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Review Article

Liver damage and muscle injury associated with the use of statins

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ABSTRACT

Pharmacological monitoring with positive and negative effects on the use of medications is an important aspect during the administration of different drugs. Adverse events generated by the misuse of medications have become one of the main causes of death worldwide and an urgent problem in the field of toxicology. Cardiovascular diseases currently occupy the top positions among the main causes of death worldwide, especially in older adults who, burdened by their different comorbidities, find themselves faced with the need to use multiple pharmacological therapies. Among them, statins are widely used to reduce bad cholesterol levels and thus be able to combat the formation of plaque at the coronary level, especially in patients with hyperlipidemia and cardiovascular diseases (CVD). Although the use of statins worldwide generates broad benefits, there are different types of adverse reactions (ARs), including liver dysfunction and muscle damage, that affect the quality of life of people who use them. This review describes the mechanisms, epidemiology and rapid identification of hepatic and muscular effects associated with the use of statins.

Keywords: Statin, Cardiovascular diseases, Liver dysfunction, Muscle injury

INTRODUCTION

Pharmacological safety is an urgent problem that must be addressed as a public health problem and allow the branch of toxicology to study them in depth.[1] Exposure to drugs produces inevitable negative effects and adverse reactions (AR), which are related to different factors such as age, category of medications and their route of administration.[2] The different adverse reactions caused by drugs can damage the health of patients and even delay the recovery of the pathologies they suffer from or even lead to fatal consequences. Drug side effects and spellings have become more prominent in recent years. In recent years, mortality rates from cardiovascular diseases (CVD) occupy the first places.[3] There are some types of CVD with complex treatments that include lipid-lowering drugs such as statins or their combination with other drugs. Different meta-analysis studies and randomized controlled trials showed that statins diluted the risk of myocardial infarction.[4] It is also noted that statins combined with another lipid-lowering agent can significantly improve the anatomy and physiology of the cardiac arteries, which reduces the rates rehospitalization due to unstable angina with ST elevation.[5] The evidence reveals the importance of the use of statins in reducing cardiovascular risk and the benefits it provides. However, problems related to adverse effects from the consumption of statins are generating concern.[6] Adverse effects not only cause additional harm to patients, they also greatly interfere with routine clinical treatment. It is necessary to question the real use of statins in clinical practice. This study is fundamentally based on the toxic liver and muscle damage associated with the consumption of statins. Consequently, it is intended to carry out detailed countermeasures to minimize the risks of statin use and

provide timely mediation with a schedule adjustment to patients.

METHODS

Study design

It is a descriptive-exploratory study type of bibliographic review. The literature search period is from 2023-2024 in electronic databases such as Pubmed, Elsevier, and web of science. The keywords used in the MesH search were statin, cardiovascular diseases, liver dysfunctions, muscle injury.

Inclusion criteria

Search terms, level of evidence, summaries and keywords, exclusion criteria: not related to the topic, outside the year limit, not available; They will be classified by year, type of study and level of evidence. For eligibility, a critical reading is carried out, level of evidence, documents available for analysis and according to the topic. A total of 33 sources were obtained for analysis and synthesis.

RESULTS

Epidemiology

Statins are 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase, which has an effect at the lipid level by inhibiting cholesterol biosynthesis.[7] Within this family we find simvastatin, pravastatin, atorvastatin and rosuvsatatin, which play the role of reducing low-density cholesterol (LDL-C) levels. Clinically they are applied in atherosclerotic cardiac diseases (ASCVD) and hyperlipidemias. They also show benefit as a first-class drug in primary and secondary prevention and treatment of cardiovascular and cerebrovascular disease.

In recent years the use of statins has increased. It is reported that the use of statins in the primary prevention of cardiovascular disease in patients over 75 years of age reaches 62.2% in the USA.[8] The increase in the prescription of statins is associated with the increase in diabetes, coronary heart disease, stroke and stroke transient ischemic.[9] A cross-sectional study carried out in Saudi Arabia with a duration of 12 months with a sample of 356 patients with acute coronary disease, the drug consumed by 93% is statins followed by antiplatelets and anticoagulants.[10] Meanwhile, the most used statin is atorvastatin, showing an increase in the last decade from 23.6% to 30.5%.[11] These studies indicate that the use of statins has increased in different countries and various indications in recent years. On the other hand, the increase in the use of these drugs creates a risk of causing liver damage and myopathy, which suggests that these patients should be monitored and studied during their use. Manifestations and epidemiology of liver dysfunction caused by statins. The mechanisms that cause liver damage are still unclear and are constantly being updated. Although liver dysfunction due to statins (mainly transaminases) is common, its incidence is approximately between 1.9% and 5.5%. Among these we observed an alteration in the values of alanine aminotransferase (ALT) elevated three times above its normal value, the statins fluvastatin 1.0-2.0%, atorvastatin 0.9-1.3%, pyravastatin 0.9%, simvastatin 0.7% and rosuvastatin less than 0.4% respectively.[13] The types of liver dysfunction caused by different statins showed differences in the same way. The majority of liver injury caused by simvastatin was hepatocellular liver injury (85%) while the liver injury caused by atorvastatin, fluvastatin, lovastatin and pravastatin were cholestatic or mixed liver injury.[14] A meta-analysis indicates that atorvastatin shows a high risk of causing transaminase elevation compared to the control group (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 14. Hepatocellular injury, cholestasis and autoimmune hepatitis may rarely appear months or years after starting statins.[15]

Countermeasures of liver dysfunction caused by statins

The dysfunction caused by statins is usually mild to moderate (ALT and/or AST<3 ULN). If the person using statins does not present symptoms or manifestations associated with liver damage, it is not necessary to reduce or suspend use of statins. However, it is recommended to monitor liver enzyme levels in 4 to 8 weeks. Patients who show transaminase values greater than 3 ULN or combined with elevated bilirubin should reduce, discontinue the use of statins or switch to cholesterol absorption inhibitors.[16] An appropriate combination of liver protectant (intravenous n-acetyl cysteine, magnesium isoglycyrrhizinate, or bicyclic alcohol) may be necessary, but liver function should be re-monitored weekly until normalized.[17] Due to the important benefit of statins in preventing coronary heart disease, it is recommended to restart treatment with low-dose statins or switch to statins such as pravastatin in patients at high and very high risk of ASCVD. Liver damage can recur and therefore it is important to maintain regular check-ups.

The lowest and most effective dose of statin should be recommended in conjunction with CYP3A4 inhibitors and avoid the use of other drugs that may cause greater liver damage such as antibiotics, macrolides, paracetamol and fibrates. Furthermore, in an observational study it was determined that patients who ingest vitamin K with statins have less liver damage compared to those who do so without vitamin K.[18] Patients who show liver alterations and biliary disease should be studied before starting use. of statins, start treatment for liver disease and start statins with normal liver function. Statins are not recommended in patients with chronic liver disease (alcoholic liver disease, autoimmune liver disease, etc.) and decompensated cirrhosis, because they decrease the

activity of CYP3A4, worsening liver damage and significantly increasing the risk of suffering from rhabdomyolysis due to increased blood concentrations of statins.[19] Patients with stable chronic liver disease and compensated cirrhosis can be started on small doses of statins depending on their changes in transaminase levels. Statins should be discontinued and liver protective therapy initiated when ALT and/or AST are >3 ULN.[19]

MUSCLE DAMAGE ASSOCIATED WITH THE USE OF STATINS

Myopathy/rhabdomyolysis is considered a disorder characterized by muscle dysfunction that can be associated with genetic factors, inflammatory factors or serious adverse effects such as the use of statins. Among the complementary tests that are usually requested as diagnostic support, it includes muscle ultrasound in B mode that allows determining muscle damage, magnetic resonance imaging, and creatine kinase (CK) levels. Symptoms include myalgia, myopathy, myositis, myonecrosis and rhabdomyolysis.[21] The mechanism that causes muscle damage associated with the use of statins is produced by the overexpression of HMG-CoA reductases in various tissues and cell types, with the activation of the cells T induces an autoimmune response which leads to muscle atrophy and degeneration.[22]

Manifestations and epidemiology of muscle injury caused by statins

Approximately between 10% to 25% of patients taking statins report muscular symptoms, while it is estimated that a true myopathy occurs between 1.5% and 5% 23. Myalgia can manifest with pain, numbness and cramps with normal CK levels while a myopathy can be characterized by muscle weakness but the CK value is not elevated. Statin-induced myopathy generates atrophy, degeneration and regeneration of muscle fibers but without obvious inflammation of lymphocytes.[24] If muscle damage develops into myositis, this can manifest with pain, redness, heat in the painful area and histopathological findings. with macrophages and T and B cells. Rhabdomyolysis is the most severe cause of muscle damage with tissue death manifested by myonecrosis with elevated CK and an increase in creatinine levels of >0.5 mg/dl.

Muscular symptoms were reported by women, especially those over 65 years of age, however rhabdomyolysis was more commonly reported in older adults over 75 years of age in approximately 33 million people according to VigBase .[25] In addition, the most commonly used drugs were genfibrozil, cyclosporine, ezetimibe, clarithromycin, amiodarone and fenofibrate. A meta-analysis of 47 controlled trials shows that simvastatin was associated with high low risk of muscle problems (OR=0.70, 95% CI: 0.55–0.90) while rosuvastatin shows a high risk (OR=1.75, 95% CI :1.17–2.61) compared to simvastatin, however simvastatin was associated with a high incidence of rhabdomyolysis followed by atorvastatin, rosuvastatin, fluvastatin, pitavastatin, pravastatin and levastatin.[25]

Risk factors and countermeasures of muscle damage caused by statins. There is some risk factors associated with the increase in muscle injury caused by statins (Figure 1).

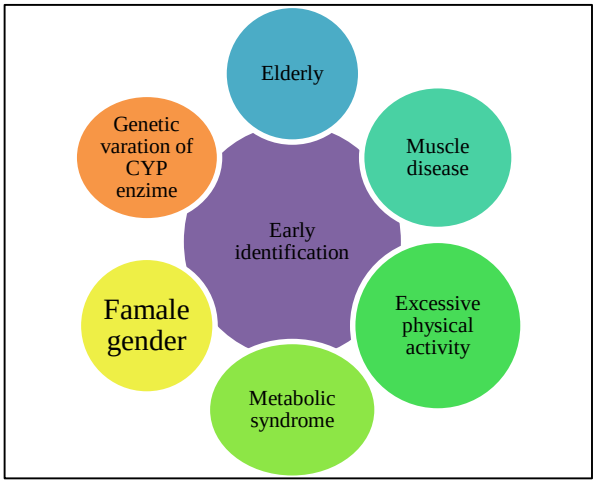

Figure 1: Early identification of risk factors.

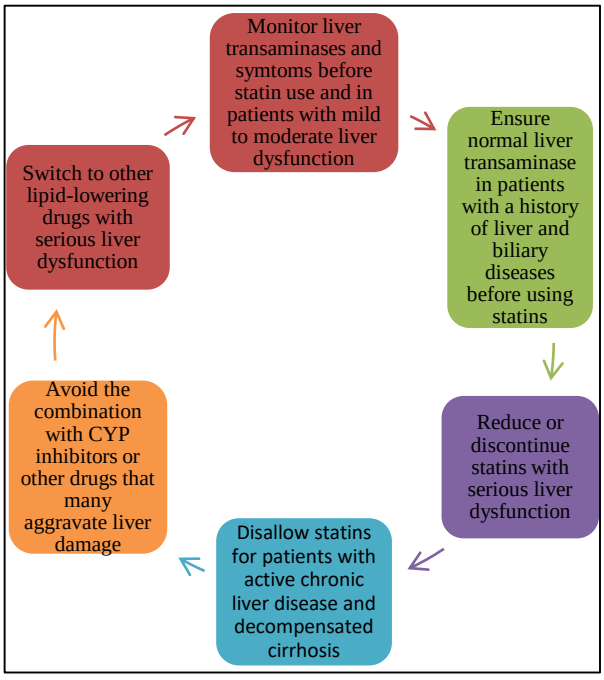

Figure 2: Countermeasures for liver injury caused by statin use.

From the patient's perspective, older adults, kidney disease, muscle pathologies, excessive exercise and genetic variants of CYP enzymes can increase the risk of muscle damage caused by statins.[26] It has been reported that lipophilic statins (atorvastatin, simvastatin, fluvastatin, lovastatin), compared to hydrophilic statins

(rosuvastatin, pravastatin) are capable of crossing the cell membrane and extrahepatic tissue, increasing muscle toxicity.[23]

Changes in the activity of CYP450 enzymes can generate major alterations and adverse effects after the use of statinsS.[27] Some statins such as lovastatin, simvastatin and atorvastatin are mainly metabolized by CYP3A4 while fluvastatin, rosuvastatin and pravastatin are mainly metabolized by CYP2C9. A systemic review shows that the interaction between CYP3A4 inhibitors (clarithromycin, amiodarone, ritonavir) and statins can increase muscle damage. Some plants used with herbal effects can alter the metabolism of CYP450 and affect the absorption of statin, causing damage at the muscle level and generating toxicity as an adverse effect. Some fruits such as oranges contain furanocmoumorins and the mechanism by which these can cause interactions by inhibiting CYP3A4.[28] Of the statins mainly used such as simvastatin, lovastatin can produce serious adverse effects such as rhabdomyolysis; people in older adulthood may be more susceptible.

From a treatment perspective, muscle injury caused by statins includes avoiding or reducing the risk factors mentioned above and switching to different statins and/or alternative lipid-lowering drugs (ezetimibe, PCSK9 inhibitors, inclisiran). It is important to consider the costs and benefits of statins versus other medications to reduce long-term risk.

DISCUSSION

Adverse effects are a natural element that can occur during the consumption of any drug and can occur at any age and cause great concern to medical personnel and pharmacists. Given the multiple benefits, its use in the prevention of cardiovascular events, its use is increasingly common and its massive consumption, liver dysfunction and muscle injuries are and will be a real health problem.[30] It is a real challenge to identify the balance between benefits and risks before using statins and focus on countermeasures that allow action once adverse effects or health risks occur.

Statins are typically used by people of advanced age and they are the ones whose physiological functions such as their immune capacity, function and drug metabolism are impaired, resulting in organ involvement and a reduced ability to respond to adverse reactions. Cardiovascular diseases that concomitantly require the use of statins and other drugs or that increase the risk of adverse effects. Therefore, it is important to determine the true use of statins and maintain follow-up with special emphasis on older adults.

A cross-sectional study involving 752 people who used statins in Jordan showed that only half of the patients (49.7%) received statins at the doses recommended by the guidelines.[31] 40.7% of the cases were on inadequate treatment for their condition. dyslipidemia and did not have adequate follow-up. The principles to ensure adequate use of statins are based on the precaution of adverse reactions related to statins, providing correct and personalized medication, avoiding unnecessary use or easy to cause serious risks of combined medication, and closely identifying the initial drug. from the patients. Countermeasures for muscle injuries related to statin use include discontinuing the drug, reducing the dose, or switching to another lipid-lowering agent that provides safe treatment (Figure 2).

It is important to mention that the tendency to consume statins in countries with high economic resources is greater due to the ease of access to health services and supplies such as medications. There is also a relationship between the consumption of statins and the incidence of cardiovascular diseases. Thus, in those countries where health policies have been adequately implemented to reduce the morbidity and mortality of cardiovascular diseases, there is a greater tendency to consume these medications.

Statins are drugs that are established as first-line drugs for the treatment of dyslipidemia and cardiovascular diseases, however with the passage of time it is determined that these drugs are related to the deterioration of liver function, classified today as a of the causes, statins currently continue to be one of the most used drugs for primary prevention of cardiovascular diseases as HMG-CoA reductase inhibitors, inhibiting cholesterol biosynthesis.[32]

Various randomized trials have reported no significant differences in the incidence of persistently elevated aminotransferases between statin therapy and placebo. A review of three pravastatin trials, with more than 112,000 patient-years of exposure, showed similar results. A meta-analysis of 35 trials found an excess risk of aminotransferase elevation with statin therapy versus placebo of 4.2 cases per 1000 patients. Reviews of clinical records have demonstrated that significant elevations in transaminases in patients taking statins are rare and, in many cases, not directly related to statin use. For instance, a five-year review of records from a health maintenance organization showed that 0.1% of patients had ALT levels more than 10 times the upper limit of normal attributable to statin therapy, with most of these cases associated with drug interactions.[33]

CONCLUSION

Statins have become the main lipid-lowering drugs for the prevention and primary and secondary treatment of cardiovascular diseases. Meanwhile, safety issues of statins have raised increasing concerns. This review describes the epidemiology and mechanisms of statin-associated liver dysfunction and muscle injury. Also, detailed management strategies. including early identification and postintervention, are presented with the

goal of minimizing the risks of statin use and ensuring timely adjustments to patients' medication schedule.

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