Open Access Epidemiology and Prevention

Journal of Renal Endocrinology

J Ren Endocrinol 2024;10:e25171.
https://www.jrenendo.com
doi: 10.34172/jre.2024.25171

Nickan Research Institute

Rapamycin-associated nephropathy; a short look at the new findings

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Abstract
Histopathologic lesions associated with rapamycin-associated nephropathy (RAN) include collapsing focal segmental glomerulosclerosis, delayed graft function with cast nephropathy, and acute renal injury with increased intratubular cast formation.
Keywords: Rapamycin, Glomerular filtration rate, Sirolimus, Rapamycin-associated nephropathy, Cast nephropathy, Acute renal injury
Citation: Nasri H, Razmjouei S, Saeifar S. Rapamycin-associated nephropathy; a short look at the new findings. J Ren Endocrinol. 2024;10:e25171. doi: 10.34172/jre.2024.25171.

Introduction

Rapamycin-associated nephropathy (RAN) is a condition that can occur in some patients who receive immunosuppressant drug rapamycin (sirolimus). Rapamycin inhibits the mammalian target of the rapamycin (mTOR) pathway, which plays a big role in cell synthesis and metabolism (1). Rapamycin can also have other effects on the body, such as inhibiting the mTORC2 pathway, which can result in diabetes-like symptoms, including decreased glucose tolerance and insulin insensitivity. It may also increase the risk of type 2 diabetes (2). Rapamycin-associated nephropathy is characterized by proteinuria, decreased kidney function, and histological changes in the kidney tissue. Researchers believe that the drug's effect on the mTOR pathway, which plays a role in cell growth and proliferation (3), is responsible for the mechanism of RAN. Risk factors for RAN include high doses of rapamycin, prolonged use, and certain genetic factors (4). The histopathologic lesions of RAN reflect a complex interplay between rapamycin-induced cellular stress, immune dysregulation, and vascular injury (5). Histopathological examination of kidney biopsies from these patients reveals findings such as interstitial fibrosis, tubular atrophy or dilation, glomerulosclerosis, and tubulointerstitial inflammation (6). Additionally, the morphologic lesions of the glomeruli in this condition cause/lead to collapsing focal segmental glomerulosclerosis. This is characterized by segmental proliferation of glomerular epithelial cells along with glomerular tuft collapse (7). Moreover, cast nephropathy is associated with tacrolimus plus rapamycin administration and is considered intratubular cast formation (8,9). Rapamycin can cause a specific pattern of acute renal injury, which is characterized by increased intratubular cast formation in protein overload nephropathy (8). In addition to these morphologic lesions, there may be evidence of inflammation and injury to the blood vessels in the kidney. This can include infiltration of immune cells, endothelial cell injury, and thrombosis. The severity of these lesions can vary depending on the duration and dose of rapamycin exposure, as well as individual risk factors for RAN (10,11). These changes are characteristic of chronic allograft rejection after transplantation or other forms of renal injury. Previous studies showed that it causes autophagosomes to accumulate in kidney tubular epithelial cells. Causing oxidative stress and apoptotic death of cells and resulting in fibrosis and tubulointerstitial atrophy (12). Risk factors include high dose, long-term use, diabetes, hypertension, obesity, age >60 years, and Black race. The diagnosis is based on histopathology showing interstitial fibrosis and tubular atrophy with a decline in glomerular filtration rate. The severity of these lesions can vary depending on the duration and dose of rapamycin exposure/usage, as well as individual risk factors for RAN (13,14). Diagnostic criteria may include the presence of proteinuria and/or acute renal injury, which can be indicated by elevated serum creatinine levels or decreased glomerular filtration rate. Management includes

Received: 7 August 2024, Accepted: 18 September 2024, ePublished: 7 October 2024

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Implication for health policy/practice/research/ medical education

Rapamycin is a mammalian target of rapamycin (mTOR) inhibitor that can cause toxicity in the kidneys, leading to a condition known as rapamycin-associated nephropathy. Rapamycin negatively affects kidney function and intratubular cast formation in protein overload nephropathy.

dose reduction or discontinuation, corticosteroids, angiotensin-converting enzyme inhibitors, and other immunosuppressants (15). The prognosis depends on the extent of damage and glomerular filtration rate decline, coupled with/led to the end-stage renal disease possible if uncontrolled (10,16).

Conclusion

Rapamycin inhibits the mTOR pathway and plays a key role in cell growth, proliferation, and metabolism. The most common morphologic lesions seen are tubulointerstitial necrosis, glomerular atrophy, interstitial fibrosis, and tubular dilatation. Other changes include vascular rarefaction, inflammation, and podocyte injury. These changes may be accompanied by proteinuria and hypertension. This inhibition can lead to decreased protein synthesis and cell proliferation within cells, which may contribute to the development of nephrotoxicity. RAN has been reported in both acute and chronic forms with different clinical presentations depending on the duration of exposure to rapamycin therapy.

Authors' contribution

Conceptualization: Hamid Nasri, Sanam Saeifar.
Data curation: Soha Razmjouei, Sanam Saeifar and Hamid Nasri.
Resources: Soha Razmjouei, Sanam Saeifar.
Validation: Hamid Nasri, Sanam Saeifar.
Writing–original draft: Hamid Nasri, Sanam Saeifar.
Writing–review and editing: Soha Razmjouei, Sanam Saeifar and Hamid Nasri.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

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

Funding/Support

None.

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