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Pleiotropic Properties of Statins in Renal Protection Among Patients with Chronic Kidney Disease: A Review of Current Clinical Evidence

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Abstract

Background

Chronic kidney disease (CKD) affects more than 10% of the global population and is associated with increased cardiovascular morbidity and mortality. Dyslipidemia contributes to CKD progression through inflammatory, atherosclerotic, and fibrotic mechanisms. Statins, widely used for lipid control, exhibit pleiotropic effects that may influence renal outcomes; however, their direct renoprotective role remains controversial.

Aim

To evaluate the efficacy and safety of statin therapy in patients with CKD, with particular emphasis on renal outcomes such as estimated glomerular filtration rate (eGFR) and proteinuria, and to analyze the molecular mechanisms underlying their pleiotropic effects.

Material and Methods

A literature review was conducted using PubMed, Google Scholar, ResearchGate, Embase, Scopus, and Web of Science. Relevant studies, including randomized controlled trials (PLANET I/II, SHARP, and CNODES) and meta-analyses, were selected according to predefined inclusion criteria.

Results

Statin therapy demonstrated a modest effect in slowing eGFR decline and reducing proteinuria; however, outcomes varied depending on the specific agent and dosage. Atorvastatin showed potential renoprotective effects, whereas high-dose rosuvastatin was associated with

deterioration in renal function. High-intensity therapy may increase the risk of acute kidney injury and rare complications such as rhabdomyolysis, particularly in patients with CKD. Proposed molecular mechanisms include anti-inflammatory, antioxidant, and endothelial-protective effects.

Conclusions

Statins remain essential for reducing cardiovascular risk in patients with CKD; however, their renoprotective effects appear limited and are not uniform across all agents. Individualized therapy is crucial to balance cardiovascular benefits against potential renal risks. Further large-scale studies are needed to optimize treatment strategies in this population.

Key words: chronic kidney disease, statins, eGFR, proteinuria, dyslipidemia.

Background

Chronic kidney disease (CKD) has emerged as a significant global health challenge, currently affecting over 10% of the world's population [1,3]

This condition is inextricably linked to a dramatic increase in cardiovascular morbidity and mortality, which is estimated to be 10 to 30 times higher in patients with renal impairment than in the general population [2]

While traditional risk factors such as hypertension and diabetes are primary drivers of disease progression, the role of dyslipidemia as a critical factor in accelerating renal decline has gained substantial attention [3]

The mechanisms through which lipid disorders damage renal tissue are multifaceted. They include accelerated intrarenal atherosclerosis and a direct toxic effect on mesangial cells, which triggers inflammatory responses and promotes interstitial fibrosis [4]

Statins, acting as HMG-CoA reductase inhibitors, have become the cornerstone for managing dyslipidemia and preventing cardiovascular events [5]

Beyond their primary lipid-lowering capabilities, statins exert significant pleiotropic effects, including antioxidant and anti-inflammatory properties, as well as the ability to improve endothelial function by increasing the bioavailability of nitric oxide (NO) through the Rho/ROCK signaling pathway [6]

Despite their established role in cardiology, the direct renoprotective capacity of statins remains a subject of ongoing clinical debate

Findings from large-scale meta-analyses suggest that statin therapy may slow the decline of the estimated glomerular filtration rate (eGFR) by 0.26[8]/0.41[9]/1.22[4] ml/min/year and modestly reduce proteinuria [3,7,8]

However, recent evidence, particularly from the PLANET I and II trials, has challenged the concept of a "class effect" in renal protection.

These studies demonstrated that while atorvastatin effectively reduced proteinuria and stabilized eGFR, high-dose rosuvastatin failed to show similar benefits and was even associated with significant renal function decline [9,10].

Understanding these molecular differences and clinical outcomes is essential for optimizing therapy and improving long-term survival for CKD patients and kidney transplant recipients.

Research materials and methods

A literature search was conducted using the following databases: PubMed, Google Scholar, ResearchGate, Embase, Scopus and Web of Science. To identify relevant publications, the databases were searched using the following keywords: “statins” AND (“chronic kidney disease” Studies published in languages other than English were excluded. Conference abstracts were also excluded from this review.

Aim

The aim of this study was to comprehensively evaluate the efficacy and safety of statin therapy in patients with chronic kidney disease, with particular emphasis on its effects on renal outcomes such as estimated glomerular filtration rate (eGFR) and proteinuria. Additionally, this review aimed to analyze the molecular mechanisms underlying the pleiotropic effects of statins, including their anti-inflammatory, antioxidant, and endothelial-protective properties.

Material and methods

The analysis presented in this review covers clinical evidence from major trials such as PLANET I/II, SHARP, CNODES, as well as large-scale meta-analyses investigating the use of HMG-CoA reductase inhibitors across the spectrum of chronic kidney disease

Safety and Adverse Event Profile of Statin Therapy in Chronic Kidney Disease

The administration of statins (HMG-CoA reductase inhibitors) in patients with CKD requires careful clinical oversight, as this population is more susceptible to adverse drug reactions due to impaired renal elimination [11] and frequent polypharmacy[12].While statins are generally considered safe, high-dose regimens may be associated with risks of acute kidney injury (AKI), new-onset diabetes, memory impairment, and rhabdomyolysis[13]

Risk of Acute Kidney Injury (AKI) and Treatment Intensity

Current clinical evidence regarding the relationship between statin potency and renal risk remains a subject of ongoing debate, characterized by conflicting findings from various study types. Pivotal data from the multicenter observational study by the Canadian Network for Observational Drug Effect Studies (CNODES) indicated that, in the general population, patients initiating high-potency statins (such as rosuvastatin ≥10 mg, atorvastatin ≥20 mg, or simvastatin ≥40 mg) faced a 34% higher risk of hospitalization for acute kidney injury (AKI) within the first 120 days compared to those on low-potency regimens. Over a two-year period, this translated to a 15% higher relative risk of renal damage for the high-potency group. However, it is important to note that observational evidence in the specific context of chronic kidney disease (CKD) has been less consistent; some studies suggest that in patients with pre-existing renal impairment, the difference in risk between high and low treatment intensities may be less pronounced or even statistically non-significant. [14] These observational concerns are further clarified by the PLANET I and II randomized controlled trials, which moved beyond general "class effects" to highlight molecule-specific outcomes. These trials revealed that rosuvastatin 40 mg was associated with a statistically significant eGFR decline of approximately 8 ml/min/1.73 m^2 per year and a higher incidence of serious renal events. In stark contrast, atorvastatin 80 mg did not adversely affect eGFR and demonstrated a potential renoprotective effect by reducing proteinuria by 15–20%. This suggests that the generalized renal risk signals observed in large-scale analyses like CNODES might be predominantly driven by the specific pharmacokinetic profile of high-dose rosuvastatin rather than being a universal feature of all high-potency statins [9,10].

Contrasting with the risks of intensive rosuvastatin, the Study of Heart and Renal Protection (SHARP) in which all patients suffered CKD provide a more favorable outlook on statin safety and efficacy. The SHARP trial established the safety of moderate-intensity therapy (simvastatin 20 mg and ezetimibe 10 mg) even in advanced CKD stages, showing no significant increase in adverse renal events.[2]

Rhabdomyolysis as a Severe Complication of Statin Therapy: Clinical Implications for Renal Health

Rhabdomyolysis represents the most severe and life-threatening form of statin-induced muscle injury, characterized by the massive lysis of myocytes and the subsequent release of intracellular contents into the systemic circulation [15]. In clinical practice, rhabdomyolysis is typically diagnosed when serum creatine kinase (CK) levels exceed 11 times the upper limit of normal. While rare—historically linked to numerous reports of fatal outcomes with cerivastatin, which led to its withdrawal—it remains a critical concern for patients with impaired renal function [1].

Pathophysiology of Myoglobin-Induced Nephrotoxicity

The primary threat to the kidneys during a rhabdomyolysis event is the release of myoglobin. This protein causes renal damage through three distinct mechanisms:

- **Mechanical Obstruction:** Myoglobin can precipitate within the renal tubules, forming casts that physically block urine flow [16].
- **Direct Cytotoxicity:** Myoglobin components exert direct toxic effects on the renal tubular epithelial cells, leading to cellular injury [16].
- **Filtration Impairment:** These processes result in abrupt changes to the estimated glomerular filtration rate (eGFR), often precipitating acute kidney injury (AKI)[14].

Clinical Presentation and Risk Factors

Patients typically present with a classic triad of symptoms: severe, diffuse muscle pain (myalgia), profound weakness, and dark, "cola-colored" urine, which is a direct indicator of myoglobinuria.

The risk of developing rhabdomyolysis is significantly influenced by several factors:

- **Drug Interactions:** The concomitant use of statins and fibrates is particularly hazardous in the chronic kidney disease (CKD) population and is generally not recommended due to the high risk of severe muscle toxicity and renal failure.[17]

- **Dose-Dependency:** Higher dosing regimens (e.g., 80 mg/day) and the use of high-potency statins are associated with a stronger signal for both muscle and renal toxicity.[1]
- **Patient Vulnerability:** Individuals with CKD are at an increased risk for these adverse events due to impaired drug elimination and the frequent necessity for polypharmacy.[14]

In summary, while the overall incidence of rhabdomyolysis remains low, its potential to cause irreversible renal damage necessitates vigilant monitoring of CK levels and renal function, particularly when implementing intensive statin regimens or when treating patients with advanced renal dysfunction.

Molecular Mechanisms of Renoprotection

The pleiotropic, or non-lipid-mediated, effects of statins play a fundamental role in the direct protection of renal tissue [3]. At the molecular level, statins inhibit the Rho/ROCK pathway by blocking the isoprenylation of small GTPases [18].

This process leads to increased mRNA stability and expression of renal endothelial nitric oxide synthase (eNOS), which improves the vascular bioavailability of nitric oxide (NO) and optimizes renal microcirculation [19].

Statins also exert potent anti-inflammatory and anti-proliferative effects by suppressing the signaling pathways of nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPK) in renal tubular cells [20]. Furthermore, these agents limit interstitial fibrosis by inhibiting the activity of monocyte chemoattractant protein-1 (MCP-1) and transforming growth factor-beta (TGF-β) [21].

An essential component of renal protection is the antioxidant activity of statins, which involves the scavenging of reactive oxygen species (ROS) and the inhibition of their intracellular production, thereby preventing the apoptosis of epithelial cells [22]. In the specific population of kidney transplant recipients, statins further modulate the immune response by blocking the mevalonate pathway [23]. This mechanism is crucial for limiting the activation, migration, and proliferation of immune cells, as well as the production of inflammatory cytokines. These multifaceted molecular mechanisms allow for the stabilization of renal excretory function and the reduction of proteinuria, independent of cholesterol lowering.

Discussion

The findings presented in this review highlight the complex and multifactorial role of statins in the management of chronic kidney disease. While their cardiovascular benefits are well established, their direct impact on renal outcomes remains less clearly defined and appears to depend on both patient characteristics and the specific statin used.

One of the key observations is the modest but consistent effect of statins on slowing the decline in renal function, as demonstrated in multiple meta-analyses. These findings suggest that statins may contribute to nephroprotection; however, the magnitude of this effect is relatively small and may not be clinically significant in all patient populations. Additionally, reductions in proteinuria, although beneficial, are generally moderate.

Importantly, evidence from randomized controlled trials, particularly the PLANET I and II studies, challenges the concept of a uniform "class effect." The differential outcomes observed between atorvastatin and rosuvastatin suggest that pharmacokinetic and pharmacodynamic properties play a critical role in determining renal effects. High-dose rosuvastatin has been associated with adverse renal outcomes, including declines in eGFR, whereas atorvastatin appears to have a more favorable safety and efficacy profile. This underscores the need for individualized treatment strategies rather than a one-size-fits-all approach.

The safety profile of statins in CKD patients also requires careful consideration. Although generally well tolerated, high-intensity statin therapy has been linked to an increased risk of acute kidney injury, particularly in the early phase of treatment. Furthermore, rare but serious complications such as rhabdomyolysis can lead to severe renal damage, especially in patients with pre-existing kidney impairment. These risks are further amplified by drug interactions and polypharmacy, which are common in this population.

At the molecular level, the pleiotropic effects of statins provide a plausible explanation for their potential renoprotective properties. By inhibiting key inflammatory pathways such as NF-κB and MAPK, reducing oxidative stress, and improving endothelial function through increased nitric oxide bioavailability, statins may mitigate several mechanisms involved in CKD progression. Additionally, their ability to modulate immune responses may be particularly relevant in kidney transplant recipients.

Despite these promising mechanisms, the translation of molecular effects into consistent clinical benefits remains incomplete. This discrepancy may be explained by differences in study design, patient populations, stages of CKD, and statin dosing regimens across trials.

Conclusion

Statins play a fundamental role in reducing cardiovascular risk in patients with chronic kidney disease and should remain a cornerstone of therapy in this population.

While evidence suggests that statins may exert modest renoprotective effects, including slowing the decline in eGFR and reducing proteinuria, these benefits are not uniform across all agents and clinical settings. The variability observed between different statins, particularly in high-dose regimens, highlights the importance of individualized treatment selection.

Overall, statin therapy in CKD should be guided by a careful balance between cardiovascular benefit and potential renal risk. Further large-scale, well-designed randomized controlled trials are needed to better define the differential effects of individual statins and to establish clear clinical guidelines for optimizing therapy in this high-risk population.

Disclosure

Authors do not report any disclosures

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