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REVIEW

Statin-Associated Liver Dysfunction and Muscle Injury: epidemiology, Mechanisms, and Management Strategies

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Abstract: Surveillance of drug safety is an important aspect in the routine medical care. Adverse events caused by real-world drug utilization has become one of the leading causes of death and an urgent issue in the field of toxicology. Cardiovascular disease is now the leading cause of fatal diseases in most countries, especially in the elderly population who often suffer from multiple diseases and need long-term multidrug therapy. Among which, statins have been widely used to lower bad cholesterol and regress coronary plaque mainly in patients with hyperlipidemia and atherosclerotic cardiovascular diseases (ASCVD). Although the real-world benefits of statins are significant, different degrees and types of adverse drug reactions (ADR) such as liver dysfunction and muscle injury, have a great impact on the original treatment regimens as well as the quality of life. This review describes the epidemiology, mechanisms, early identification and post-intervention of statin-associated liver dysfunction and muscle injury based on the updated clinical evidence. It provides systematic and comprehensive guidance and necessary supplement for the clinical safety of statin use in cardiovascular diseases.

Keywords: statin, cardiovascular diseases, liver dysfunction, muscle injury, countermeasures

Introduction

Drug safety, an urgent problem in clinical pharmacology and toxicology, is one of the primary health programs.[1,2] Drug exposure inevitably produces negative effects such as adverse drug reaction (ADR), which is related to many influencing factors such as age, drug categories, and route of administration.[3] ADR could damage patients' health, even delay the disease process, or lead to fatal consequences. The drug safety issues have become increasingly prominent.

In recent years, the disease burden from cardiovascular diseases consistently ranks the primary contributor among all diseases.[4] There are many types of cardiovascular diseases with complex treatment strategies which include lipid-lowering drugs such as statins or its combination with other drugs. Recent pairwise, network, and dose-response meta-analyses of 47 randomized controlled trials showed that statins decreased the risk of myocardial infarction (OR = 0.66, 95% CI: 0.61–0.71, P < 0.001), stroke (OR = 0.78, 95% CI: 0.72–0.84, P < 0.001), death from cardiovascular diseases (OR = 0.77, 95% CI: 0.72–0.83, P < 0.001) and all-cause death (OR = 0.83, 95% CI: 0.79–0.88, P < 0.001).[5] Statin combined with other lipid-lowering drug therapy could also significantly improve the anatomical and physiological

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function of the coronary arteries and down-regulate the re-hospitalization rate due to unstable angina in ST elevation myocardial infarction patients with non-infarct-related artery.[6] A retrospective study found that statins reduced the intubation, ICU admission, and mortality in COVID-19 patients.[7] These evidence reveal the importance of statins in lowering cardiovascular diseases risk and potential additional benefits of comorbidities.

However, the issues of ADR-related drug safety of statins have also aroused great concerns.[8] ADR not only causes additional harm to patients, but also greatly interferes with clinical routine treatment. It is necessary to put on the agenda to systematically manage the use of statins in clinical practice. This study describes the typical toxic consequences and epidemiological characteristics of statin-associated liver dysfunction and muscle injury in clinical practice. Besides, detailed countermeasures accordingly are presented to minimize the risks of statins use and ensure timely medication schedule adjustments for patients.

Epidemiology of Statins Use

Statins are 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors that reduce bad lipid levels by inhibiting the biosynthesis of cholesterol.[9] Several drugs including simvastatin, pravastatin, atorvastatin, and rosuvastatin, are currently on the market to reduce the bad cholesterol such as low-density lipoprotein cholesterol (LDL-C). Clinically, it is mainly applicable to atherosclerotic cardiovascular diseases (ASCVD) and hyperlipidemia. Statins have also become the main drug class for the primary and secondary prevention and treatment of cardiovascular and cerebrovascular diseases.

In recent years, statins have been increasingly used. It is reported that the use of statins in the primary prevention of cardiovascular disease in patients over 75 years old was as high as 62.6% in USA.[10] In a retrospective analysis of more than 125,000 patients receiving post-carotid endarterectomy in USA, statin use gradually increased from 36.2% to 62% during 2013 to 2021.[11] New statin prescriptions were associated with higher rates of diabetes, coronary heart disease, stroke, and transient ischemic attack.[11] A 12-month prospective cross-sectional study of 356 patients with acute coronary syndrome demonstrated that the most prescribed drug was statins (93%), followed by antiplatelet drugs and anticoagulants in Saudi Arabia.[12] In a database from Australia's Pharmaceutical Benefits Scheme, the prevalence of long-term statins users over the age of 65 had increased 35.6% with ten years.[13] Meanwhile, atorvastatin is the most commonly used statin in each year and the new use of high-intensity statins had also increased from 23.6% to 30.5% in a 10-year trend analysis.[13] In China, the overall rate of statins prescription for ASCVD patients was as high as 58.8%.[14]

These studies demonstrate that the reported use of statins has been rising in different countries and diverse indications in recent years. However, such scale of real-world use also exposes the risk of of statin-associated liver dysfunction and myopathy, suggesting that these patients need to be more closely concerned and monitored.[15]

Liver Dysfunction Caused by Statins

Liver dysfunction had attracted considerable attentions in a large number of drug types such as statins. The auxiliary examination methods for diagnosis of liver injury including B-mode ultrasound, hepatic arteriography, pathology, and hepatic enzyme examination. The deteriorated liver function, especially the increase of serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), is one of the most common side effects of statins. It is of great significance to correctly understand and evaluate the liver dysfunction caused by statins during the use of statins.

In vitro experiments have found that the damage of liver mitochondria caused by statins is time-dependent and dose-dependent.[16] Statins can result in a decrease in membrane potential and a significant increase in superoxides in mitochondria, which then lead to serious mitochondrial damage.[17] Some statins (atorvastatin, simvastatin, and lovastatin) are metabolized by the enzyme CYP3A4 in the liver. When it is used in large doses or in combination with CYP3A4 inhibitors (such as macrolides), both of the drug concentration and the liver load increase significantly, which can directly cause liver damage.[15] In addition, gene polymorphisms of statin metabolizing enzymes are also associated with liver dysfunction.[18]

Manifestations and Epidemiology of Liver Dysfunction Caused by Statins

The reported mechanisms of hepatotoxicity caused by statins are constantly being updated. Although statin-induced liver dysfunction (mainly liver transaminase abnormalities) is common in clinical practice, the incidence of statins-induced liver injury is 1.9% to 5.5%.[19] Among which the incidence rates of ALT ≥ 3 times upper limit of normal (ULN) were fluvastatin 1.0– 2.0%, atorvastatin 0.9–1.3%, pitavastatin 0.9%, simvastatin 0.7%, and rosuvastatin <0.4%, respectively.[20] The types of liver dysfunction caused by different statins were also different. Most of the liver injury caused by simvastatin was hepatocellular liver injury (85%), while most of the liver injury caused by atorvastatin, fluvastatin, lovastatin and pravastatin was cholestatic or mixed liver injury.[21] A meta-analyse indicated that atorvastatin showed a higher risk of transaminase elevations than non-statin control (OR = 4.0, 95% CI: 2.2–7.6), pravastatin (OR = 3.49, 95% CI: 1.77–6.92) and simvastatin (OR = 2.77, 95% CI: 1.31–5.09), respectively.[5] Besides, an Emax dose–response relationship was identified for the effect of atorvastatin on transaminase elevations.[5] Hepatocellular, cholestasis, and autoimmune hepatitis may infrequently appear months to years after the initiation of statins.[22]

Countermeasures of Liver Dysfunction Caused by Statins

Firstly, statin-induced liver dysfunction is usually mild to moderate (ALT and/or AST < 3ULN), among whom the elevated ALT and/or AST may voluntarily decrease. If the statins users are in the absence of other relevant clinical manifestations of liver damage, it is not necessary to reduce or stop statins. However, it is recommended to recheck the liver function every 4 to 8 weeks. Secondly, patients with elevated liver enzymes ≥3ULN or combined with elevated total bilirubin should reduce or discontinue statins, or switch to cholesterol absorption inhibitors or PCSK9 inhibitors.[23] An appropriate combination of liver protectant (intravenous N-acetylcysteine, magnesium isoglycyrrhizinate, or bicyclic alcohol) may be needed, but the liver function should be rechecked weekly until normal.[24] Due to the important benefits of statins in coronary plaque regression,[25] restarting low-dose statin therapy or switching to other statins such as pravastatin is still encouraged for patients at high and very high risk of ASCVD. The liver damage may occur again after switching to another statin, so the hepatotoxicity should also be carefully monitored. However, it has been reported that prospective monitoring of statin-induced liver injury is not justified unless the patient would otherwise benefit from such monitoring.[22]

Thirdly, the lowest effective dose of statins should be recommended, and the combination with CYP3A4 inhibitors or other drugs that may aggravate liver damage should be avoided, eg macrolide antimicrobials, acetaminophen, fibrates. Besides, in patients who used both vitamin K antagonists and statins, the risk of ADR observed was lower than that of concomitant treatment with non-vitamin K antagonist oral anticoagulants and statins in an observational cross-sectional study.[26] Fourthly, a history of liver and biliary diseases should be checked before using statins. If the liver transaminase is elevated, differential diagnosis and treatment should be performed, and statins should be started after the transaminase has returned to normal.

Fifthly, statins are not recommended for patients with active chronic liver disease (alcoholic liver disease, autoimmune liver disease, etc.) and decompensated cirrhosis, which is due to that decreased CYP3A4 activity in such patients not only worsens liver damage, but also significantly increases the risk of rhabdomyolysis due to significant increased blood concentrations of statins.[22] The last but not least, the patients with stable chronic liver disease and liver cirrhosis compensatory stage can start with a small dose of statins and monitor changes in liver function. Statins should be discontinued and liver protection therapy should be performed when ALT and/or AST ≥ 3ULN.[22]

Muscle Injury Caused by Statins

Myopathy/rhabdomyolysis is a disorder characterized by muscle dysfunction that could be linked to genetics, inflammation, or a serious side effect of medications such as statins.[27] The auxiliary examination methods for diagnosis of muscle injury including B-mode ultrasound, magnetic resonance imaging, and creatine kinase (CK) examination. Clinical features of different statin-associated muscle symptoms including myalgia, myopathy, myositis, myonecrosis, and rhabdomyolysis, are complex.[28] The mechanism of muscle injury caused by statins was reported related to the overexpression of HMG-CoA reductase in various tissues and cell types, and then activate T cell receptors to induce autoimmunity, which ultimately leads to muscle fiber atrophy and degeneration.[29]

Manifestations and Epidemiology of Muscle Injury Caused by Statins

There are appropriate 10% to 25% of patients treated with statins report statin-related muscle symptoms, while the real incidence of myopathy was 1.5% to 5%.[30] Myalgia can manifest as aches, tenderness, and cramps with normal CK level, while myopathy can characterized by muscle weakness, but the CK level may not elevated[28] Pathological staining of statin-induced myopathy showed atrophy, degeneration, and regeneration of muscle fibers, but without obvious lymphocyte inflammation.[29] If the muscle injury develops into myositis, it may manifest as pain, redness, and elevated temperature with histopathological features of macrophages and inflammatory T and B cells. Rhabdomyolysis is the most severe muscle injury state with dead tissue, manifested by myonecrosis with varying degrees of elevated CK levels, as well as the increase of serum creatinine ≥0.5 mg/dL from baseline.[28]

Statin-associated muscle symptoms were higher in female, younger subjects (age < 65 years), and those who reported physical activity.[31] However, rhabdomyolysis was reported more common in elder patients ≥ 75 years of age than in younger patients and in male than female among a 33 million report in VigiBase®.[32] Besides, the most commonly co-reported drugs were gemfibrozil, cyclosporine, ezetimibe, clarithromycin, amiodarone, and fenofibrate, indicating a great risk of interacting with these drugs. The meta-analyses of 47 randomized controlled trials showed that simvastatin was associated with a lower risk of muscle problems (OR = 0.70, 95% CI: 0.55–0.90), while rosuvastatin showed a higher risk (OR = 1.75, 95% CI: 1.17–2.61) when compared with atorvastatin.[5] However, simvastatin was associated with the highest incidence of rhabdomyolysis, followed by atorvastatin, rosuvastatin, fluvastatin, pitavastatin, pravastatin, and lovastatin.[32]

Risk Factors and Countermeasures of Muscle Injury Caused by Statins

Many risk factors seem to increase the potential of muscle injury caused by statins, and avoiding which can early identify the risk (Figure 1A). From the patient perspective, elderly, kidney disease, muscle disease, excessive physical activity, and genetic variants of CYP isoenzymes lead to increased likelihood of muscle injury caused by statins.[30,33]

It has been reported that lipophilic statins (atorvastatin, simvastatin, fluvastatin, lovastatin), compared with hydrophilic statins (rosuvastatin, pravastatin), are able to cross the cell membrane of extrahepatic tissue in a non-selective manner, and thus increasing muscular toxicity.[30] A meta-analysis of randomized controlled trials found that lipophilic

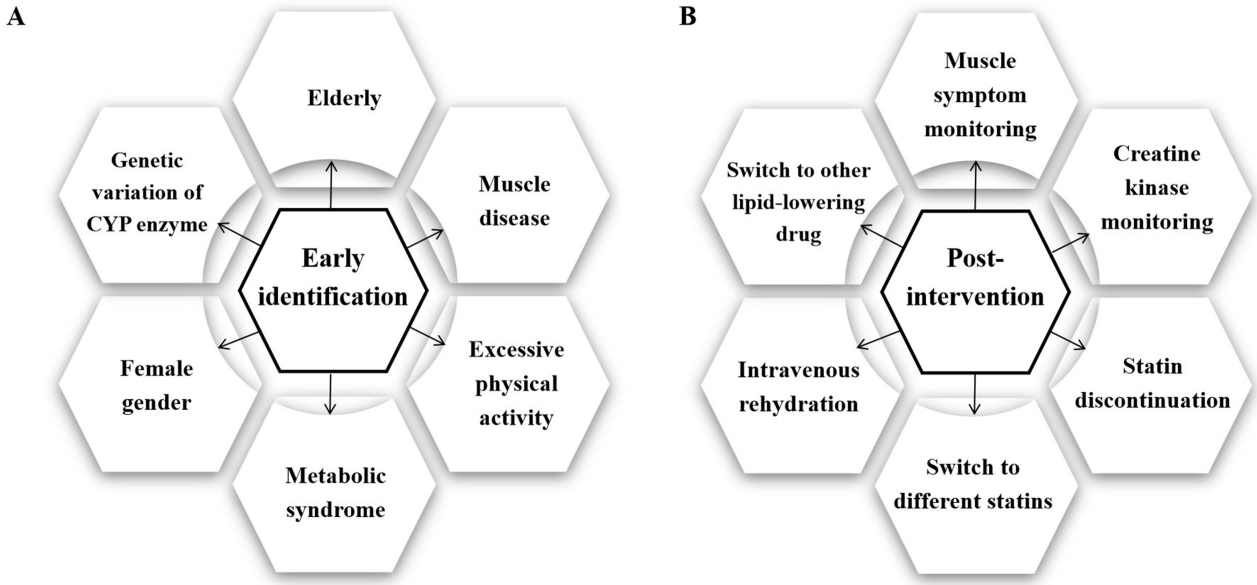

Figure 1 Early identification of risk factors (**A**) and intervention strategies (**B**) for statin-related muscle injury.

statins were associated with a greater risk of muscle injury caused by statins.[34] It may reveal a lower risk of muscle injury when using hydrophilic statins than that of lipophilic statins.

Change of CYP450 enzyme activity is also a key factor affecting the adverse reactions of statins.[35] Most statins such as lovastatin, simvastatin, and atorvastatin are mainly metabolized by CYP3A4 enzymes, while fluvastatin, rosuvastatin, and pravastatin are mainly metabolized by CYP2C9 enzymes. A systematic review showed that the drug-drug interactions between CYP3A4 inhibitors (eg clarithromycin, amiodarone, ritonavir) and statins would increase statin-related muscle injury.[35] Thus, it is suggested to avoid CYP3A4 inhibitors in combination with simvastatin, lovastatin, or atorvastatin, reduce the dose of pitavastatin or pravastatin, but can continue to use fluvastatin or rosuvastatin. Additionally, a systematic review showed that the adverse effects in muscle in the elderly showed an increased risk of 16% with high-intensity statins comparing with low/moderate-intensity statins.[34] Adverse herb–drug interaction based on CYP450 may also affect the metabolism of statins. It proved that Jiangzhi Recipe, a traditional Chinese medicine compound, can inhibit the activity of CYP3A4, enhance the blood concentration and bioavailability of atorvastatin, which could cause or aggravate the side effect of statins (eg muscular toxicity).[36] It has been reported that the SCLO1B1 genotype can inform the risk of statin-related muscle symptoms, and new users of statins in particular may benefit from pharmacogenomic testing of the SCLO1B1 gene.[37]

It has also been demonstrated that the food like Grapefruit and Seville oranges contain furanocoumarins, and the mechanisms by which these furanocoumarins would cause food–drug interactions focus on inhibiting CYP3A4.[38] Of the current statins, simvastatin, lovastatin, and atorvastatin can be significantly enhanced by interaction with grapefruit and its juice, while pravastatin, fluvastatin and rosuvastatin seem least likely to interact, and these interactions can produce serious adverse effects such as rhabdomyolysis, to which the elderly may be most susceptible.[38,39] Because food–drug interactions vary from person to person and are difficult to predict, at the very least, interactions that are known to help prevent ADR should be avoided, and thus requiring careful daily dietary advice for patients.

From the management perspective, muscle injury caused by statins includes avoiding or reducing above risk factors, and switching to different statins and/or alternative lipid-lowering drug (eg ezetimibe, PCSK9 inhibitors, inclisiran). It is also important to consider weighing the costs and benefits of statins versus other medications to reduce long-term atherosclerotic cardiovascular disease events.

Discussion and Future Perspectives

ADR is a natural element during drug use, which can occur at any age and has attracted great concerns from doctors and pharmacists.[40] In face of the successful benefits and high proportion use of statins in the prevention of adverse cardiovascular events for more than 40 years, the statin-related liver dysfunction and muscle injury have been health care challenge.[41] It is certainly far-sighted to identify the balance of benefits and risks before using statins, and to focus on the countermeasures once those risks occur.

Statins are typically used by elderly patients whose physiological functions such as immune capacity, rehabilitation function, and drug metabolism are deteriorating, resulting in damaged organ and decreased ability to respond to ADR. In addition, the cardiovascular diseases of statin users often require multiple drugs, which increases the incidence of ADR caused by drug interactions to some extent. Therefore, in the actual clinical application of statin, medical staff should pay attention to the monitoring of the elderly population, reduce the incidence of adverse reactions, and improve the treatment effect and quality of life. A cross-sectional study enrolling 752 statins users in Jordan showed that only half of the patients (49.7%) received statin treatment at the intensity recommended by the guidelines.[42] Besides, 40.7% cases were undertreated with statins, and the management of dyslipidemia was not accompanied by appropriate follow-up.[42] Statin users who are older, have been on statins for a longer period of time, and have a history of angina or stroke, should be given sufficient follow-up to determine patient compliance and treatment response including the potential ADR.[42]

The precautionary principles of statin-related ADR are to ensure correct and personalized medication, avoid unnecessary or easy to cause serious risks of combined medication, and closely identify the patients' initial drug response. The countermeasures for statin-related muscle injury (Figure 1B) and liver dysfunction (Figure 2) including stopping the suspected drug; reducing statin dosage; changing to another lipid-lowering agent; and taking effective treatment measures using liver protectors and hydration treatments, for instance. It is worth mentioning that the adverse

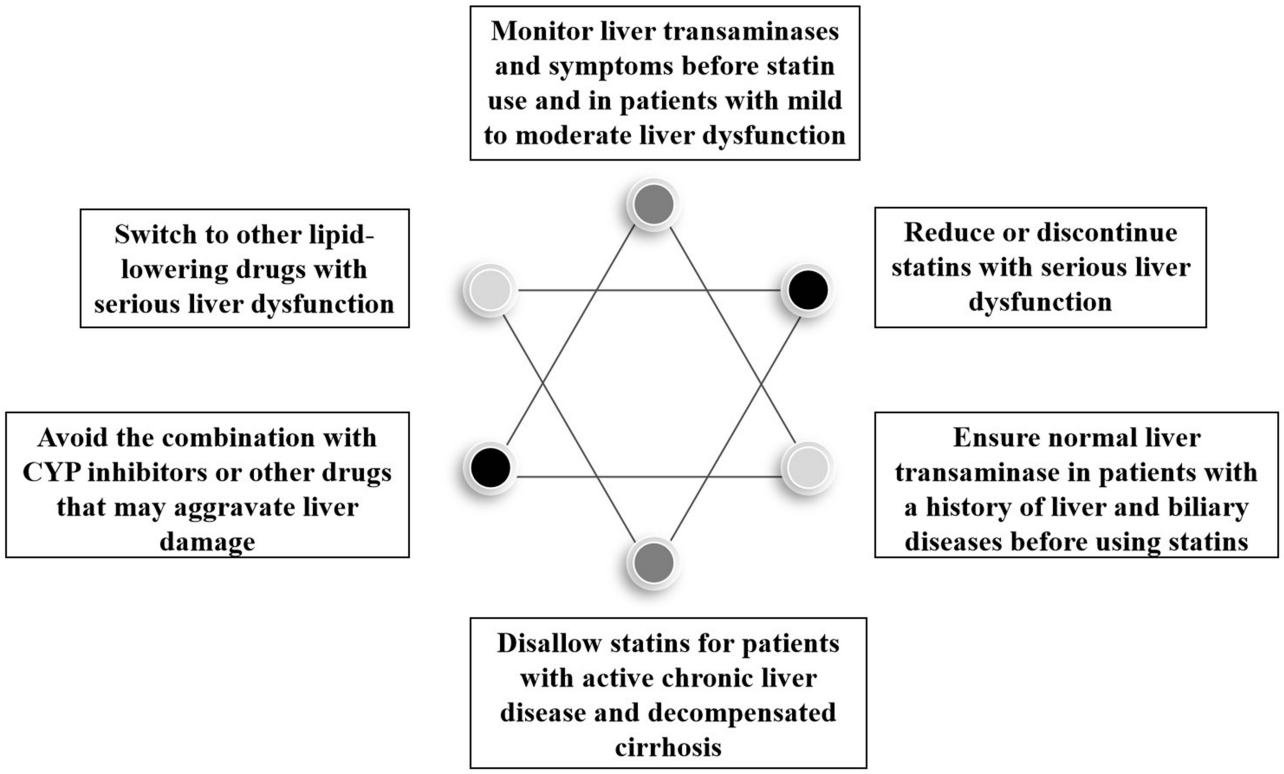

Figure 2 Countermeasures of liver dysfunction caused by statins.

interactions between herbs and drugs are often ignored. Even in the USA, 40% of herbal users reported potential adverse herb–drug interactions.[43] There is evidence that traditional Chinese medicine flavonoids can raise plasma levels of statins and increase the risk of statin induced myopathy by interacting with the liver CYP450 enzyme, OATP uptake, or HMG-CoA reductase.[44]

A large body of evidence shows that the benefits of statin therapy far outweigh any actual or perceived risks.[45] Whether the adverse effects of statins are caused by the effects of statins or nocebo is still debated. Recent study included 3027 statin users showed that high-intensity statin was statistically significant in resulting in an LDL-C level < 40 mg/dL when compared with low- and moderate-intensity statin, but the rate of ADR related to different intensity statin showed no statistical significance.[46] A retrospective cohort study showed that high-intensity atorvastatin was associated with an increased incidence of ADR.[47] These studies have yielded conflicting conclusions about whether different intensity doses of statins are associated with an increased incidence of adverse reactions. Therefore, detailed studies on the adverse risks of statins are needed in the future.

Firstly, it is necessary to accurately extract, clean, and standardize the flow of adverse reaction records involving statins and their combination drugs (Chinese medicine and Western medicine). Then the gender, age, route, appropriate statin intensity dose, time of administration, symptoms, and severity of the patients should be analyzed via multivariate analysis of variance. Secondly, the real-world discovery may provide an accurate basis for the identification of drug use risk.[1,48,49] Thirdly, too low LDL-C level may lead to unexpected adverse events, but there was evidence showing that the lipid-lowering drugs such as PCSK9 inhibitors have been shown not only to be harmless but also to produce additional cardiovascular benefits.[50] Whether there is an optimal minimum safe level of LDL-C after statin treatment for different types of patients needs further study.

Conclusions

Statins have become the main lipid-lowering drugs for the primary and secondary prevention and treatment of ASCVD. Meanwhile, the issues of drug safety of statins have aroused increasing concerns. This review describes the epidemiology

and mechanisms of statin-associated liver dysfunction and muscle injury. Besides, detailed management strategies including early identification and post-intervention are presented aiming to minimize the risks of statins use and ensure timely medication schedule adjustments for patients.

Abbreviations

ADR, adverse drug reaction; ALT, alanine aminotransferase; ASCVD, atherosclerotic cardiovascular diseases; AST, aspartate aminotransferase; CK, creatine kinase; HMG-CoA, 3-hydroxy-3-methylglutaryl-Coenzyme A; LDL-C, low density lipoprotein cholesterol; ULN, upper limit of normal.

Data Sharing Statement

No data was used for the research described in the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, review design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflicts of interest in this work.

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