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Statins in Alcoholic and Non-Alcoholic Fatty Liver Disease and Chronically Elevated Liver Enzymes

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Abstract

The prevalence of alcoholic liver disease and non-alcoholic liver disease patients has nearly doubled over the past decades worldwide. Alcoholic liver disease among patients with chronic liver disease has increased with arisen due to alcohol consumption and obesity. The diagnosis plays a crucial role in treating such conditions based on the stages of liver functioning. The elevated liver enzymes are the key characterizing of identifying the alcoholic liver disease (ALD) and NAFLD. Later on, there is a progression of the disease conditions by developing fibrosis and cirrhosis, leading to liver carcinoma. The other state, steatohepatitis, is associated with an increase in liver-related and can lead to mortality. Risk factors for both diseases are growing, leading to various complications in health. There is no specific treatment up to date for these conditions, but statins play a crucial role in managing several liver disease conditions. The commonly used drug is hydroxymethylglutaryl coenzyme A (HMG Co-A) reductase inhibitors. It is also known as statins, which help normalize liver enzymes in patients with elevated plasma aminotransferases. As a result, external liver damage is considered safe for the liver as the Statin medication at low to moderate dose usage. **OBJECTIVES:** The main scope of this review is to study the various factors like pharmacological actions, adverse events, and biochemical and liver cell imaging results in patients with ALD and NAFLD. The different types of statins used in alcoholic and non-alcoholic patients' clinical data for the safety of the statin therapy were concluded in this review. Fatty liver changes of both liver disease conditions were studied using different drugs. The other liver enzymes like Alanine transaminase (ALT), Aspartate transaminase (AST), Gamma-glutamyl Transferase (GGT), and the effectiveness of Statin therapy are considered vital concepts in this review.

Keywords

Statin Therapy, Liver Enzymes, Alcohol, Steatosis, Fibrosis, Hepatocellular Carcinoma, Liver toxicity, Steatohepatitis

1. Introduction

1.1. Alcoholic Liver Disease

Regular intake of alcohol causes three stages of liver diseases: fatty liver progression, leading to alcohol hepatitis, and the final stage of cirrhosis. The fat gets accumulated in the hepatocytes; this condition is a fatty liver. This event is categorized into two types based on alcohol consumption; ALD. NAFLD is a condition that occurs without alcoholic consumption. Alcoholic fatty liver is also known as alcoholic people hepatitis, a kind of liver disease caused by excessive alcohol consumption. This condition can be treatable with abstinence. [1] [2]. It can also be treated with moderation and maintained. By managing moderation, the fat predisposing factor in patients can be controlled, which stops leading to chronic liver type disease. On progression, it causes alcohol hepatitis, which has liver inflammation where it is developing due to heavy alcohol drinking. This condition gradually leads to liver cell damage which interferes with the organ's ability to function normally.

Cirrhosis is an end-stage chronic alcohol liver disease. Cirrhosis can be characterized by replacing the normal hepatic parenchyma with fibrous tissue that looks like a thicker band. We can also absorb regenerating nodules that can progress to portal hypertension and liver damage. Alcoholic hepatitis is an alcohol-induced liver impairment that can occur at the starting stage, and this event happens after consuming a substantial amount of alcohol over a long period. In this condition, the severity may occur as symptomatic. However, one can see the liver's biochemical abnormalities, leading to death [3].

We can see that ALD occurs as the most common disease worldwide. The progression of the alcoholic fatty liver can tend to alcohol steatohepatitis (ASH). This event is a condition where hepatic inflammation can lead to fibrosis, leading to cirrhosis, and, in some cases, lead to hepatic cellular cancer (HCC) and Alcohol steatohepatitis. This condition can be seen with or without cirrhosis and can cause alcoholic hepatitis on any clinical presentation of alcohol liver disease, leading to mortality [4].

1.2. Non-Alcoholic Liver Diseases

In NALD, there is a condition where we can see fat in hepatocytes, but there is no liver damage. Non-alcoholic steatohepatitis is when the hepatocytes are filled with fat content in the liver. The characterization of NASH includes inflammation, liver cell destruction, and elevated liver enzymes. The aggressive fatty liver disease can be traced by liver inflammation, converting from non-alcoholic sim-

ple steatosis to non-alcoholic steatohepatitis. Upon progression of non-alcoholic steatohepatitis can also lead to severe liver cirrhosis. These conditions can lead to subacute liver failure and lead to a dangerous situation of hepatocellular carcinoma. This condition is similar to the harm produced by excess alcohol consumption. The induction of the inflammation in the hepatocytes tends to various diseases like NASH, Cirrhosis, fibrosis, and finally leads to hepatic carcinoma, which leads to death. This event can even link with the serious harmful events of metabolic diseases such as obesity and diabetes mellitus type 2 (DM-2). Cardiovascular disease is the most common risk factor in both ALD and NASH, where there is a chance of mortality.

In western countries, non-alcoholic liver disease drastically increases day by day [5]. In the US, CLD affects one-quarter of the population. Studies are conducted on ALD, which is the liver manifestation related to metabolic syndromes such as obesity, DM type 2, hypertension, and increased lipid levels (dyslipidemia) [6]. Here, NASH has features like liver inflammation. This item can even be seen in patients with severe scarring such as cirrhosis and liver failure [7]. Many studies, such as large-scale studies and well-conducted, randomized clinical trials, have concluded that they had evidence of the long-term use of statin. The study stated that there is significant harm to coronary diseases and vascular diseases in patients, has decreased risk when used on statins. This event can develop an average level of lipid levels in both primary prevention and secondary prevention [8]. Hence, statins are now prescribed for people with diagnostic NAFLD in several world areas.

The hepatic histology is evaluated with elevated liver enzymes before and after statin therapy for NAFLD patients. In addition, the initial and the later compassion of the historical, logical output of NAFLD patients were studied. In present studies, there was discovered that increases in the liver enzymes in hyperlipidemic individuals are not more likely joint in the development of hepatotoxicity when compared to hyperlipidemic patients with normal transaminases.

There is a study that only 24% of more alcoholic fatty liver disease patients undergoing the medication on statin move through the stage of fibrosis. Statin can promote hepatic lipogenesis, which influences the hepatic LDL receptor expression. These effects may increase hepatic fatty infiltration. The impact of statin therapy on hepatic histology in non-alcoholic fatty liver disease is unclear [9] [10] [11] [12]. Hence, the pathophysiology of NAFLD disease is still poorly elucidated [13]. The identification of NAFLD by identifying an asymptomatic increased in the frequent liver enzymes. Non-alcoholic hypertransaminasemia is used as a critical surrogate measure for NAFLD. The current label, statins, should be used with active liver disease patients and patients with increased aminotransferases. Presently, the gastric and liver specialists are consulting to refer the Physicians about Statin use in patients with increased serum transaminases. This event is due to the lack of clinical history or serum markers that would explain the liver biochemistry abnormalities. In patients with NAFLD, liver enzymes increase by up to 90% [14].

1.3. Role of Statins

The statin comes under the category of coenzyme known as HMG-CoA reductase inhibitors. This event is commonly used all over well-developed countries as a prescription drug. Statin is considered a subclass in HMG Co-A reductase classification, where the pharmacological effects will be different. The oral bioavailability and protein binding changes in the statin compared to the HMG Co-A reductase. The group of starting such as atorvastatin, Lovastatin, simvastatin, and Fluvastatin has a nature lipophilic they get metabolized with the help of cytochrome p450. The other statin, such as Pravastatin and Pitavastatin, are hydrophilic and undergo metabolism compared to the other class of drugs. The rosuvastatin has an intermediate profile in the liver metabolism. Statin is sometimes restricted as a prescription drug concerned with some side effects: muscle and liver damage. They have a chance of developing hepatotoxicity, which changes the biochemical nature of the liver enzymes; thus, it is a concern in liver disease to prescribe statins.

As the statin is causing hepatotoxicity, the Physicians are much more worried about the patient; hence it is less under-prescribed for patients with ALD and NAFLD. It is unfolding that Statin liver damage is in rare conditions. The new results on Statin prescription have potentially had a higher impact showing a positive effect in the patients. In this review, we tried to explain the statin's role in the development and how it functions during the progression of various diseases such as cirrhosis, fibrosis, and the Vaso protector efforts on portal hypertension [15]. We also concluded the Statin possibility of resolving hepatic fibrogenesis. This review concludes with the role of statins in different conditions of liver diseases, such as the development, progression, and complications.

The statin should not be administered in such patients if conditions such as active liver disease and chronic aminotransferases increase levels. The consultation of the positions such as gastroenterologist has advised that the safety of the statin has had no evidence for the abnormal liver biochemistry in the conditions of elevated serum liver enzymes. Asymptomatic liver enzymes increase due to liver impairment is a diagnostic parameter for hepatic diseases during statin therapy [16] [17].

1.4. Symptoms

Symptoms are common for both ALD and NAFLD. The symptoms depend on the severity of the disease condition. It starts with abdominal pain and tenderness, which leads to an increase in thirst and dry mouth. Next, there is an increase in liver enzymes, which leads to jaundice and yellowish discoloration of the eyes. In this condition, there is weight loss and loss of appetite. Non-alcoholic steatohepatitis is ballooning with an increase in the inflammation of lobes in the liver without fibrosis. In a state of steatohepatitis, there is an increase in fat up to 5% than normal liver, leading to insulin resistance syndrome. This condition may lead to metabolic syndromes such as obesity, diabetes mellitus, and dyslipi-

demia. There's also the condition of hypertension polycystic ovarian syndrome and the risk of cardiovascular disease in this condition.

1.5. Prevalence

The occurrence of alcoholic liver disease is due to excess alcohol intake daily. The NAFLD prevalence is the intake of mild or no alcohol intake, but it is considered a global health problem that affects 6% to 45% of the general population. In Western countries, as a daily basis it is growing up to 30% worldwide. In Asian countries, more than 40% of the population has liver disease. Hence, diabetes mellitus is considering the most critical risk factor for the progression of hepatic fibrosis. Based on the condition of ALD and NAFLD, there is a chance of occurring metabolic syndromes like obesity and DM. There is a chance of 40% cases in an advanced condition of NASH from NAFLD.

The secondary causes might include hepatic fat infiltration and other conditions like viral hepatitis and autoimmune hepatitis. There can be a cause of drug-induced liver diseases, which may cause complications with the liver condition. Alcohol abuse condition where there is >30 g/per day of alcohol for men and >20 g/day of alcohol per day for women as a diagnosis of ALD.

1.6. Pathogenesis

The pathogen causes NAFLD estriol, and the advancement of the pathogenesis of this it's still not well explained. The primary step is to store high-fat content in the liver cells, leading to inflammation. Progression of this condition can link to hepatocellular damage and cause inflammation in the fibrosis condition. There are a variety of variables that contribute to the different types of biochemical changes that occur in the hepatocytes. The changes include IR and changes in the adipose tissue Harmons. The changes in the dietary factors can also change the gut flora, which can also lead to liver Impairment. So, that is also a chance of change, and the genetic factors are the epigenetic factors that lead to liver damage.

There are different types of pathogenic factors that cause NAFLD diseases. The one with the most common factor is the genetic polymorphism that occurs in the patatin, which contains three gene proteins such as IR oxidative stress and adipokines. The adipokines are the diagnostic tool for non-alcoholic fatty liver disease, advancing participation for the endocrine disruptor. This event ultimately leads to studying the therapeutics which target NAFLD treatment.

The liver tissue captures all the excess chemicals caused by the free radicals, alcohol, and other harmful metabolites, mainly by the liver and parenchymal cells. The ROS process is due to the effect of oxygen-containing free radicals, which alter the critical signaling in the cells; hence there is a disturbance in the regulation of lipids and glucose metabolism. In addition, the ROS can directly influence the proteins and the DNA, which causes excessive oxidative stress but increases the RIS within the cells, which directly affects the proteins and DNA.

1.7. Gut Flora Leading to NAFLD

Alcohol affects the liver by increasing the chances of leakiness in the intestinal cell wall. This event causes the entry of the gram-negative bacteria as an endotoxin, which enters the blood and causes the immune response. As the process undergoes, there is an activation of the immune system leading to the activation of the immune cells known as Kupffer cells. These cells are macrophages mainly involved in removing bacteria and the foreign proteins that have entered the blood. [15] [18] [19]. The primary response is when the blood that enters the liver gets purified from the poisonous foreign particles in the liver. The activation of macrophages helps release the Kupffer cells leading to the activation of tumor necrosis factor (TNF) and different interleukins (IL). In addition, the release of the macrophages leads to the condition of inflammation in the hepatocytes.

1.8. How Does Inflammation Begin?

The National Institute of Health said Kupffer cells' role in responding to the endotoxin that enters the body results in liver disease [19] [20] [21]. The Kupffer cells and other immune cells in the parenchyma cells are being responded to, expressed in the liver; there is a pattern recognition receptor. These pattern recognition receptors combine with the toll-like receptors, which help detect the pathogen-related molecular signals and then start the process of inflammation. There is an involvement in the response of the co-receptors like CD14 and TLR4 [22]. These co-receptors help in the reaction of activating Kupffer cells in the alcoholic liver damage [23]. Later on, it starts releasing the cytokinin and activation of Kupffer cells, which leads to the activation of generating ROS in the liver. This event leads to increased oxidative stress and impairs fatty acid oxidation and cellular functioning. This event also activates hepatic macrophages leading to the inflammatory Cascade [24] [25].

There are many negative consequences of alcoholic liver disease, which is caused mainly due to inflammation, which leads to the progression of the liver cell death and regenerating nodules that also form scar tissue known as fibrosis and then leads to cirrhosis. The disturbing result in the molecular signaling pathway leads to consequences that are still unknown. The alcohol interacts with the Kupffer cells, resulting in the leaking of the endotoxin into the stomach. Here, it starts releasing inflammatory mediators like TNF-alpha and cytokinin, which leads to the production of inflammatory cytokines such as IL1, IL6, and IL8 [26] [27] [28]. Suppose there is the persistent release of the cytokinesis and the inflammatory mediators. There is an increase in inflammatory responses in the liver, leading to the progression of the disease to hepatitis, fibrosis, and cirrhosis. There is also an influence by inflammatory cytokines that lead to a process known as programmed cell death, which might be apoptosis.

The cytokines and chemokines play an essential role in the progression of inflammatory responses in ALD. In the condition of alcoholic hepatitis, there is an increase in cytokine levels like TNF alpha, IL1, and IL6. Interleukin 8 plays a vi-

tal role in neutrophil infiltration and inflammation in alcoholic liver disease. The areas of injury and inflammation and mainly attracted by the monocyte chemoattractant protein MCP1. The MCP1 attracts monocytes and macrophages, leading to the inflammatory response of alcoholic liver disease patients. The process of inflammation and fibrosis is progressing by the presence of chemokines like MCP1 and RANTES1. This event helped boost the stellate cell activity. This activation of stellate cells leads to severe fibrosis conditions in the liver [29].

1.9. Stellate Cells in Liver Diseases

Stellate cells in the liver placed a crucial role in forming fibrosis; this also helps heal the liver injury tissue. This event involves the activation of IL8 and MCP-1, where their activity leads to many therapeutic implications. Stellate cells can respond to the injury and help heal certain types of damage in the liver. That is also a recent study about the impacts of the sterlet cells, which can inhibit certain kinds of chemokines [30] [31].

2. Risk Factors for NAFLD and ALD

2.1. Age

The prevalence of ALD and NAFLD increases with an increase in age [32] [33] [34]. NAFLD prevalence related to non-alcoholic fatty liver fibrosis increases with age. A study was made by Frith and colleagues on 351 patients who had undergone biopsy-proven NAFLD. The patients, based on their age, were categorized into three groups. The oldest group is greater than 60 years, the middle-aged people are between 50 and 60 years old, and the younger group is less than 50 years old [35]. They have identified a connection between age and the frequency of non-alcoholic liver diseases linked with fibrosis conditions. The older group has considered at a higher risk and NAFLD such as increased hypertension, diabetes, and increased lipid levels that are hyperlipidemia and diseases like obesity are Common.

Another study on NAFLD incidence in hospitalized geriatric patients is studied. A prevalence rate of 46% is found, which is high compared to the general population study [36]. In the study, there is no link between NAFLD and metabolic syndrome. Therefore, there is no cardiovascular risk in this category.

The pathophysiology of NAFLD may vary in different age groups. The prevalence of NAFLD is related to the age correlation where older people have a higher risk of disease progression, which sometimes leads to death [37] [38] [39] [40].

The progression of the disease conditions such as hepatic fibrosis eventually leads to hepatocellular cancer, which leads to comorbid conditions like diabetes mellitus, which increases with age [41] [42]. A study on liver donors found an age-independent risk for severe hepatic steatohepatitis. Elderly diabetic individuals have a higher risk of cirrhosis, known as burnt-out non-alcoholic hepatitis. Still, the condition here is that the patient is obese presently or in the past [43].

As per the research conducted by Frithet, the older patient has a greater risk of hepatic fibrosis and cirrhosis. Age plays a crucial role in the condition of cirrhotic patients. Younger people were affected by increased ALT activity. There was no clear explanation for the liver enzyme increase with the hepatic steatosis condition [44]. In the research conducted by Hui and his colleagues, they did not find a significant variation between the age groups and the progression of the disease NAFLD. There is no link between the age groups getting NAFLD and fibrosis yet. It is essential to know the association between age and the incidence of non-alcoholic and alcoholic liver diseases, which helps to see the progression of the disease like fibrosis and cirrhosis.

2.2. Race and Ethnicity

During the condition of liver biopsy, it is hard to find the frequency of NAFLD. According to a study conducted by Wagenknecht and his colleagues on the liver disease condition, the visceral any positive virus in different ethnic groups. In Hispanics, they are different types of coordination such as age, triglycerides, and PAI1 in the conditions of liver diseases. On the other hand, serum adiponectin levels in African Americans due to the influence that genetic and environmental factors cannot explain [43] [44] [45]. There is research on the genotype in data relating to the epidemiology of liver disease with genomic medicine in this present world.

The family clustering shows the genetic variations studied as extensive family-based coherent studies that have the heritability in the disease to the condition such as hepatic steatosis, which is about 0.27% [46] [47]. A gene such as PNPLA3 produces adiponectin, a significant genetic contribution to the ALD and NAFLD [50] [51]. In Caucasians, it is at 0.23%. Assuming the same genes promote the increase of liver enzymes by 28% in non-steatosis individuals. The homozygote, I148M, is the more common condition of non-alcoholic steatohepatitis [48] [49].

The regression analysis has taken the sequence of two genes contributing to 72% of hepatic fat changes observed in different ethnic groups. The gene PNPLA3 losses its functions and leads to the condition of hepatic steatosis. In a study of 592 participants, the biopsy-proven underground with the condition hepatic steatosis did Sean the result of having polymorphisms in fat accumulation in the liver, which is due to PNPLA3. Many other genres, such as NCAN, GCKR, and LYPLAL1 when they undergo genetic variation, they play a significant role in the contribution of the ALD and NAFLD. For example, a gene known as 70 GCKR is associated with identifying ALD and NAFLD diseases in Chinese patients.

2.3. Gender

Liver impairment is assumed to be more frequent in females, but this research has been proven false [52] [53] [54] [55]. A study was fibrosis conducted by 527

Asian people who had done medical health checks have liver disease prevalence with 31% in males and 16% in women [56] [57]. In India, a study mentioned the clinicopathological characteristics where men can have a high majority of liver failure. There is also a link in the increase in liver enzymes, and historical findings of non-alcoholic steatohepatitis and hepatic fibrosis in men are prevalent. This event can lead to mortality in the NAFLD.

There is only a little research regarding the female link between NAFLD and fibrosis. One of the research projects mentioned a high risk for females to have NASH in individuals with metabolic syndrome. Based on these results, the ALD and NAFLD act differently in men and women. According to the physicians, the upper and the lower limit of the liver enzyme ALT activity in the woman show up like ULN£30 UL AND ULN£ 19 UL, respectively [58] [59]. Kunde and colleagues had explained the old and new aminotransferases thresholds. Prevalence of liver disease in women increases in liver enzymes with obesity is up to 28%, and at the unique point, the percentage has increased up to 63%. Analogous studies which relate to the aminotransferase threshold in men have been declining.

2.4. Metabolic Conditions

NAFLD is commonly seen in patients already having metabolic syndromes in the general world. Diabetes mellitus with this condition having a liver impairment is most prevalent. There is a prevalence rate of 69%, and the patients have diabetes mellitus type 2 with changes in the ultrasonographic report. In conditions such as obesity and hypertriglyceridemia, there is a condition of ALD and NAFLD with increased liver enzymes. There is no link between diabetic degenerative sequence and the prevalence of ultrasonic changes in liver disease [60].

A recent study shows a high frequency of liver impairment in people with Diabetic Type 2, progressing to liver diseases. The ultrasonography changes in 127 in 204 people with diabetic people have a fatty liver. A study says that 87% who had been accepted for the liver biopsy and exhibited heavy liver changes in Ultrasonography have been diagnosed with alcoholic fatty liver disease [61]. The study findings can confirm an increased incident rate of non-alcoholic steatohepatitis, which tends to be a metabolic syndrome. The non-alcoholic steatohepatitis with severe fibrosis has a condition of the report diabetic with no symptoms indicated in abnormal liver enzymes.

A polycystic ovarian syndrome is an ovarian manifestation of metabolic syndrome in a study with the polycystic ovarian syndrome in women with hepatic steatosis up to 55% [62] [63]. Another study said that 41% of women with polycystic ovarian syndrome have NAFLD with the symptoms of hepatic steatosis and elevated ALT levels with an incident rate of 19%. Individuals with obese PCOS have a higher risk of NASH and NAFLD [64] [65].

2.5. Chronic Infections Associated with Fatty Liver

Hepatitis virus C (HCV) can lead to metabolic dysfunction that can increase in-

sulin resistance (IR), increase blood glucose levels, and lead to diabetes mellitus type 2. NAFLD consists of cases with hepatitis C virus (HCV). The steatohepatitis condition occurs in almost all patients suffering from hepatitis C virus-infected individuals. Patient with HCV has a high frequency of HIV positive [66] [67] [68]. There is a high incidence of fatty liver in patients with chronic HCV and HIV infection [69] [70] [71].

3. Search Methods

The review has been concluded based on several searches on databases such as MEDLINE and PUBMED. Review of clinical trials related to the liver enzymes elevated in conditions of alcoholic and non-alcoholic liver diseases such as ALT, GGT, and AST in response to the Statin therapy. The literature on the topic and a comprehensive evaluation are the considerations to identify the effect of statin use in ALD and NAFLD. The keywords are chosen based on the subject we searched the articles in PubMed; the last search date is on February 10th), 2022. The keywords in the investigation include "statin treatment, fibrosis, hepatic histology, steatosis, inflammation, oxidative stress, liver enzymes, hepatocellular cancer, liver toxicity, dyslipidemia, alcoholic liver disease".

3.1. Electronic Searches

The literature is collected using different online search engines Like Medline PubMed databases. All the review articles related to the liver enzymes like ALT and AST, elevating commonly in Alcohol and NAFLD. In this search, the response of statin in both conditions is considered. In the research evaluating the effect of statin in the use of alcoholic and non-alcoholic diseases, a comprehensive evaluation of the literature is collected. The data literature is searched in the online search engine PubMed based on keywords. The last search date is February 10th, 2022.

3.2. Data Collection and Analysis

Study Selection

After evaluating the abstracts and titles of the publications that I found in the database searches to identify research that could be acceptable for further evaluation, later, we assessed the study, which is compatible with our topic based on suitability and completeness. We have divided the study selection into different parts. First, we selected the case and searched the electronic databases based on the chosen set of keywords. Then based on the inclusion and exclusion criteria, the data was selected. Finally, all the data was gathered, and the reports were studied.

A final study of the complete papers decided on the report's title, relevant to the topic. The evaluation of the article for the relevance of the title and the abstract will bring evaluated. The two review orders had given eligibility criteria review without any limitations on the paper.

3.3. Selection Criteria

3.3.1. Inclusion

We considered most clinical studies submitted on liver enzymes before and after statin therapy.

This review includes case-control studies that reported liver transaminase levels in both the case and control groups.

We only selected English-language articles having full-text access.

We included case reports from ALD and NAFLD patients who responded to various statins.

In this review, Statin alone groups are selected.

3.3.2. Exclusion

Studies with fewer patients that are fewer than 15 patients were, excluding.

Dual and multidrug therapy has been banned, except only statin treatment.

The other language studies except English are not in this review.

This review did not include the editorials and comments; we also stopped the letters and animal experiment studies.

3.4. Criteria for This Review

3.4.1. Types of Study

There is no specific module, so the randomized clinical studies compared different types of people taking different kinds of lipid-lowering medications and the other with the control. The randomly assigned participants were considered regardless of the count or the publishing status, such as the publication's year and language. The reports were being evaluated for the non-randomized studies, and the Adverse Events of each study were concluded.

3.4.2. Types of Interventions

Different statins include Lovastatin, atorvastatin, simvastatin, pravastatin, and rosuvastatin. Fluvastatin was given to the patients for three months and, at a minimal dose, was considered an experimental intervention study. The participants in this exploratory study were compared with the placebo patients. They were not given any medications in the other group as those receiving another type of lipid-lowering medication. The route of administration in these patients is only the oral route. Finally, the data report was included as per the result obtained by the different groups.

3.5. Outcomes Measures

3.5.1. Primary Outcomes

The primary outcomes considered the mortality that might occur due to any cause and the adverse effects. And that caused hepatitis is regarded in the mortality condition as an adverse event, including the number and the kind of adverse effects and the severity of the event's damaging effects. In addition, the International Conference on harmonization (ICH-GCP 1997) is an additional con-

sideration.

3.5.2. Secondary Outcomes

The secondary outcomes include the logical history response, which consists of the biochemical and Imaging reactions in the disease patients. The number of people who had significant changes in their history reports related to the fatty liver infiltration or the inflammation in the hepatocytes. There is also a condition of fibrosis. In the biochemical response, the subjects are testing serum liver enzymes such as AST and ALT levels. Where has a fantastic response, including Ultrasonography and CT scan or MRI, which are high in usage in the current diagnosis. This response clearly states the condition of the liver damage based on the Imaging report showing the fatty liver infiltration, fat accumulation, inflammation conditions, and fibrosis. This event is advantageous in differentiating various stages of liver disease, mild-moderate or severe, as per the classification.

4. Diagnosis and Classification

The diagnosis of ALD and NAFLD includes two types of tests. The first is the blood test. The rest is the Imaging tests such as an ultrasound, CT scan, and MRI scan. The blood test helps detect liver function by showing the results of elevated liver enzymes [72]. In addition, the lipid profile measuring the cholesterol levels, blood triglycerides, and LDL levels allows the detection of NAFLD.

4.1. Mechanism of Action of Statins

Statins improve alcoholic and non-alcoholic liver diseases by different types of mechanisms. They improve hepatic steatosis hepatitis by reducing LDL levels. They also act by the proteins known as activating sterol regulating element-binding proteins (SREBPs), which help improve transcription and maintain lipid homeostasis [73]. The peroxisome proliferator-activated receptor alpha (PPAR) plays an essential role in reducing inflammatory responses of NAFLD.

4.2. Anti-Inflammatory and Anti-Fibrotic Effects

Statins act as an anti-inflammatory by inhibiting the small GTPase prenylation, decreasing the downstream signaling [74]. In the initial stages of fibrosis, the stains can work by reducing the bile acids by activating the pregnane X receptor and PPAR-α. Anti-fibrotic effect of statin can be seen by paracrine signaling of the liver cells on the hepatic stellate cells, which then block the hepatic stellate cell's activation. Hence the fibrogenesis is blocked [75]. The hepatic stellate cell pathway is activated by the Rho kinase [76]. The fibrosis gets improved by inhibiting the RhoA.

The role of statin in portal hypertension works by the following mechanism: an increase in the intrahepatic resistance imbalance, which affects the regulation of RhoA and nitric oxide signaling pathway, leading to vasoconstriction.

5. Treatment

5.1. Liver Toxicity Caused by Statin

There is a rare chance of liver damage by statin therapy, but they can be dangerous Adverse Events using statins. An asymptomatic increase in serum ALT has been prevented in statin-treated people here. There is a risk of observation in liver damage in a few cases. Asymptomatic raises in ALT during statin treatment are not considered evidence of ongoing liver disease or injury [77].

The word "transaminitis" is characterized by hepatic enzyme leaking that does not result in hepatotoxicity that may explain many types of blood ALT increases in statin-treated patients [78]. There is a widespread agreement that ALT is More effective than AST in detecting the potential hepatotoxicity because AST levels can arise either in muscle or liver damage. Hence, ALT level increase is a successive test because a single ALT increase is more similar to transaminitis than liver injury. The treatment of the different types of statins has clearly stated the uses and dosage in **Table 1**.

In the previous case report, there is a condition where statin use caused autoimmune hepatitis [79] [80] [81] [82]. There is a study about three cases of autoimmune hepatitis. There is induction of hepatitis after treatment with Fluvastatin in two cases. The third case is atorvastatin-induced autoimmune hepatitis. Lovastatin use, particularly at high doses of 80 mg per day, has a modest increase in the liver enzyme up to 5% of patients [83] [84] [85] [86]. There is a chance of developing centrilobular necrosis, fulminant liver failure, and cholestasis [87]. Simvastatin can lead to liver damage due to drug-drug interactions with the self-drug [88].

5.2. Role of Statin in Abnormal Liver Test Patients

The primary issue in clinical practice is an increase in the serum liver enzyme, which is usually caused by concomitant comorbid diseases like obesity, pre-diabetic, and diabetic conditions, as well as dyslipidemia, which has the typical characteristics of NAFLD. Statin therapy decreases the cardiovascular risk in people with low to moderate levels of abnormal liver tests. Hence, statin therapy is considered safe and can even improve the liver test.

The liver blood tests should be repeated as soon as possible to declare an increase in the levels. Before starting the Statin treatment, the diagnosis part plays a crucial role. The quality of evidence is less Baseline liver enzyme testing is adjusted before starting the Statin therapy. Before beginning the statin therapy, a low grade of strength was observed.

5.3. Statin Treatment in Dislipidemia

Hyperlipidemia is considered atherogenic dyslipidemia and can be characterized by an increase in the serum triglycerides and low HDL cholesterol, which is regarded as good cholesterol, and the presence of small LDL particles. In addition, atherogenic dyslipidemia is symptomized by insulin resistance and metabolic syndrome, including obesity, diabetes mellitus, and hypertension.

Table 1. Details of various stains usage in different liver disease conditions based on severity along with their doses [89] [90] [91].

STATIN	TREATMENT	DOSE
CERIVASTATIN	Decreases elevated liver enzymes.	10 - 80 mg/day
ATORVASTATIN	Increased serum transaminases. Autoimmune hepatitis.	10 - 80 mg/day
LOVASTATIN	Resolving hepatic fibrogenesis. Increased serum transaminases.	80 mg/day
SIMVASTATIN	Cirrhosis	20 mg/day
PRAVASTATIN	Steatosis	20 - 80 mg/day
FLUVASTATIN	Fibrosis of liver	80 mg/day
ROSUVASTATIN	Hyperlipidemic liver diseases.	10 - 80 mg/day

It can be safely treated with a statin, which treats hyperlipidemia. Furthermore, statin hepatotoxicity is very low in these patients; hence, NAFLD and NASH can be clinically treated with statins.

Statins play a crucial role in managing increased lipid levels in NAFLD patients by decreasing the lipid levels. The statins successfully reduce cholesterol levels in people with non-alcoholic liver disease. But one statin that helps reduce the incidence rate of cardiovascular events is atorvastatin [92].

Many studies consider the safety of Statin therapy for this lipidemia in patients with NAFLD. It is regarded as a safe and well-tolerated treatment with pravastatin at 80 mg/day with reduced LDL, TC, and TGs in Hypercholesterolemic Patients with NAFLD. However, there is an increase in serum ALT levels in patients with NAFLD and NASH when treated with a statin. Consequently, under treatment with a statin patient with NAFLD has frequently been a source of worry [93].

5.4. Role of Statin in Non-Alcoholic Liver Disdisease

Statin is an antithrombotic, anti-inflammatory, and antioxidant independent of lipid-lowering activity [94] [95]. The statin treatment plays a significant role in NAFLD and NASH as both the conditions have inflammation and oxidative stress [96]. There is an increase in NOX2-related oxidative stress in patients with NAFLD associated with severe liver steatosis [96].

Up to date, there is no data showing medication for NAFLD. As of now, there is less evidence relating to the effects of statins in NAFLD [97] [98]. The GTPase plays a significant role and non-alcoholic steatohepatitis through signal transmission, protein synthesis, cell differentiation, and intracellular vesicle movement. Statin helps by preventing non-alcoholic steatohepatitis by decreasing GTPases. The PPARs play a significant role in inflammation, metabolic pathways, and non-alcoholic steatohepatitis Statin acts on The PPAR receptors and helps degrade fatty acids. Paraoxonase 1(PON1) is present in the liver and acts

as an antioxidant enzyme with anti-inflammatory and Antiatherogenic properties [99]. The Statin therapy improves PON1, decreasing due to lipid peroxidation [100].

Simvastatin improved the progression of non-alcoholic steatohepatitis-related fibrosis in animal models (rats). Endothelial and inducible nitric oxide synthase production can restrict the stellate cell activation. After four years of therapy with Atorvastatin 20 mg, 71% of patients with NAFLD had improved and reduced their risk [101].

6. Newer Studies with Various Targets

The Statin metabolism involves several cotransporters and enzymes, affecting the effectiveness and tolerance of the statin administration in these patients. In addition, the hepatic action can also be affected by the cotransporters and enzymes by administering the statins.

In chronic liver disease, as the patients have a poor liver function, the safety of the individuals is more concern; hence, statins are subsequently being as potential therapeutic options in both ALD and NAFLD are still under examination. Some polymorphisms affect the gene, which impacts the statin pharmacodynamics and pharmacokinetic properties and changes the course of fatty liver disease and the lipid metabolism of NAFLD [102]. As the patients with NAFLD have a high level of P450-2E1, this issue leaves the polymorphism in PPAR Alpha and Gamma 2, leading to an increase in the risk for the patients.

Since recent research indicates that patients with elevated baseline liver enzyme levels can benefit from statins, optimism has increased that these medications can reduce cholesterol and decrease NAFLD-related liver damage [103] [104].

7. Conclusions

Statins are prescribed to people with high liver enzymes due to ALD and NAFLD. Observational studies revealed no impact, suggesting that statins are safe for ALD and NAFLD patients' livers. What're more stains work effectively in all conditions of liver problems, from the stage of Fatty liver to cirrhosis and portal hypertension.

The review mainly discusses the summarization of the role of statins and ALD and NAFLD. They primarily focused aspects of this review paper on a statin role in endothelial dysfunction in chronic liver disease caused by alcohol and non-alcoholic. The other aspects as modulating hepatic fibrogenesis and the Vaso protective effects in portal hypertension were discussed. In this review, we mainly focused on the data representing the role of statins in the various conditions of ALD and NALD. The progression of the disease conditions and the complications of cirrhosis are critically assessed in this review paper.

Liver failure worldwide is considered very rare, with an occurrence rate of 2 in 1 million treated patients. The most helpful treatment in the present day for

ALD and NAFLD is statin therapy, as it is well-tolerated and safe for the patients. Statin therapy shows minor side effects such as myalgia in a few patients and Rhabdomyolysis in other patients, significantly less commonly seen. The adverse impact seen is an increase in the liver enzymes like aminotransferases, which might be harmful to the patient. The increase in temporary asymptomatic aminotransferases is commonly seen in a tiny percentage of patients, nearly 0.1 - 3. Statin tends to change the ultrasound readings. The patients having the adverse symptoms of 1.8% to 12% have a significantly elevated risk of cardiovascular problems.

8. Discussion

There is no specific efficacious treatment for NAFLD, even though NAFLD is an emerging disease condition worldwide. Hence, pharmacological medication must be considered for this condition as soon as possible to improve the health care system. The use of statins and NAFLD and alcoholic liver disease has been commonly prescribed worldwide. This treatment has been used to reduce the comorbid conditions eventuality as the cardiovascular risk associated with non-alcoholic steatohepatitis.

The statin treatment also improves the conditions of alcoholic liver disease with the comorbid conditions of metabolic syndrome and type 2 diabetic Mellitus. Many factors like liver-related mortality, liver histology, plasma liver enzyme activity, and ultrasonographic abnormalities were investigated when taken by the statin treatment. We can see many changes in the patient's liver with the NAFLD and ALD.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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