatosis [19]. A significant proportion of patients with cirrhosis may exhibit symptoms of end-stage liver disease. Approximately 48-100% of non-alcoholic steatohepatitis (NASH) cases can be asymptomatic and are often incidentally discovered during medical assessments for unrelated reasons. Although clinical signs of chronic liver failure are infrequently observed in this demographic, one study suggests that splenomegaly is present in 25% of patients at the time of diagnosis [19].

Frequently, diagnoses like NASH or NAFLD are established based on abnormal liver function tests, such as aminotransferases (ALT and AST), or the fortuitous discovery of liver steatosis during abdominal radiological examinations. Hepatomegaly may become evident during physical examinations, attributed to fat infiltration in the liver [19].

Prevalence

In their study, Riazi et al. [20] The global prevalence of non-alcoholic fatty liver disease (NAFLD) among adults was estimated to be 32% after analyzing data from 72 studies that involved 1,030,160 individuals. The prevalence is more prevalent among men than women (40% vs. 26%, $P < 0.0001$). In studies conducted between 2005 and 2016 or later, the prevalence of NAFLD increased from 26% to 38%. Interpreting the data from Riazi and co-workers' study should be approached cautiously [20], as the data is only available from 17 countries, making it unclear whether the estimates from this study truly reflect 'global' prevalence. The shortage of studies highlights the necessity of enhancing data collection in areas like Africa, Oceania, and South America, which are still lacking in data. Le et al. [21] estimated the global prevalence of non-alcoholic fatty liver disease (NAFLD) to be 29.8% after compiling data from 245 research involving 2,699,627 persons. This finding is consistent with that of Riazi. But, like with Riazi's work, this analysis lacks or has little data from Africa, Oceania, North America, and South America.

Pathogenesis

Clinical research and translational studies in specific animal models have helped expand our understanding of the pathogenesis of non-alcoholic fatty liver disease (NAFLD) [22]. The development of obesity and insulin resistance in adipose and hepatic tissues is believed to be the cause of early events in NAFLD [23]. Together, these conditions result in an increased flow of free fatty acids (FFA) into the liver, originating from the non-esterified fatty acid (NEFA) pool through dysregulation of peripheral lipolysis, de novo lipogenesis (DNL), and dietary fat. Accumulation of lipotoxic intermediates such as diacylglycerol (DAG) leads to hepatic insulin resistance [24]. he increased flow of FFA into the liver, in turn, places hepatocytes under significant metabolic

burden and promotes hepatocellular lipotoxicity and endoplasmic reticulum (ER) stress [24, 25]. Accumulation of triglycerides (TAG) in hepatocyte cytoplasm (steatosis) is a histologically reflective epiphenomenon of these metabolic changes and is best considered an early adaptive response where potentially lipotoxic FFA is sequestered into inert intracellular TAG for storage [26]. Ultimately, this assault is combined with additional effects of endotoxin-induced cytokine release through Toll-like receptor 4 (TLR4) by Kupffer cells and immune system-mediated hepatocellular injury, leading to cellular damage and activation of cell death pathways, marking the transition to steatohepatitis (NASH) [27, 28]. As these processes persist, stellate cell activation, collagen deposition, and liver fibrosis occur [28].

Role of Statins

Statins, as part of the HMG-CoA reductase inhibitor group, are commonly used in advanced countries as prescription drugs. The HMG Co-A reductase classification includes statins, which have differing pharmacological effects. Statins and HMG Co-A reductase have different oral biological availability and protein binding. The metabolism of lipophilic statins like atorvastatin, lovastatin, simvastatin, and fluvastatin is assisted by cytochrome P450. In contrast to other drug classes, other statins, such as pravastatin and pitavastatin, are hydrophilic and undergo metabolism. Rosuvastatin's profile of hepatic metabolism is moderate. Statins are sometimes restricted as prescription drugs due to their side effects, such as muscle and liver damage, as well as the risk of hepatotoxicity altering the biochemical nature of liver enzymes; therefore, administering statins in liver disease is a concern.

According to recent research findings, the use of statins in patients with active liver disease and chronic elevation of aminotransferase levels needs attention. Speaking with experts, such as gastroenterologists, reveals that there is no proof aberrant liver biochemistry occurs when blood liver enzyme levels are raised, indicating that statin treatment is safe. When using statins, an asymptomatic liver enzyme rise brought on by liver abnormalities becomes a diagnostic measure for liver disease [29, 30]. However, new research on statin prescriptions has demonstrated benefits for individuals. This study aims to clarify how statins act and what role they play in the development of different illnesses such cirrhosis, fibrosis, and portal hypertension, which protects blood vessels. The review also suggests that statins have the ability to resolve hepatic fibrogenesis and have a role in the development, progression, and consequences of a variety of liver disorders [31].

2. Risk Factors for NAFLD

Numerous studies now show a high correlation between each risk factor linked to Metabolic Syndrome (MS) and Non-Alcoholic Fatty Liver Disease (NAFLD) [32-34], especially obesity, Type 2 Diabetes Mellitus (T2DM), and dyslipidemia [35].

Obesity

Non-Alcoholic Fatty Liver Disease will affect more than 95% of extremely obese individuals receiving bariatric surgery (NAFLD) [36-39], underscoring the close pathogenic relationship between these two disorders. Notably, individuals with NAFLD between the ages of 40 and 60 commonly exhibit obesity. In fact, NAFLD and obesity across the board—from overweight to severe obesity—are related. Given that the existence of NAFLD and the rate at which the illness progresses are positively correlated with both body mass index (BMI) and waist circumference, obesity is acknowledged as a major risk factor for NAFLD [40].

Nonetheless, a subset of NAFLD patients who have a normal BMI are classified as lean or non-obese. This subgroup appears to have a milder type of NAFLD than obese people, as evidenced by the absence of obesity-related comorbidities [41], albeit in this case more investigation is required. Liver disease that goes untreated affects this particular demographic since there are no obvious risk factors; its prevalence ranges from 5 to 26 percent worldwide [42]. Lean NAFLD is more common in rural Asian regions than in America, with a 30% prevalence against 7% in the United States. [2]. When compared to healthy persons, slim NAFLD patients often have disrupted metabolism, which is defined by higher circulating triglycerides and insulin resistance. However, they also have a smaller waist circumference and a lower prevalence of metabolic syndrome than obese NAFLD

patients [43]. People with lean NAFLD are susceptible to developing severe fibrosis and Non-Alcoholic Steatohepatitis (NASH) even though they only have mild metabolic abnormalities [44].

Lipotoxicity and glucotoxicity are important factors in the developmental path from basic hepatic steatosis to NASH. Obese people often follow high-fat, high-carb diets, which promote the formation of fat in the liver through a number of processes, such as endoplasmic reticulum damage, oxidative stress, and mitochondrial damage [45, 46]. Intrahepatic inflammation is caused by ineffective management of basic hepatic steatosis. [47]. As a result, the liver's innate immune cells activate, penetrating the liver tissue and releasing cytokines that stimulate inflammation. This also helps to trigger the fibrogenic process, which is usually linked to persistent inflammation [48]. In addition, obesity stimulates the liver's production of hormones and adipokines (such as leptin and adiponectin), which accelerates the development of NAFLD into NASH, cirrhosis, and hepatocellular carcinoma (HCC) [48, 49].

Metabolic Syndrome

Increased waist circumference, hypercholesterolemia, dyslipidemia, and systemic hypertension are some of the symptoms of metabolic syndrome (MS), which has several accepted classifications [50]. Similar to Non-Alcoholic Fatty Liver Disease (NAFLD), multiple sclerosis (MS) has become more common in recent years, and the two conditions are thought to be closely connected [33, 51, 52]. The correlation between NAFLD and MS characteristics is typically positive, particularly when it comes to diabetes and hypertension. MS raises the risk of NAFLD, and treating NAFLD and NASH can also improve certain MS symptoms. This is important because people with NAFLD are more likely to die and experience severe cardiovascular events when they have MS [51, 52].

The ability of insulin to regulate the synthesis of glucose is diminished in MS patients, resulting in moderate hypercholesterolemia. This, in turn, promotes the release of insulin, resulting in hyperinsulinemia. Usually, insulin reduces the formation of liver or the process of adipose tissue lipolysis, which lowers the level of Very Low-Density Lipoprotein (VLDL) [53]. One major factor leading to elevated blood triglycerides in both MS and NAFLD patients is insulin's inability to inhibit lipolysis, the liver's creation of triglyceride-rich VLDL particles [54][53]. This dyslipidemia is characterized by decreased HDL cholesterol and increased VLDL-induced formation of tiny, dense, highly atherogenic LDL particles [55]. Consequently, these individuals are more likely to experience cardiovascular disease.

Diabetes and Insulin Resistance

Non-Alcoholic Fatty Liver Disease (NAFLD) development and Type 2 Diabetes (T2DM) have been found to be strongly correlated; over 50% of T2DM patients also have NAFLD [56, 57]. In addition to being a prevalent comorbidity of non-alcoholic fatty liver disease (NAFLD), diabetes also plays a significant role in the disease's progression towards non-alcoholic steatohepatitis (NASH), which accelerates the development of liver fibrosis and hepatocellular carcinoma (HCC) [58-62]. T2DM affects the propensity for NAFLD, much like MS does, and vice versa.

Insulin Resistance (IR) has been identified as a crucial cellular dysfunction that contributes to the development of both Type 2 Diabetes and Non-Alcoholic Fatty Liver illness (NAFLD) [63], and it deteriorates as the illness advances. Increased gluconeogenesis and reduced hepatic glycogen production are two characteristics of IR in the liver [64]. In turn, there is a negative correlation between liver fat content and insulin-stimulated hepatic glycogen production [64]. Therefore, NAFLD patients have an increased chance of acquiring diabetes, same like MS patients [65].

The role of the inflammatory pathway in the development of IR is becoming more well acknowledged. When the inflammatory process starts is yet unknown, but [66, 67]. Furthermore, there are several mechanisms other than inflammation that are involved in the complicated etiology of IR [68]. For example, dysbiosis of the digestive system may be one of the early events in the formation of both IR and NAFLD, in addition to dysregulation in fatty acid metabolism [69].

3. Search Methods

The conclusion of this review was reached after doing many searches in databases including Pubmed, Sciencedirect, and Scopus. The evaluation concentrated on clinical studies concerning the rise in liver enzymes (ALT, GGT, and AST) in response to statin medication in liver disorders resulting from alcohol and non-alcohol. The consequences of statin usage in non-alcoholic fatty liver disease (NAFLD) were examined by reviewing relevant literature and conducting a thorough study. Keywords were chosen based on the subject of the articles sought; the last search date was on January 25, 2024. The keywords in this investigation include "statin, hydroxymethylglutaryl-CoA reductase inhibitor, non-alcoholic steatohepatitis, HMG-CoA reductase inhibitor, atorvastatin, mevastatin, lovastatin, fluvastatin, cerivastatin, simvastatin, rosuvastatin, pravastatin, pitavastatin, safety, therapeutic use, fibrosis, liver histology, steatosis, inflammation, oxidative stress, liver enzymes, liver toxicity, dyslipidemia."

Study Selection

We assessed the database's abstracts and titles to find research that may be further evaluated. Next, we assessed the completeness and applicability of papers that were pertinent to our topic. The study selection process involved several steps, starting with selecting cases and conducting electronic database searches using specific keywords, followed by data selection based on inclusion and exclusion criteria. Subsequently, we collected all relevant data and thoroughly examined the reports. The final step involved a comprehensive review of the full papers, leading to the determination of the most suitable titles for our topic. The assessment considered the relevance of both titles and abstracts. Two reviewers independently assessed the papers for eligibility criteria without imposing restrictions on the papers.

4. Diagnosis and Classification

Two different tests are used to diagnose NAFLD. Blood testing is the first one. On the other hand, imaging tests like CT, MRI, and ultrasound are part of the other. By revealing higher liver enzyme values, blood tests aid in the detection of liver function [70]. Furthermore, lipid profiles that measure LDL, triglyceride, and blood cholesterol levels make it possible to diagnose NAFLD.

Mechanism of Action of Statins

Statins increase liver disease, whether caused by alcohol or not, through different mechanisms. By reducing LDL levels and acting through proteins called activating sterol-regulating element-binding proteins (SREBPs), which support transcription and preserve lipid homeostasis, they lessen hepatic steatosis [71]. In NAFLD, PPAR (peroxisome proliferator-activated receptor alpha) is essential for lowering the inflammatory response.

Anti-Inflammatory and Anti-Fibrotic Effects

A statin reduces downstream signaling by preventing small GTPase prenylation, which is how it works as an anti-inflammatory [72]. Statins can reduce bile acids in the early stages of fibrosis by activating PPAR-α and the pregnane X receptor. Through paracrine communication from liver cells to hepatic stellate cells, which in turn inhibits hepatic stellate cell activation, statins have anti-fibrotic effects. Fibrogenesis is therefore stopped [73]. Rho kinase is responsible for activating the hepatic stellate cell pathway [74]. RhoA inhibition can improve fibrosis. By increasing the imbalance of intrahepatic resistance, which impacts the regulation of the RhoA and nitric oxide signaling pathways and causes vasoconstriction, statins have a role in portal hypertension.

5. Treatment

Statins Safety in NAFLD Patients

Statins are generally safe for those with increased transaminase levels, according to several observational studies. NAFLD appears to be the most common cause of increased transaminases in patients who do not report alcohol misuse or hepatitis C or B [75]. During the first 12 weeks of treatment, an asymptomatic rise in serum aminotransferases is frequently linked to statin-induced hepatotoxicity, with no hepatopathological changes seen [76]. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations were seen in several phase II and III clinical trials.

Onofrei [77] Transaminase levels increased significantly but substantially with the majority of rosuvastatin, atorvastatin, simvastatin, pravastatin, and lovastatin dosages [78]. Transaminase levels increased significantly but substantially with the majority of rosuvastatin, atorvastatin, simvastatin, pravastatin, and lovastatin dosages [78]. This increase sparked worries that statins can exacerbate liver disease. Because of this, pharmaceutical companies advise against using statin medication in those who have underlying liver disease and unexplainedly increased aminotransferases. It was previously recommended that people taking statins evaluate their LFTs both before and after a 12-week increase in dose [77]. A transient elevation brought on by alcohol intake, obesity, diabetes mellitus, statin treatment, or other drugs causes the spontaneous rise in aminotransferase levels [79].

Numerous investigations have been carried out to determine if statin medication causes or contributes to notable liver damage. One study from the "Adverse Event Database Merck Worldwide" examined 232 cases of acute liver failure associated with lovastatin, revealing a risk of fulminant liver failure of two per one million individuals [76].

Between 1990 and 2002, the U.S. performed approximately 51,741 liver transplants, with only three surgeries notably related to statin therapy [77]. Avins [80] carried out a retrospective cohort research to evaluate the hepatic consequences of lovastatin exposure in liver disease patients. Primary outcomes included examining whether there were abnormalities in liver tests associated with a poor prognosis according to the Hy Law for drug-induced liver disease patients. Avins et al. [80] defined the Hy Law as "a liver test profile dominantly associated with a poor prognosis for patients with drug-induced liver disease." Secondary outcomes involved liver injury, liver failure, or the development of clinical cirrhosis. Exposure to lovastatin was often linked to a reduction in the prevalence of severe to moderate liver damage, along with liver failure or cirrhosis. After receiving atorvastatin 80 mg/day or simvastatin 20–40 mg/day, 1,081 patients had a decrease in transaminase levels (< 2 times the upper normal value), leading this study to conclude that lovastatin is not linked to an increased risk of adverse liver outcomes [81].

Statin Effect on the Cardiovascular Morbidity in NAFLD Patients

Statins may prevent cardiovascular events in those with high transaminase levels, maybe as a result of NAFLD, according to post-hoc analysis of three randomized controlled trials (RCTs). In the three-year Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) clinical study, atorvastatin medication reduced cardiovascular events in those with normal transaminase levels by 39% [82]. Conversely, in individuals with coronary heart disease (CHD) and elevated transaminase levels, atorvastatin limited cardiovascular events by 68% (P = 0.0074 compared to the decreased CVD risk in patients with normal transaminase levels) [82]. In individuals with Metabolic Syndrome (MetS), a 42-month atorvastatin treatment that targeted low-density lipoprotein cholesterol (LDL-C) levels < 100 mg/dL and elevated transaminase levels reduced cardiovascular events more than atorvastatin treatment that targeted LDL-C levels < 130 mg/dL (P = 0.024) [83]. The IDEAL clinical trial was the subject of a second post-hoc analysis, which revealed that atorvastatin treatment (80 mg/day) frequently reduced cardiovascular events more than simvastatin treatment (20–40 mg/day) only in patients with elevated transaminase levels and not in patients with normal transaminase levels (P for heterogeneity = 0.0277) [81]. As a result, early results indicate that statins usually lower cardiovascular morbidity in individuals with NAFLD. Nevertheless, according to American and European criteria, the therapy of dyslipidemia is unaffected by the existence of NAFLD [83, 84].

Statins Effects on Liver Histology in NAFLD Individuals

Involving oxidative stress, increased apoptosis in the pathogenesis of NAFLD, and subclinical inflammation, statins play a role in improving liver histology in these patients through their pleiotropic effects [85]. On the other hand, a few uncontrolled, small-scale investigations that looked at how statins affected human hepatic steatosis using CT or ultrasound have largely demonstrated improvement [86, 87]. Overall, atorvastatin and combination treatment (atorvastatin + fenofibrate) were found to reduce hepatic echogenicity and be more effective than fenofibrate alone in a larger randomized controlled study (RCT) [88]. An further RCT showed that, in terms of decreasing hepatic steatosis on CT, atorvastatin 10–20 mg/day was thought to be equally beneficial as

pitavastatin 2-4 mg/day [89]. Regarding the impact of statins on liver histology, however, very little information is known. Numerous studies examining the impact of statins on liver histology in persons with non-alcoholic fatty liver disease (NAFLD) have used prospective uncontrolled designs that have limited sample sizes. Most of these investigations support the notion that statin therapy often lowers hepatic steatosis [90, 91], whereas a few others showed no differences [91], others improved inflammation [91], and yet others did not report any changes at all. Except for a preliminary tiny study on six individuals receiving rosuvastatin for six months, no other trials revealed a reduction in fibrosis [91].

Role of Statin in Non-Alcoholic Liver Disdisease

Statins have anti-inflammatory, antithrombotic, and antioxidant properties apart from their ability to decrease cholesterol levels [92, 93]. Due to the involvement of oxidative stress and inflammation in both NAFLD and NASH, statin treatment is important [94]. When severe hepatic steatosis is present in NAFLD patients, there is an increase in oxidative stress linked to NOX2 [94].

There are currently no data on a particular NAFLD therapy. There is currently little data on how statins affect non-alcoholic fatty liver disease [95, 96]. Through signal transduction, protein synthesis, cell differentiation, and intracellular vesicle mobility, GTPases are important in non-alcoholic steatohepatitis. By lowering GTPases, statins aid in the prevention of non-alcoholic steatohepatitis. Inflammation, metabolic processes, and non-alcoholic steatohepatitis are all significantly impacted by PPARs. Statins help break down fatty acids by activating PPAR receptors. The liver contains the antioxidant enzyme paraoxonase 1 (PON1), which also has anti-inflammatory and anti-atherogenic effects [97]. Lipid peroxidation causes PON1 to decrease, whereas statin medication increases it [98].

In a rat model of non-alcoholic steatohepatitis, simvastatin enhances the advancement of fibrosis. Stellate cell activation may be restricted by endothelial and inducible nitric oxide synthase production. Following four years of Atorvastatin 20 mg medication, 71% of NAFLD patients exhibited improvement and decreased risk [99].

6. CONCLUSIONS

Significant progress has been made in understanding the natural history, prevalence, and pathogenesis of NAFLD. Nonetheless, there hasn't been any significant advancement in therapeutic management to far. For those with increased transaminase levels as a result of NAFLD, statins are regarded as safe. Statins may lower cardiovascular morbidity in the population under study, according to post-hoc analysis of randomized clinical trials (RCTs). On the other hand, there is ongoing debate over the effect of statins on the histology of the liver in people with non-alcoholic fatty liver disease. RCTs that are conducted now, and in the future will help determine if statins are useful in the treatment of NAFLD. In order to improve NAFLD identification and find the most effective techniques for diagnosing advanced fibrosis, more study is required.

REFERENCE

- Estes, C., et al., *Modeling nafld disease burden in china, france, germany, italy, japan, spain, united kingdom, and united states for the period 2016–2030.* Journal of hepatology, 2018. **69**(4): p. 896-904.
- Younossi, Z.M., *Non-alcoholic fatty liver disease–a global public health perspective.* Journal of hepatology, 2019. **70**(3): p. 531-544.
- Hyogo, H., et al., *Efficacy of atorvastatin for the treatment of nonalcoholic steatohepatitis with dyslipidemia.* Metabolism, 2008. **57**(12): p. 1711-1718.
- Hyogo, H., et al., *Atorvastatin improves disease activity of nonalcoholic steatohepatitis partly through its tumour necrosis factor-α-lowering property.* Digestive and Liver Disease, 2012. **44**(6): p. 492-496.
- Maroni, L., et al., *Lipid targets during statin treatment in dyslipidemic patients affected by nonalcoholic fatty liver disease.* The American journal of the medical sciences, 2011. **342**(5): p. 383-387.

- de Keyser, C.E., et al., *Statin therapy is associated with a reduced risk of non-alcoholic fatty liver in overweight individuals.* Digestive and Liver Disease, 2014. **46**(8): p. 720-725.
- Oni, E.T., et al., *Statin use is not associated with presence of and severity of nonalcoholic fatty liver disease.* Archives of Medical Research, 2014. **45**(1): p. 52-57.
- Loomba, R. and A.J. Sanyal, *The global NAFLD epidemic.* Nature reviews Gastroenterology & hepatology, 2013. **10**(11): p. 686-690.
- Struben, V.M.D., E.E. Hespenheide, and S.H. Caldwell, *Nonalcoholic steatohepatitis and cryptogenic cirrhosis within kindreds.* The American journal of medicine, 2000. **108**(1): p. 9-13.
- Violi, F., et al., *Statins as antithrombotic drugs.* Circulation, 2013. **127**(2): p. 251-257.
- Pelli, N., et al., *Autoimmune hepatitis revealed by atorvastatin.* European journal of gastroenterology & hepatology, 2003. **15**(8): p. 921-924.
- Caldwell, S.H., J.S. Zaidman, and E.E. Hespenheide, *The liver and statin drug therapy: uncertain navigation in the sea of risk-benefit.* pharmacoepidemiology and drug safety, 2003. **12**(4): p. 303-306.
- Ma, P., et al., *Mevinolin, an inhibitor of cholesterol synthesis, induces mRNA for low density lipoprotein receptor in livers of hamsters and rabbits.* Proceedings of the National Academy of Sciences, 1986. **83**(21): p. 8370-8374.
- Rehm, J., et al., *Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis.* Drug and alcohol review, 2010. **29**(4): p. 437-445.
- Shieh, K., J.M. Gilchrist, and K. Promrat, *Frequency and predictors of nonalcoholic fatty liver disease in myotonic dystrophy.* Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine, 2010. **41**(2): p. 197-201.
- Angulo, P., *Current best treatment for non-alcoholic fatty liver disease.* Expert Opinion on Pharmacotherapy, 2003. **4**(5): p. 611-623.
- Daniel, S., et al., *Prospective evaluation of unexplained chronic liver transaminase abnormalities in asymptomatic and symptomatic patients.* The American journal of gastroenterology, 1999. **94**(10): p. 3010-3014.
- Bacon, B.R., et al., *Nonalcoholic steatohepatitis: an expanded clinical entity.* Gastroenterology, 1994. **107**(4): p. 1103-9.
- Riazi, K., et al., *The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis.* Lancet Gastroenterol Hepatol, 2022. **7**(9): p. 851-861.
- Le, M.H., et al., *2019 Global NAFLD Prevalence: A Systematic Review and Meta-analysis.* Clin Gastroenterol Hepatol, 2022. **20**(12): p. 2809-2817.e28.
- Anstee, Q.M. and R.D. Goldin, *Mouse models in non-alcoholic fatty liver disease and steatohepatitis research.* International journal of experimental pathology, 2006. **87**(1): p. 1-16.
- Anstee, Q.M., G. Targher, and C.P. Day, *Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis.* Nature reviews Gastroenterology & hepatology, 2013. **10**(6): p. 330-344.
- Samuel, V.T., K.F. Petersen, and G.I. Shulman, *Lipid-induced insulin resistance: unravelling the mechanism.* The Lancet, 2010. **375**(9733): p. 2267-2277.

- Yang, L., et al., *Defective hepatic autophagy in obesity promotes ER stress and causes insulin resistance.* Cell metabolism, 2010. **11**(6): p. 467-478.
- Yamaguchi, K., et al., *Inhibiting triglyceride synthesis improves hepatic steatosis but exacerbates liver damage and fibrosis in obese mice with nonalcoholic steatohepatitis.* Hepatology, 2007. **45**(6): p. 1366-1374.
- Malhi, H., G.J. Gores, and J.J. Lemasters, *Apoptosis and necrosis in the liver: a tale of two deaths?* Hepatology, 2006. **43**(S1): p. S31-S44.
- Anstee, Q.M., et al., *Impact of pan-caspase inhibition in animal models of established steatosis and non-alcoholic steatohepatitis.* Journal of hepatology, 2010. **53**(3): p. 542-550.
- Patti, G., et al., *Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: a collaborative patient-level meta-analysis of 13 randomized studies.* Circulation, 2011. **123**(15): p. 1622-1632.
- Taylor, F., et al., *Statins for the primary prevention of cardiovascular disease.* Cochrane database of systematic reviews, 2011(1).
- De Castro, M., et al., *Acute cholestatic hepatitis after atorvastatin reintroduction.* Gastroenterologia y Hepatologia, 2006. **29**(1): p. 21-24.
- Nascimbeni, F., et al., *From NAFLD in clinical practice to answers from guidelines.* Journal of hepatology, 2013. **59**(4): p. 859-871.
- Hsiao, P.J., et al., *Significant correlations between severe fatty liver and risk factors for metabolic syndrome.* Journal of gastroenterology and hepatology, 2007. **22**(12): p. 2118-2123.
- Marchesini, G., et al., *Nonalcoholic fatty liver disease: a feature of the metabolic syndrome.* Diabetes, 2001. **50**(8): p. 1844-1850.
- Chalasani, N., et al., *The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases.* Hepatology, 2018. **67**(1): p. 328-357.
- Subichin, M., et al., *Liver disease in the morbidly obese: a review of 1000 consecutive patients undergoing weight loss surgery.* Surgery for Obesity and Related Diseases, 2015. **11**(1): p. 137-141.
- Masuoka, H.C. and N. Chalasani, *Nonalcoholic fatty liver disease: an emerging threat to obese and diabetic individuals.* Annals of the new York Academy of Sciences, 2013. **1281**(1): p. 106-122.
- Ng, M., et al., *Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013.* The lancet, 2014. **384**(9945): p. 766-781.
- Rinella, M. and M. Charlton, *The globalization of nonalcoholic fatty liver disease: prevalence and impact on world health.* Hepatology, 2016. **64**(1): p. 19-22.
- Angulo, P., *Nonalcoholic fatty liver disease.* New England Journal of Medicine, 2002. **346**(16): p. 1221-1231.
- Leung, J.C.F., et al., *Histological severity and clinical outcomes of nonalcoholic fatty liver disease in nonobese patients.* Hepatology, 2017. **65**(1): p. 54-64.
- Wang, A.Y., J. Dhaliwal, and M. Mouzaki, *Lean non-alcoholic fatty liver disease.* Clinical nutrition, 2019. **38**(3): p. 975-981.

- Younossi, Z., et al., *Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention.* Nature reviews Gastroenterology & hepatology, 2018. **15**(1): p. 11-20.
- Fracanzani, A.L., et al., *Risk of nonalcoholic steatohepatitis and fibrosis in patients with nonalcoholic fatty liver disease and low visceral adiposity.* Journal of hepatology, 2011. **54**(6): p. 1244-1249.
- Caviglia, G., et al., *Liver fibrosis: the 2017 state of art.* Panminerva Medica, 2017. **59**(4): p. 320-331.
- Mota, M., et al., *Molecular mechanisms of lipotoxicity and glucotoxicity in nonalcoholic fatty liver disease.* Metabolism, 2016. **65**(8): p. 1049-1061.
- Polyzos, S.A., J. Kountouras, and C.S. Mantzoros, *Adipose tissue, obesity and non-alcoholic fatty liver disease.* Minerva endocrinologica, 2016. **42**(2): p. 92-108.
- Polyzos, S.A., J. Kountouras, and C.S. Mantzoros, *Adipokines in nonalcoholic fatty liver disease.* Metabolism, 2016. **65**(8): p. 1062-1079.
- Boutari, C., N. Perakakis, and C.S. Mantzoros, *Association of adipokines with development and progression of nonalcoholic fatty liver disease.* Endocrinology and Metabolism, 2018. **33**(1): p. 33-43.
- Huang, P.L., *A comprehensive definition for metabolic syndrome.* Disease models & mechanisms, 2009. **2**(5-6): p. 231-237.
- Allen, A.M., et al., *Nonalcoholic fatty liver disease incidence and impact on metabolic burden and death: a 20 year-community study.* Hepatology, 2018. **67**(5): p. 1726-1736.
- Käräjämäki, A.J., et al., *Non-alcoholic fatty liver disease with and without metabolic syndrome: different long-term outcomes.* Metabolism, 2017. **66**: p. 55-63.
- Adiels, M., et al., *Overproduction of very low–density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome.* Arteriosclerosis, thrombosis, and vascular biology, 2008. **28**(7): p. 1225-1236.
- Kotronen, A., et al., *Increased liver fat, impaired insulin clearance, and hepatic and adipose tissue insulin resistance in type 2 diabetes.* Gastroenterology, 2008. **135**(1): p. 122-130.
- Tchernof, A. and J.-P. Després, *Pathophysiology of human visceral obesity: an update.* Physiological reviews, 2013.
- Williams, C.D., et al., *Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study.* Gastroenterology, 2011. **140**(1): p. 124-131.
- Loomba, R., et al., *Association between diabetes, family history of diabetes, and risk of nonalcoholic steatohepatitis and fibrosis.* Hepatology, 2012. **56**(3): p. 943-951.
- Leite, N.C., et al., *Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus.* Liver international, 2009. **29**(1): p. 113-119.
- Bril, F. and K. Cusi, *Nonalcoholic fatty liver disease: the new complication of type 2 diabetes mellitus.* Endocrinology and Metabolism Clinics, 2016. **45**(4): p. 765-781.
- Fruci, B., et al., *Nonalcoholic fatty liver: a possible new target for type 2 diabetes prevention and treatment.* International Journal of Molecular Sciences, 2013. **14**(11): p. 22933-22966.
- Goessling, W., et al., *Aminotransferase levels and 20-year risk of metabolic syndrome, diabetes, and cardiovascular disease.* Gastroenterology, 2008. **135**(6): p. 1935-1944. e1.

- Fukuda, T., et al., *The impact of non-alcoholic fatty liver disease on incident type 2 diabetes mellitus in non-overweight individuals.* Liver International, 2016. **36**(2): p. 275-283.
- Choudhury, J. and A.J. Sanyal, *Insulin resistance and the pathogenesis of nonalcoholic fatty liver disease.* Clinics in liver disease, 2004. **8**(3): p. 575-594.
- Krssak, M., et al., *Alterations in postprandial hepatic glycogen metabolism in type 2 diabetes.* Diabetes, 2004. **53**(12): p. 3048-3056.
- Ballestri, S., et al., *Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis.* Journal of Gastroenterology and Hepatology, 2016. **31**(5): p. 936-944.
- Tilg, H. and A.R. Moschen, *Inflammatory Mechanisms in the Regulation of Insulin Resistance.* Molecular Medicine, 2008. **14**(3): p. 222-231.
- Johnson, Andrew M.F. and Jerrold M. Olefsky, *The Origins and Drivers of Insulin Resistance.* Cell, 2013. **152**(4): p. 673-684.
- Moller, D.E. and K.D. Kaufman, *Metabolic Syndrome: A Clinical and Molecular Perspective.* Annual Review of Medicine, 2005. **56**(1): p. 45-62.
- Moschen, A.R., S. Kaser, and H. Tilg, *Non-alcoholic steatohepatitis: a microbiota-driven disease.* Trends in Endocrinology & Metabolism, 2013. **24**(11): p. 537-545.
- Jiménez-Alonso, J., et al., *Atorvastatin-Induced Cholestatic Hepatitis in a Young Woman With Systemic Lupus Erythematosus.* Archives of Internal Medicine, 1999. **159**(15): p. 1811-1817.
- Lefkowitch, J.H., *Morphology of Alcoholic Liver Disease.* Clinics in Liver Disease, 2005. **9**(1): p. 37-53.
- Yu, A.S. and E.B. Keeffe, *Elevated Ast Or Alt To Nonalcoholic Fatty Liver Disease: Accurate Predictor of Disease Prevalence?* Official journal of the American College of Gastroenterology | ACG, 2003. **98**(5).
- Chong, L.-W., et al., *Fluvastatin attenuates hepatic steatosis-induced fibrogenesis in rats through inhibiting paracrine effect of hepatocyte on hepatic stellate cells.* BMC Gastroenterology, 2015. **15**(1): p. 22.
- Marrone, G., et al., *The transcription factor KLF2 mediates hepatic endothelial protection and paracrine endothelial–stellate cell deactivation induced by statins.* Journal of Hepatology, 2013. **58**(1): p. 98-103.
- Younossi, Z.M., et al., *Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008.* Clin Gastroenterol Hepatol, 2011. **9**(6): p. 524-530.e1; quiz e60.
- Tzefos, M. and J.L. Olin, *3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitor use in chronic liver disease: a therapeutic controversy.* J Clin Lipidol, 2011. **5**(6): p. 450-9.
- Onofrei, M.D., et al., *Safety of statin therapy in patients with preexisting liver disease.* Pharmacotherapy, 2008. **28**(4): p. 522-9.
- Söderberg, C., et al., *Decreased survival of subjects with elevated liver function tests during a 28-year follow-up.* Hepatology, 2010. **51**(2): p. 595-602.
- DeNicola, E., et al., *Obesity and public health in the Kingdom of Saudi Arabia.* Rev Environ Health, 2015. **30**(3): p. 191-205.
- Avins, A.L., et al., *Hepatic effects of lovastatin exposure in patients with liver disease: a retrospective cohort study.* Drug Saf, 2008. **31**(4): p. 325-34.

- Tikkanen, M.J., et al., *Effect of intensive lipid lowering with atorvastatin on cardiovascular outcomes in coronary heart disease patients with mild-to-moderate baseline elevations in alanine aminotransferase levels.* Int J Cardiol, 2013. **168**(4): p. 3846-52.
- Athyros, V.G., et al., *Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis.* The Lancet, 2010. **376**(9756): p. 1916-1922.
- Catapano, A.L., et al., *ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS).* Atherosclerosis, 2011. **217**(1): p. 3-46.
- Stone, N.J., et al., *2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* Circulation, 2014. **129**(25 Suppl 2): p. S1-45.
- Tziomalos, K., *Lipid-lowering agents in the management of nonalcoholic fatty liver disease.* World J Hepatol, 2014. **6**(10): p. 738-44.
- Hatzitolios, A., et al., *Efficacy of omega-3 fatty acids, atorvastatin and orlistat in non-alcoholic fatty liver disease with dyslipidemia.* Indian journal of gastroenterology: official journal of the Indian Society of Gastroenterology, 2004. **23**(4): p. 131-134.
- Kimura, Y., et al., *Atorvastatin decreases serum levels of advanced glycation endproducts (AGEs) in nonalcoholic steatohepatitis (NASH) patients with dyslipidemia: clinical usefulness of AGEs as a biomarker for the attenuation of NASH.* J Gastroenterol, 2010. **45**(7): p. 750-7.
- Athyros, V.G., et al., *Effect of multifactorial treatment on non-alcoholic fatty liver disease in metabolic syndrome: a randomised study.* Curr Med Res Opin, 2006. **22**(5): p. 873-83.
- Han, K.H., et al., *Evaluation of short-term safety and efficacy of HMG-CoA reductase inhibitors in hypercholesterolemic patients with elevated serum alanine transaminase concentrations: PITCH study (PITavastatin versus atorvastatin to evaluate the effect on patients with hypercholesterolemia and mild to moderate hepatic damage).* J Clin Lipidol, 2012. **6**(4): p. 340-51.
- Georgescu, E.F. and M. Georgescu, *Therapeutic options in non-alcoholic steatohepatitis (NASH). Are all agents alike? Results of a preliminary study.* Journal of gastrointestinal and liver diseases: JGLD, 2007. **16**(1): p. 39-46.
- Kargiotis, K., et al., *Effect of rosuvastatin on non-alcoholic steatohepatitis in patients with metabolic syndrome and hypercholesterolaemia: a preliminary report.* Curr Vasc Pharmacol, 2014. **12**(3): p. 505-11.
- Piton, A., et al., *Factors associated with serum alanine transaminase activity in healthy subjects: consequences for the definition of normal values, for selection of blood donors, and for patients with chronic hepatitis C.* Hepatology, 1998. **27**(5): p. 1213-1219.
- Wagenknecht, L.E., et al., *Correlates and heritability of nonalcoholic fatty liver disease in a minority cohort.* Obesity, 2009. **17**(6): p. 1240-1246.
- Del Ben, M., et al., *NOX2-generated oxidative stress is associated with severity of ultrasound liver steatosis in patients with non-alcoholic fatty liver disease.* BMC gastroenterology, 2014. **14**: p. 1-8.
- Schwimmer, J.B., et al., *Heritability of nonalcoholic fatty liver disease.* Gastroenterology, 2009. **136**(5): p. 1585-1592.

- Tanaka, K., et al., *Coffee consumpation and decreased serum gamma-glutamyltransferase and aminotransferase activities among male alcohol drinkers.* International journal of epidemiology, 1998. **27**(3): p. 438-443.
- Athyros, V.G., et al., *Effect of multifactorial treatment on non-alcoholic fatty liver disease in metabolic syndrome: a randomised study.* Current medical research and opinion, 2006. **22**(5): p. 873-883.
- Wheeler, M.D., et al., *The role of Kupffer cell oxidant production in early ethanol-induced liver disease.* Free Radical Biology and Medicine, 2001. **31**(12): p. 1544-1549.
- Foster, T., et al., *Atorvastatin and antioxidants for the treatment of nonalcoholic fatty liver disease: the St Francis Heart Study randomized clinical trial.* Official journal of the American College of Gastroenterology| ACG, 2011. **106**(1): p. 71-77.