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Possible nephrotoxic effects of high dose statin therapy; current knowledge

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ABSTRACT

Implication for health policy/practice/research/medical education:
The 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) inhibitors (i.e., statins) offer several cardiovascular health benefits, however, the adverse effects of these compounds should be carefully considered. High-dose statin therapy could be associated with renal toxicity. The nephrotoxic effects of statins are directly related to higher treatment doses and indirectly related to interactions with other agents, which may increase the serum concentration of statins. Possible mechanisms that can underlie statin-induced nephrotoxicity include changes in cell membrane permeability, reduced ubiquinone levels, and depletion of isoprenoids due to the inhibition of cholesterol production..

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Epidemiology and Prevention

Introduction

The 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) inhibitors (i.e., statins) are recommended as a first-line of cholesterol-lowering medication for lipid control. Statins reduce low-density lipoprotein cholesterol (LDL-c), a chief contributor to atherosclerotic cardiovascular disease, which helps prevent cardiovascular disease.

Recent studies demonstrate that high-dose statins augment LDL-c reduction and lead to improving cardiovascular outcomes compared to low- or moderate-dose statin therapy in atherosclerotic cardiovascular disease patients (1). The benefits of high-dose statin therapy on cardiovascular risks have increased prescribing of high-dose statins.

Despite beneficial effects with statin therapy, treatment with these agent is also associated with adverse events. These adverse effects range from nonthreatening asymptomatic presentations to severe organ dysfunction, especially of the kidneys and liver. Severe adverse effects associated with statin treatment include muscle damage, renal failure, liver dysfunction and polyneuropathy. Specific side effects of renal origin include rhabdomyolysis, proteinuria and acute kidney injury (AKI).

Acute kidney injury

Several clinical studies propose that high-dose statin treatment will increase the risk of AKI. However, cardiovascular surgery patients may respond differently to the type and dose of statin therapy. For instance, high-dose statins are associated with a high risk of AKI in patients of the general population. In contrast, equivalent doses of those statins in cardiovascular surgery patients demonstrated renoprotective effects (2). Numerous studies suggest that high-dose statins will significantly increase the risk of contrast-induced AKI. A previous study has demonstrated a relationship between the high dose of atorvastatin and renal injury if administered alone or in combination with high doses of garlic; while a low-dose of atorvastatin in combination with high doses of garlic has negligible nephrotoxic effects (3). Statins should be administered cautiously in coronary artery disease patients undergoing coronary angiography (3,4). Hospitalization due to AKI was 34% higher in the cohort that received high-dose statin therapy compared to the cohort that administered low-dose statin therapy (2). High doses of atorvastatin have nephrotoxic effects, while lower doses have beneficial effects on renal function and structure (2) suggesting that, high doses of statins may be

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associated with renal tubular cell damage (3). Meanwhile, a Cochrane review could not find a benefit of statins on AKI after cardiac surgery (5). Additionally, some studies showed that statins are not renoprotective against AKI after contrast administration following cardiac surgery (6-8). Likewise, there is a 25-fold increased relative risk of AKI associated with high-dose statins over low-dose statins in patients with congestive heart failure (2). In a retrospective cohort study, administration of statins was associated with a greater incidence of AKI and chronic kidney disease; therefore, long-term administration of statins might also be associated with higher morbidity and mortality rates due to higher rates of chronic kidney disease (9) and diabetes mellitus (10).

Some case studies also reported a dose-dependent association between statins and acute tubular necrosis (11) due to rhabdomyolysis (12).

Proteinuria

Some reports show that statin treatment, especially in high doses, can induce proteinuria (13,14). For example, a study showed that 10 of 120 (8.3%) of patients with high cholesterol administered 40 mg/d of simvastatin developed proteinuria (14). Higher occurrences of proteinuria and hematuria were observed with high doses of rosuvastatin (80 mg) as well (15). Electrophoresis of urine in patients administered rosuvastatin detected tubular patterns of proteinuria, confirming a high level of low-molecular-weight protein excretion, such as microglobulins. Statins inhibit mevalonate synthesis, which is a precursor of isoprenoid pyrophosphates. Isoprenoid pyrophosphates are needed for the prenylation of GTP binding proteins and can reduce low-molecular-weight protein reabsorption in proximal tubular cells by decreasing receptor-mediated endocytosis (13). In this regard, the ERICABEL trial has recently reported a relation between statin administration and microalbuminuria, which may have previously been overlooked in patients presenting with microalbuminuria (16). Therefore, it could be expected that patients treated with some types of statins present higher urinary albumin excretion. This adverse-effect should be investigated with new generations of statins (17,18).

Conclusion

High-dose statin therapy is associated with nephrotoxicity, likely related to the inhibition of HMG-CoA activity and the mevalonate metabolic pathway. Possible mechanisms underlie statin-induced nephrotoxicity include changes in cell membrane permeability, reduced ubiquinone levels, and depletion of isoprenoids due to inhibited cholesterol production.

Authors' contribution

Conceptualization, resources, visualization, supervision: MF. Validation, project management, data curation: FA and MF. Research: FA, ZJ, MR, AJ and MF. Writing—original draft preparation: MF, AJ and MR. Writing—reviewing and editing: FA, ZJ, MR and AJ.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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References

1. Escobar C, Echarri R, Barrios V. Relative safety profiles of high dose statin regimens. Vasc Health Risk Manag. 2008;4:525-33. doi: 10.2147/vhrm.s2048.
2. Dormuth CR, Hemmelgarn BR, Paterson JM, James MT, Teare GF, Raymond CB, et al; Canadian Network for Observational Drug Effect Studies. Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases. BMJ. 2013;346:f880. doi: 10.1136/bmj.f880.
3. Cai L, Bai X, Lei H, Wu H, Liu Y, Zhu Q, et al. High Plasma Exposure of Statins Associated With Increased Risk of Contrast-Induced Acute Kidney Injury in Chinese Patients With Coronary Artery Disease. Front Pharmacol. 2018;9:427. doi: 10.3389/fphar.2018.00427.
4. Chung YH, Lee YC, Chang CH, Lin MS, Lin JW, Lai MS. Statins of high versus low cholesterol-lowering efficacy and the development of severe renal failure. Pharmacoepidemiol Drug Saf. 2013;22:583-92. doi: 10.1002/pds.3433.
5. Lewicki M, Ng I, Schneider AG. HMG CoA reductase inhibitors (statins) for preventing acute kidney injury after surgical procedures requiring cardiac bypass. Cochrane Database Syst Rev. 2015; CD010480. doi: 10.1002/14651858.CD010480.pub2.
6. Schetz M, Oudemans-Van Straaten H. Statins do not prevent cardiac surgery-associated AKI: is ubiquinone the missing link? Intensive Care Med. 2016;42:1464-6. doi: 10.1007/s00134-016-4424-2.
7. Billings FT 4th, Hendricks PA, Schildcrout JS, Shi Y, Petracek MR, Byrne JG, et al. High-dose perioperative atorvastatin and acute kidney injury following cardiac surgery: a randomized clinical trial. JAMA. 2016;315:877-88. doi: 10.1001/jama.2016.0548.
8. Brealey DA, Singer M, Terblanche M. Potential metabolic consequences of statins in sepsis. Crit Care Med. 2011;39:1514-20. doi: 10.1097/CCM.0b013e31820eb74f.
9. Acharya T, Huang J, Tringali S, Frei CR, Mortensen EM, Mansi IA. Statin Use and the Risk of Kidney Disease With Long-Term Follow-Up (8.4-Year Study). Am J Cardiol. 2016;117:647-55. doi: 10.1016/j.amjcard.2015.11.031.
10. Ahmadizar F, Ochoa-Rosales C, Glisic M, Franco OH, Muka T, Stricker BH. Associations of statin use with glycaemic traits and incident type 2 diabetes. Br J Clin Pharmacol. 2019;85:993-1002. doi: 10.1111/bcp.13898.

11. Verdoodt A, Honore PM, Jacobs R, De Waele E, Van Gorp V, De Regt J, et al. Do statins induce or protect from acute kidney injury and chronic kidney disease: an update review in 2018. J Transl Int Med. 2018;6:21-25. doi: 10.2478/jtim-2018-0005.
12. Mendes P, Robles PG, Mathur S. Statin-induced rhabdomyolysis: a comprehensive review of case reports. Physiother Can. 2014;66:124-32. doi: 10.3138/ptc.2012-65.
13. Agarwal R. Statin induced proteinuria: renal injury or renoprotection? J Am Soc Nephrol. 2004;15:2502-3. doi: 10.1097/01.ASN.0000143720.71748.79.
14. Deslypere JP, Delanghe J, Vermeulen A. Proteinuria as complication of simvastatin treatment. Lancet. 1990;336:1453. doi: 10.1016/0140-6736(90)93164-k.
15. Agarwal R. Effects of statins on renal function. Mayo Clin Proc. 2007;82:1381-90. doi: 10.4065/82.11.1381.
16. van der Tol A, Van Biesen W, Van Laecke S, Bogaerts K, De Lombaert K, Warrinnier H, et al. Statin use and the presence of microalbuminuria. Results from the ERICABEL trial: a non-interventional epidemiological cohort study. PLoS One. 2012;7:e31639. doi: 10.1371/journal.pone.0031639.
17. Robles NR, Velasco J, Mena C, Polo J, Angulo E, Espinosa J. Increased frequency of microalbuminuria in patients receiving statins. Clin Lipidol. 2013;8:257-62.
18. Chiang CK, Ho TI, Hsu SP, Peng YS, Pai MF, Yang SY, et al. Low-density lipoprotein cholesterol: association with mortality and hospitalization in hemodialysis patients. Blood Purif. 2005;23:134-40. doi: 10.1159/000083529.