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# Nephrotoxicity of checkpoint inhibitors; a current challenge

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## ABSTRACT

Immune checkpoint inhibitors work by blocking the “checkpoint” mechanism that tumors use to hide from the immune system, therefore also weakening the immune system. Consequently, checkpoint inhibitors can cause autoimmune reactions, resulting in adverse effects. Prompt identification and management of adverse effects are critical for patients under checkpoint inhibitor therapy due to the potential severity and unpredictability of these immune-related adverse events.

**Keywords:** Checkpoint inhibitors, Nephrotoxicity, Acute kidney injury, Immune complex-mediated glomerulonephritis, Checkpoint inhibitor-associated nephrotoxicity, Hypertension, Proteinuria, Hematuria, Acute renal failure

### Implication for health policy/practice/research/medical education:

Checkpoint inhibitors can cause various adverse effects that need close monitoring and management, as prompt identification and proper management are critical. Patients under checkpoint inhibitor therapy should undergo regular monitoring and close communication with their clinical team to identify the signs and symptoms of any adverse reactions that may arise and manage them effectively.

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## Introduction

Drug-induced kidney toxicity develops following proximal renal tubular damage and acute tubular necrosis, tubular obstruction by crystals or casts comprising drugs or even crystals, and after interstitial nephritis stimulated by drugs and their metabolites (1). Immune checkpoint inhibitors, such as PD-1 and PD-L1 inhibitors, have emerged as effective immunotherapies in treating solid tumors by breaking the immune tolerance to these tumors (2). However, these immunotherapies have been linked to various adverse effects, including nephrotoxicity. Nephrotoxicity of immune checkpoint inhibitors refers to the potential damage or dysfunction of the kidney's function, leading to acute kidney injury, renal impairment, or other forms of kidney damage. The incidence and severity of checkpoint inhibitor-induced nephrotoxicity vary across different cancers and regimens (3). This narrative review summarizes the available literature on checkpoint inhibitor-associated nephrotoxicity, including its mechanism, clinical presentation, and management.

## Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Google Scholar, Scopus, Directory of Open Access Journals (DOAJ) and Embase using different keywords such as nephrotoxicity, acute kidney injury, include immune complex-mediated glomerulonephritis, immune checkpoint inhibitor-associated nephrotoxicity, hypertension, proteinuria, hematuria, acute renal failure, combination immunotherapy. Immune checkpoint inhibitor, acute interstitial nephritis, Meta-analysis, and glomerulonephritis.

## Characteristics of immune checkpoint inhibitors

Immune checkpoint inhibitors are effective immunotherapies for treating various solid tumors by breaking immunoresistance. However, like any medication, immune system modulation can cause adverse effects, and immune checkpoint inhibitors are not exempted (4,5). The most commonly reported adverse effects of immune checkpoint inhibitors are immune-related adverse events.

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They occur when the immune system mistakenly targets normal tissue, leading to an over-amped autoimmune response (6).

### **Adverse effects of immune checkpoint inhibitors**

The severity of immune-related adverse events can range from mild to life-threatening, and the symptoms' onset may vary, depending on the immune-related system affected (7). Skin toxicity is among immune checkpoint inhibitors' most common and early-onset adverse effects. It includes rash, pruritus, vitiligo, and Stevens-Johnson syndrome (8). These agents can also affect the tissues lining the gastrointestinal tract, resulting in gut inflammation or mucositis symptoms, leading to diarrhea, colitis, nausea, vomiting, gastritis, and anorexia (9,10). Moreover, immune checkpoint inhibitors can negatively affect the thyroid gland and pituitary gland, which can lead to hypothyroidism and thyroiditis. In rare cases, immune checkpoint inhibitors can cause insulin-dependent diabetes or disruption in other hormone-synthesis pathways (11,12). Checkpoint inhibitors can also cause severe liver damage, including drug-induced liver injury, hepatic necrosis, autoimmune hepatitis, and various liver function abnormalities (13,14). Likewise, these compounds can lead to myocarditis or heart failure, leading to reduced heart function, arrhythmia, or sudden cardiac death (15). Meanwhile, immune checkpoint inhibitor therapy can negatively affect the nervous system, resulting in peripheral neuropathy, myositis, or other neurological effects (16). Finally, immune checkpoint inhibitor therapy has been linked to various forms of kidney damage, including acute kidney injury, acute interstitial nephritis, and glomerulonephritis (3,17).

### **Mechanism of immune checkpoint inhibitor-induced kidney toxicity**

Various studies have proposed different mechanisms for how immune checkpoint inhibitors induce nephrotoxicity, some of which include:

#### ***Immune complex-mediated glomerulonephritis***

Immune checkpoint inhibitor therapy can cause autoimmunity by producing immunoglobulin G (IgG) immune complexes against specific antigens, which may form and deposit in the kidney's glomerular basement membrane, leading to immune-complex-mediated glomerulonephritis (17,18).

#### ***T-Cell-mediated inflammatory processes***

Immune-mediated processes involved in regulating T-cell activity, including immune checkpoint ligands' suppression, play a vital role in maintaining renal homeostasis. Under immune checkpoint inhibitor therapy, T-cell activation may lead to inflammation and toxicity in the kidneys (17,19).

### ***Direct renal toxicity***

Immune checkpoint inhibitors may also cause direct toxicity to kidneys' intrinsic cells, leading to acute interstitial nephritis (3).

### **Clinical presentation of immune checkpoint inhibitor-induced nephrotoxicity**

Checkpoint inhibitor-induced nephrotoxicity can manifest in different forms, including hypertension, proteinuria, hematuria, and acute renal failure (20,21).

### ***Management of immune checkpoint inhibitor-induced nephrotoxicity***

The initial treatment of immune checkpoint inhibitor-induced nephrotoxicity is discontinuing the therapy and performing supportive care measures (22,23). Other general measures include correcting electrolyte imbalances, dehydration, or acidosis. Specific immunosuppressive therapy may also be necessary for specific disease scenarios. Treatments usually involve the use of systemic corticosteroids. However, sometimes adding rituximab or another cyclophosphamide may be necessary in refractory cases of immune-complex-mediated glomerulonephritis (18,24,25).

### **Literature review on Kidney adverse events of immune checkpoint inhibitors**

Hu et al in a study on a total of 30,602,758 reports from the database, with 4578 reports for immune checkpoint inhibitors -associated kidney adverse events. Kidney adverse events were more frequently reported in the anti-PD-1/PD-L1 versus anti-CTLA-4 monotherapy groups. Likewise, they were more commonly detected in immune checkpoint inhibitor poly-therapy other than the monotherapy group. Notably, immune checkpoint inhibitors and chemotherapy strategies reported more nephrotoxicity than single immune checkpoint inhibitor administration while exhibiting lower fatality outcome rates. Notably, acute kidney injury and renal failure were the top two most commonly reported immune checkpoint inhibitor-associated Kidney adverse events, which were also detected with the most fatality outcome rates (26). Recently, Qu et al identified a total of 7,204 reports of kidney adverse events. They showed that kidney adverse events were most commonly reported for nivolumab in 46.84% of cases. In the clinical application of immune checkpoint inhibitors, attention should be directed towards male patients with acute renal failure, nephritis, and other nephrotoxic adverse events since the administration of immune checkpoint inhibitors is likely to worsen their condition (27). In a recent meta-analysis, Tan et al studied the renal toxicity of combination therapy by immune checkpoint inhibitor in advanced kidney cell carcinoma cases. This meta-analysis was conducted on seven randomized controlled trials consisting of 5239 patients. This study showed that immune checkpoint

inhibitor-combination therapy shows more kidney toxicity than sunitinib in advanced kidney cell carcinoma (28).

### Conclusion

Immune checkpoint inhibitor-induced nephrotoxicity is a known immune-related adverse event that can lead to acute kidney injury, proteinuria, hematuria, and renal failure. The mechanisms of immune checkpoint inhibitor-induced nephrotoxicity may include immune complex-mediated glomerulonephritis, T-cell-mediated inflammatory processes, and direct renal toxicity. Prompt identification and management of the condition are critical to prevent further injury and harm to the patient. General measures and immunosuppressive therapy are under consideration for treating immune checkpoint inhibitor-induced nephrotoxicity. Future studies are necessary to understand better the mechanism involved in these events so that the impact of these complications can be minimized and managed most effectively.

### Authors' contribution

**Conceptualization:** Leila ALem, Ali Azarpey, Samaneh Zandifar.

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### Conflicts of interest

The authors declare that they have no competing interests.

### Ethical issues

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