Dose-Dependent Proteinuria and Renal Dysfunction With High-Intensity Rosuvastatin: Case Report and Literature Review

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ABSTRACT

Introduction: Rosuvastatin is a widely prescribed, high-potency statin for cardiovascular risk reduction. Rare cases of nephrotoxicity have been reported, particularly in patients with reduced kidney function.

Case Presentation: We present a case of a 57-year-old Black man who developed proteinuria and declining renal function following initiation of high-dose rosuvastatin (40 mg daily) after an acute coronary event. After other causes were excluded, the rosuvastatin was gradually reduced to 10 mg, resulting in improvement of renal function and resolution of proteinuria.

Discussion: Prior reports have linked rosuvastatin to acute interstitial nephritis and tubular injury, with recovery following drug discontinuation. This case is notable because the patient's baseline creatinine level was normal prior to rosuvastatin initiation, and recovery occurred with dose reduction rather than complete drug cessation.

Conclusions: Clinicians should consider rosuvastatin-associated nephrotoxicity in patients with unexplained renal dysfunction or proteinuria. Early recognition and dose reduction or drug discontinuation may prevent long-term renal sequelae while maintaining adequate lipid control.

INTRODUCTION

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a key enzyme for hepatic cholesterol synthesis. These lipid-lowering medications are widely prescribed for the management dyslipidemia and for the primary and secondary prevention of cardiovascular events. Statin-induced myopathy and hepatotoxicity are well-recongized side effects; however, statin-associated renal toxicity may be less widely recognized. Two large observational studies found an association between statin use and a significantly increased risk of acute kidney injury, with greater risk observed at higher-potency doses across all statins.[1,2] While a 2013 meta-analysis of 23 trials involving 29 147 participants found that rosuvastatin was not associated with worsening renal function or proteinuria, cases of rosuvastatin-associated nephrotoxicity with rosuvastatin without rhabdomyolysis have been described since its approval by the US Food and Drug Administration.[3-5] Additionally, a 2022 observational study reported that, compared with atorvastatin, rosuvastatin was associated with an increased risk of hematuria, proteinuria, and kidney failure. The risk was greater risk at higher rosuvastatin doses and among patients with lower kidney function (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m2).[6]

We present a case of reversible kidney dysfunction and subnephrotic-range proteinuria in a patient receiving high-dose rosuvastatin that resolved after dose adjustment. This case highlights the importance of timely recognition of this form of renal toxicity and provides an opportunity to compare our findings with the few reported cases of rosuvastatin-related proteinuria without rhabdomyolysis in the literature.

CASE PRESENTATION

A 56-year-old Black man with a history of hypertension, hyperlipidemia, and coronary artery disease was found to have worsening renal function and proteinuria. His cardiovascular history was significant for ST-segment elevation myocardial infarction (STEMI) 1.5 years earlier. The STEMI was complicated by cardiac arrest

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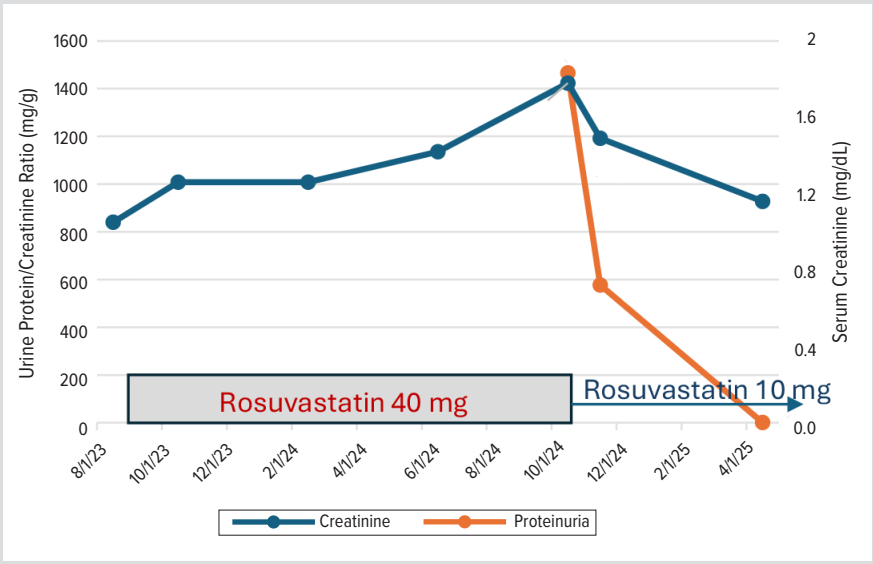
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due to ventricular fibrillation. After resuscitation, he underwent percutaneous coronary intervention, and 6 drug-eluting stents (DES) were placed. He subsequently made a full recovery.

During the index cardiac hospitalization, a lipid panel revealed a total cholesterol level of 209 mg/dL and elevated low-density lipoprotein (LDL) cholesterol level of 139 mg/dL. He was started on rosuvastatin 40 mg daily for secondary prevention in addition to guideline-directed medical therapy. Renal function at that time was normal, with a serum creatinine of 1.0 mg/dL (eGFR 89 ml/min/1.73 m^2, calculated using the 2021 CKD-EPI creatinine equation without a race coefficient). He did have reduced left ventricular systolic function (ejection fraction 40%), and sacubitril-valsartan was initiated, with a subsequent increase in serum creatinine to 1.2 to 1.5 mg/dl.

Figure. Patient's Trend in Kidney Function and Proteinuria Over Time With Rosuvastatin Dosing



Six months after his initial cardiac hospitalization, he presented to the emergency department with chest pain and was found to have a non-STEMI, which required balloon angioplasty, and 1 additional DES was placed.

Six months later, during a routine cardiology follow-up visit, his creatinine level had increased to 1.78 mg/dL (eGFR 44 ml/min/1.73 m^2). He denied recurrent chest pain but reported persistent shoulder and muscle pain. He did not report gross hematuria, flank pain, or dysuria. He denied use of nonsteroidal anti-inflammatory drugs. He was a lifelong nonsmoker and did not drink alcohol or use illicit drugs. Medications included low-dose aspirin, famotidine, metoprolol succinate, sacubitril-valsartan, ticagrelor, rosuvastatin, and as-needed sublingual nitroglycerin.

On examination he was afebrile, his pulse was 52 beats/min, and his blood pressure was 119/69 mm Hg. He was not acutely ill-appearing and was clinically euvolemic. Laboratory testing showed a normal complete blood cell count. Urinalysis showed a specific gravity of 1.010, pH 6.5, trace protein, +1 blood, and negative leukocyte esterase and nitrites. Automated microscopic examination of the urine showed no white blood cells, red blood cells, bacteria, or squamous epithelial cells. Creatine kinase (CK) was mildly elevated at 216 U/L (reference range 50-170 U/L). The urine protein-creatinine ratio was markedly elevated at 1467 mg/g (reference range, < 150 mg/g). A 24-hour total urine collection revealed an elevated total protein excretion of 990 mg. Urine protein electrophoresis was positive for albumin and various globulin fractions, but no monoclonal protein was identified. Renal ultrasound showed no abnormalities of the kidneys, ureters, or bladder.

Given his symptoms and laboratory abnormalities, sacubitril-valsartan was discontinued, and the rosuvastatin was reduced to 30 mg daily. Repeat testing showed an improvement in creatinine to 1.49 mg/dL, but CK remained elevated at 260 U/L. Rosuvastatin was further reduced to 10 mg daily, which resulted in normalization of the serum CK level. Six months after the initial laboratory abnormalities, while remaining on rosuvastatin 10 mg daily, the patient's renal function had significantly improved, with a serum creatinine level of 1.16 mg/dL (eGFR 72 ml/min/1.73 m^2). Urinalysis was negative for blood and protein, and urine protein-creatinine ratio was undetectable because of the absence of urinary protein. A fasting lipid profile showed a total cholesterol level of 131 mg/dL, triglyceride 56 mg/dL, high-density lipoprotein cholesterol 86 mg/dL, and LDL cholesterol 34 mg/dL.

DISCUSSION

Rosuvastatin at high-intensity doses (20-40 mg daily) has the potential to cause nephrotoxicity, as was demonstrated in our patient, who developed marked proteinuria and a concurrent decline in renal function, both of which improved after rosuvastatin dose reduction without evidence of new chronic kidney disease. Our case is consistent with previously published reports of rosuvastatin-associated nephrotoxicity (Table). Previous cases involved older adults receiving rosuvastatin doses of 20 mg daily or greater who developed subnephrotic-range proteinuria without rhabdomyolysis or alternative etiologies of renal disease. Our patient developed musculoskeletal symptoms and mild elevation in serum CK. Among previously reported cases, 2 patients (66%) had either myalgias or elevated muscle enzyme levels, and 1 patient had no clinical or laboratory evidence of muscle injury. Drug cessation led to resolution of proteinuria and recovery of renal function in all cases. Subsequent lipid-lowering therapy was achieved with an alternative statin in all previously reported

Table. Case Reports of Nephrotoxicity Related to Rosuvastatin Without Rhabdomyolysis

Report	Age (years)/ Sex	Dose (mg)	Duration of Statin Therapy Before Renal Injury (months)	Peak Serum Creatinine	Proteinuria (g/g)	Musculoskeletal Symptoms or Muscle Enzyme Elevation	Additional Finding	Outcomes With Dose Reduction or Rosuvastatin Discontinuation
van Zyl-Smit et al, 2004[4]	58/M	80	19	1.58 mg/dL	UPC 1.6	None	Urine microscopy: granular casts Kidney biopsy: acute and chronic TIN EM-increased size of many mitochondria of the proximal tubules	Resolution of proteinuria, no CKD
Ward et al, 2017[5]	53/F	40	15	1.86 mg/dL	UPC 1.8	CK 301 (ref range <195 U/L)	Urine microscopy: granular casts, isomorphic RBCs Kidney biopsy: proximal tubular toxicity, interstitial edema	Resolution of proteinuria, no CKD
Goyal et al, 2025[13]	70/F	20	3	0.70 mg/dL	UAC 0.3	+Myalgias	NR	Resolution of proteinuria

Abbreviations: CKD, chronic kidney disease; EM, electron microscopy; NR, not reported; TIN, tubulointerstitial nephritis; UAC, urine albumin/creatinine ratio; UPC, urine protein/creatinine ratio.

patients. However, our patient was able to continue rosuvastatin at a moderate-intensity dose of 10 mg daily, which maintained his LDL cholesterol level at < 70 mg/dL, a recommended target following acute coronary syndrome.[7]

The renal injury associated with rosuvastatin appears predominantly tubular in nature. Urine microscopy in 2 reported cases revealed granular casts, and renal biopsy findings have demonstrated tubular damage characterized by luminal ectasia, loss of brush border, variegated cytoplasmic staining, and shedding of renal tubular cells into the tubular lumen.[4,5] It has been hypothesized that inhibition of HMG-CoA reductase by rosuvastatin interferes with receptor-mediated endocytosis in proximal tubular cells, leading to proteinuria.[8] Mitochondrial toxicity related to oxidative stress has also been implicated, based on the finding of enlarged mitochondria in renal tubular cells on electron microscopy.[4]

This case highlights the differential diagnosis clinicians should consider in patients with proteinuria or renal dysfunction while receiving rosuvastatin. Rhabdomyolysis is an uncommon cause of statin-related renal toxicity that can be severe enough to require kidney replacement therapy. Myoglobin is a low-molecular-weight protein that is freely filtered by the glomerulus and is normally present urine only in very low concentrations. Elevated serum myoglobin levels during rhabdomyolysis result in increased filtration of myoglobin into the urinary space, causing direct tubular injury. The macroscopic appearance of the urine in rhabdomyolysis is characteristically reddish-brown to dark brown and is often described as tea- or cola-colored. Because myoglobin cross-reacts with the peroxidase on urine dipstick testing, urinalysis in patients with rhabdomyolysis is typically positive for hemoglobin despite a negative microscopic examination for visible red blood cells (RBCs).[9] Our patient's urinalysis demonstrated this characteristic discrepancy; however, rhabdomyolysis was not the cause of his kidney dysfunction because CK levels in rhabdomyolysis are typically more than 5 times the upper limit of normal, with levels > 5000 U/L are associated with an increased risk of acute kidney injury.[10]

Drug-induced acute interstitial nephritis (AIN) should also be considered as a possible intrinsic cause of kidney injury when renal function worsens. Statins are generally not regarded as a high-risk medication class for AIN. In the case described by van Zyl-Smit et al, kidney biopsy demonstrated evidence of acute and chronic interstitial nephritis.[4] Additionally, 1 case of biopsy-confirmed AIN attributed to rosuvastatin has been reported. The patient was an 83-year-old man with chronic kidney disease who developed significant worsening of renal function and proteinuria (500 mg/day) after 3 weeks of exposure to rosuvastatin. Following kidney biopsy diagnosis, drug discontinuation, and a 4-week tapering course of prednisolone, renal function returned to baseline.[11] A high index of suspicion is necessary when renal dysfunction occurs in the context of new drug exposures. Prompt withdrawal of the offending medication may improve renal function. In more severe cases or in patients with persistent renal dysfunction despite drug cessation, glucocorticoid therapy may attenuate renal damage.

As in our patient, who was also receiving guideline-directed medical therapy (GDMT) for ischemic heart disease and heart failure with reduced ejection fraction, clinicians must consider the impact of medications other than statins on renal function. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors (ARNIs), sodium-glucose cotransporter-2 inhibitors, and mineralocorticoid receptor antagonists all have hemodynamic effects at the glomerular level. An acute decline in eGFR up to 50% with multidrug therapy may be tolerable in the absence of hyperkalemia or symptomatic hypotension because cardiorenal outcomes are improved with GDMT.[12] Our patient's creatinine level increased from 1.0 mg/dL to 1.2 to 1.5 mg/dL after initiation of an ARNI following

acute coronary syndrome. The ARNI was discontinued because of worsening renal function after recovery of left ventricular function. This resulted in partial improvement in GFR, as would be expected following withdrawal of an angiotensin receptor blocker; however, further improvement in renal function and resolution of proteinuria did not occur until the rosuvastatin dose was further reduced.

Our case adds to the growing literature on rosuvastatin-associated nephrotoxicity. Clinicians should remain vigilant for this important adverse effect, which may manifest as proteinuria with variable accompanying findings, including mild muscle injury, hematuria, or declining renal function. Patients receiving high-potency doses (≥ 20 mg daily) and those with preexisting chronic kidney disease (eGFR < 30 mL/min per 1.73 m^2) appear to be particularly vulnerable. Accordingly, rosuvastatin should be reduced to 5 to 10 mg daily in patients with eGFR < 30 mL/min per 1.73 m^2 to avoid nephrotoxicity. In suspected cases, clinicians should promptly obtain assessment of renal function, muscle enzyme levels, urinalysis, and quantification of proteinuria. Renal biopsy and additional serologic testing may be warranted in selected cases. However, rosuvastatin-associated proteinuria and renal injury appear to resolve with rosuvastatin cessation or dose reduction. Long-term renal outcomes following cases of rosuvastatin-associated renal injury are currently unknown. For patients who previously experienced rosuvastatin nephrotoxicity, ongoing lipid management with reduced-dose rosuvastatin or a less potent statins may be indicated to achieve lipid goals while reducing future cardiovascular risk.

CONCLUSIONS

This case highlights the importance of considering rosuvastatin-associated nephrotoxicity in patients with unexplained renal dysfunction or proteinuria. Early recognition combined with timely dose adjustment or discontinuation of rosuvastatin may facilitate renal recovery and reduce the risk of long-term kidney damage while maintaining satisfactory lipid control.

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