J Prev Epidemiol. 2026;11(2):e39332 Review

doi 10.34172/jpe.39332 Journal of Preventive Epidemiology http jprevepi.com

Molecular mechanisms driving renal dysfunction following burn injury; implications for therapeutic targeting

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Received: 8 Feb. 2026
Revised: 20 May 2026
Accepted: 5 Jun. 2026
ePublished: 29 Jun. 2026

Keywords: Burn, Cytokines, Acute kidney injury, Rhabdomyolysis, Hypertension, Hypovolemia, Reactive oxygen species, Burn injury

Abstract

Burn injuries trigger a profound systemic inflammatory response marked by the excessive release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), into the bloodstream. These cytokines play pivotal roles as mediators of inflammation, orchestrating complex cellular and molecular events that have widespread effects on various organs, particularly the kidneys. Elevated levels of these inflammatory mediators are strongly implicated in the onset of systemic inflammatory response syndrome (SIRS), a condition characterized by extensive inflammation that can severely impair renal function. Likewise, TNF-α, among these cytokines, has been shown to induce renal vasoconstriction, which reduces renal blood flow and diminishes the glomerular filtration rate. This vasoconstriction leads to renal ischemia, which aggravates damage to tubular epithelial cells, thereby heightening the risk of acute kidney injury (AKI) following burn trauma. Simultaneously, IL-1 and IL-6 contribute to endothelial dysfunction by increasing vascular permeability, facilitating the extravasation of plasma components into interstitial spaces. This fluid shift results in hypovolemia and a decrease in effective circulating blood volume, further compromising renal perfusion. Taken together, these cytokine-driven mechanisms create a vicious cycle of inflammation, vascular dysfunction, and renal injury. Understanding the roles of TNF-α, IL-1, and IL-6 in modulating renal hemodynamics and promoting tubular injury provides critical insights for developing targeted therapeutic strategies aimed at mitigating AKI in burn patients. Effective management of this inflammatory cascade is essential to improve renal outcomes and overall survival in individuals suffering severe burn injuries.

Citation: Khavanin A, Mohajerian A, Rafati Navaei A. Molecular mechanisms driving renal dysfunction following burn injury; implications for therapeutic targeting. J Prev Epidemiol. 2026;11(2):e39332. doi: 10.34172/jpe.39332.

Introduction

Burn injuries are not only associated with immediate local tissue damage but also entail systemic complications, among which acute kidney injury (AKI) holds significant concern due to its high prevalence and impact on patient outcomes (1). The epidemiology of renal involvement in burn patients reflects notable variations based on factors such as burn severity, patient demographics, and coexisting comorbidities (2). Recent studies indicate that the incidence of AKI among burn patients can range widely, with various reports (3). The likelihood of AKI significantly increases amongst patients with severe burns. Specifically, individuals with burns covering more than 20% of total body surface area (TBSA) demonstrate a heightened risk, with some studies reporting AKI rates exceeding 50% in this population (4). Additionally, other research has shown that approximately 36% of severely burned patients develop AKI, with the condition appearing in either early or late forms following injury (3). The variation in the incidence often reflects the methodologies adopted in identifying AKI, whether through serum creatinine levels, urine output, or historically-derived classification systems like the KDIGO criteria (5). Furthermore, epidemiological aspects such as patient demographics—including age, sex, and underlying health conditions—must be acknowledged when evaluating the incidence and effects of kidney injury resulting from burns (6). Multiple factors contribute to the risk of developing AKI in burn patients, Primary among them is the extent of the burn (3). Studies have established that larger TBSA burns correlate with elevated incidences of AKI due to fluid loss, hypovolemia, and the accompanying systemic inflammatory response (7). In addition, older age has been indicated as a significant risk factor, with elderly burn victims more prone to renal dysfunction and subsequent complications (8).

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Key point

Hypovolemia is a key mechanism contributing to renal injury in burn victims, primarily resulting from significant fluid loss through the damaged skin surfaces. In the acute phase following a burn injury, especially in cases where burns cover more than 20% of the total body surface area (TBSA), extensive fluid shifts occur from the intravascular compartment into the interstitial space due to increased capillary permeability and loss of skin barrier function. This fluid loss leads to a reduction in intravascular volume, causing hypotension and decreased renal perfusion pressure. The resulting hypoperfusion of the kidneys can trigger acute kidney injury (AKI) by impairing glomerular filtration and promoting ischemic damage to renal tissues. Additionally, inflammatory mediators released during the burn injury may exacerbate renal vasoconstriction and further compromise kidney function. Effective early fluid resuscitation is critical in managing these patients to restore circulating blood volume, improve renal blood flow, and prevent the progression of renal injury.

Meanwhile, comorbidities such as diabetes, hypertension, and pre-existing renal disease further strengthen the risk of renal injury in burn patients (9). Diabetic burn victims, for example, face an increased probability of renal impairment due to underlying diabetic nephropathy, resulting in complications post-injury (10). Likewise, hypertension and renal diseases further contribute to a deteriorating renal function trajectory in the context of burn injuries, accentuating the need for vigilant monitoring and management strategies to address these pre-existing conditions (11). Moreover, the development of AKI can occur as a result of factors related to the management of burns, such as fluid resuscitation practices (3). Inadequate or excessive fluid resuscitation can lead to both poor renal perfusion and fluid overload conditions that compromise kidney function (1,12). The recognition that the choice of resuscitation protocols, such as the Parkland formula, can influence outcomes is crucial, as it underscores the importance of tailored hydration strategies in preventing renal complications (13). Previous investigations detected that, AKI significantly increases hospital length of stay, healthcare costs, and the likelihood of requiring renal replacement therapy, thereby amplifying morbidity and mortality rates among affected individuals (3,14). Likewise, factors such as inhalation injury, rhabdomyolysis, and the requirement for mechanical ventilation can further compound the risk of renal impairment (15). The phenomenon of "fluid creep," where patients receive excessive IV fluids beyond recommended levels, can lead to abdominal compartment syndrome and renal dysfunction as a consequence of intra-abdominal pressure exceeding safe limits (16). Furthermore, patients who experience AKI may be at a heightened risk for long-term chronic kidney disease, affecting their post-discharge quality of life (17). The association between AKI and increased mortality is particularly pronounced in patients with severe burns (18). It is noteworthy to member that, burn patients with AKI face substantially higher mortality compared to those without AKI (3). In This review, we therefor sought to examine the incidence of AKI in burn victims, the risk factors influencing its development, and its implications for morbidity and mortality.

Search strategy

For this narrative review, we conducted a literature search across multiple databases, including PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase, using a variety of relevant keywords such as 'burn', 'rhabdomyolysis', 'cytokines', 'acute kidney injury', 'hypertension', 'burn injury', 'hypovolemia' and 'reactive oxygen species'.

Mechanism of post-burn renal injury

Following burn injuries, renal dysfunction at the onset is often attributable to hypovolemia, resulting from substantial fluid loss associated with extensive burns (19). The loss of fluid through damaged skin dramatically reduces circulating blood volume, which critically diminishes renal perfusion (20). When fluid resuscitation is insufficient or delayed, the intravascular volume remains inadequate to sustain proper kidney blood flow, leading to ischemia in renal tissues (1,21). This ischemic insult primarily affects renal tubular cells, causing acute tubular necrosis, which is a major pathological feature leading to AKI in burn patients (22). The extent of fluid loss varies widely depending on the burn size and depth, but burns involving a large proportion of TBSA are particularly high risk, with AKI incidence reported to be significantly elevated in such individuals (3). This condition significantly worsens prognosis and is associated with elevated mortality rates, underscoring the importance of early and aggressive fluid management to prevent renal hypoperfusion (19). In addition to hypovolemia, the burn injury triggers a complex systemic inflammatory response that further exacerbates renal damage (19). Burn trauma causes widespread tissue destruction, releasing danger signals that activate immune responses and lead to the secretion of inflammatory cytokines (23). Key inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) are rapidly released into the circulation (24). These cytokines promote endothelial activation and increase vascular permeability, resulting in fluid leakage from blood vessels to the interstitial space (25). Consequently, edema develops, further compromising effective circulating volume and renal perfusion (26). Beyond hemodynamic effects, these inflammatory cytokines induce direct injury by promoting oxidative stress within renal tubular cells (27). The activation of oxygen free radicals leads to lipid peroxidation, protein denaturation, and DNA damage in tubular epithelial cells (28). This oxidative injury amplifies the severity of acute tubular necrosis and impairs tubular cell regeneration, a crucial process needed for kidney repair and functional recovery (29,30). Moreover, extensive muscle damage often

accompanies severe burn injuries, releasing substantial amounts of intracellular proteins into the bloodstream, including myoglobin and hemoglobin (31,32). Myoglobin, in particular, poses a significant nephrotoxic threat (33). Elevated plasma myoglobin can accumulate and precipitate within the renal tubules, causing tubular obstruction and direct cytotoxicity (34). This process compounds the risk for AKI by inducing intra-tubular cast formation and tubular epithelial injury (35). The presence of these denatured proteins also triggers vasoconstriction of the afferent arterioles, decreasing glomerular filtration rate and worsening renal ischemia (36). The combination of protein-induced tubular obstruction and vasoconstriction establishes a feedback loop that intensifies renal stress and cellular injury (34). As such, rhabdomyolysis following burn trauma is a recognized precipitant of severe kidney damage and is managed clinically with volume expansion and renal protective strategies (37). In parallel, the systemic inflammatory response syndrome (SIRS) often develops in the acute phase following major burns (23,24). SIRS involves a widespread inflammatory reaction and often heralds the onset of sepsis (38). The immunosuppressive state induced by burns increases susceptibility to infections, which may rapidly progress from localized to systemic infection (24,39). When sepsis ensues, it further aggravates renal injury through a multifaceted mechanism involving persistent inflammation, microvascular dysfunction, and altered coagulation pathways (12). Inflammatory cascades in sepsis lead to endothelial damage, impaired microcirculation, and tissue hypoxia (40,41). Furthermore, activation of coagulation results in microthrombi formation inside the renal vasculature, mechanically obstructing blood flow and exacerbating ischemic injury (42,43). These changes manifest clinically as multi-organ dysfunction syndrome, in which the kidney is often one of the first organs to fail (44). The presence of septic AKI is associated with a steeper decline in renal function, poorer outcomes, and greater challenges in clinical management (45). Several studies found that, oxidative stress plays a pivotal role in the progression of renal injury after burns (46). The excessive production of reactive oxygen species (ROS) overwhelms cellular antioxidant defenses, causing direct damage to renal tubular epithelial cells (28). Reactive oxygen species induces lipid membrane peroxidation, protein oxidation, and mitochondrial dysfunction, driving apoptosis and necrosis within tubular cells (30, 47). Moreover, oxidative stress interferes with important intracellular signaling pathways, thereby impairing cellular homeostasis and exacerbating inflammation (48). The continuous production of ROS sets off a vicious cycle, maintaining pro-inflammatory signaling and sustaining tissue damage within the renal interstitium (28,49). Over time, this cascade can contribute to tubulointerstitial fibrosis, a chronic pathological hallmark that compromises kidney structure and function long after the initial injury (50). Such fibrosis reduces nephron viability and disrupts normal electrolyte and water reabsorption, contributing to persistent renal impairment in burn survivors (20,51). Meanwhile, endothelial dysfunction is another critical factor in burn-related renal injury (19). Normally, renal endothelial cells regulate vascular tone and maintain glomerular filtration through the release of vasodilators such as nitric oxide (NO) (52,53). Following burns, inflammatory cytokines suppress NO synthesis and bioavailability, leading to sustained vasoconstriction of renal arterioles (27). TNF-α and other mediators induce endothelial activation, promoting leukocyte adhesion and increasing vascular permeability, further disrupting renal hemodynamics (54,55). Reduced NO levels elevate renal vascular resistance, aggravating ischemic conditions in the kidney (56). Moreover, these dysfunctional endothelial cells contribute to a pro-thrombotic state, facilitating the formation of microvascular thrombi within renal capillaries and post-capillary venules (57). The occlusion of these microvessels impairs perfusion and nutrient delivery to renal tissue, accelerating tubular cell injury and necrosis (58). Moreover, immune cell infiltration adds another layer of complexity to renal damage following burns (31,59). Neutrophils and macrophages are recruited to injured kidney tissue in response to inflammatory signals (60). These cells not only contribute to pathogen clearance but also produce reactive oxygen species, proteases, and pro-inflammatory cytokines that intensify local tissue damage (61). Macrophage polarization plays a crucial role in the inflammatory response and repair processes (62). The balance between M1 macrophages, which promote inflammation, and M2 macrophages, involved in tissue resolution and repair, influences the outcome of renal injury (63,64). In burn patients, persistent dominance of M1 macrophages sustains inflammation and hinders recovery, whereas inadequate M2 polarization limits regenerative capacity (65). This dysregulated immune response delays tissue healing, leading to prolonged renal dysfunction and fibrosis (66). The interplay between systemic inflammation, endothelial dysfunction, tubular injury, and immune cell activity establishes a complex scenario in which renal recovery is severely compromised after burn trauma (67). Patients in SIRS or sepsis states are particularly vulnerable to renal hypoperfusion and ischemic injury (68). The resulting AKI contributes significantly to the overall severity of illness and is closely linked to increased length of intensive care stay, higher rates of mechanical ventilation, and mortality (12). Furthermore, the late phase of AKI often occurs in association with sepsis and multiple organ dysfunction syndrome, complicating both clinical management and prognosis (45). Identification the molecular mechanisms underlying burn-induced renal injury has fostered exploration of therapeutic strategies aimed at modulating inflammation and oxidative stress to

preserve kidney function (20). For instance, antioxidants and anti-inflammatory agents are being investigated to attenuate ROS-mediated tubular damage and suppress deleterious cytokine release (69). Additionally, maintaining adequate intravascular volume during fluid resuscitation remains a critical cornerstone to prevent initial hypovolemia and ischemic insult (70). Strategies targeting endothelial stabilization and preventing microvascular thrombosis have also gained attention to improve renal perfusion and reduce ischemic injury (71, 72). Recent studies points to the importance of early detection and monitoring of renal biomarkers in burn patients to identify those at risk of developing AKI (73, 74). Biomarkers such as neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and cystatin C have shown promise in detecting subclinical tubular injury before overt declines in glomerular filtration rate occur (73). Early identification of renal impairment allows for timely interventions to mitigate progression and improve outcomes (75). Furthermore, preventing sepsis through infection control measures and immunomodulatory therapies is critical to reducing the incidence of late-onset AKI in burn patients (76).

Long-term outcome

Hypovolemia is a major mechanism leading to renal injury in burn victims, primarily caused by substantial fluid loss through damaged skin surfaces (76). When a burn injury occurs, the skin barrier is disrupted, resulting in increased capillary permeability and allowing fluids and proteins to leak from the intravascular compartment into the interstitial space (67). This phenomenon is especially pronounced in extensive burns involving a large portion of the TBSA (77). During the acute phase following the burn, these fluid shifts lead to a significant reduction in circulating blood volume, causing hypovolemia (78). The decreased intravascular volume subsequently results in hypotension and diminished renal perfusion pressure, which compromises blood flow to the kidneys (79). Reduced renal perfusion can impair the kidney's ability to filter blood effectively, leading to AKI (79). This happens because ischemia deprives renal tissues of oxygen and nutrients, causing cellular injury and dysfunction in the glomeruli and tubules (58). Additionally, the burn injury triggers a systemic inflammatory response characterized by the release of various inflammatory mediators such as cytokines and vasoactive substances (67). These mediators can intensify renal vasoconstriction, worsening renal hypoperfusion and further aggravating kidney injury (67). Moreover, burn-related hypovolemia can promote the activation of the renin-angiotensin-aldosterone system, which attempts to conserve fluid but may also contribute to renal vasoconstriction and sodium retention, complicating renal recovery (80, 81). Early and adequate fluid resuscitation is therefore essential to restore circulating volume, maintain adequate blood pressure, and optimize renal blood flow (82). This approach helps to reduce the risk of progression to severe AKI, improves patient outcomes, and supports overall recovery in burn patients (83). Close monitoring of hemodynamic status and renal function during initial treatment is crucial for preventing long-term kidney complications (1).

Conclusion

Renal injury in burn patients fundamentally arises from a complex interplay of interrelated pathophysiological mechanisms, including hypovolemia, profound inflammatory responses, the release of denatured proteins, and the subsequent development of sepsis. Initially, hypovolemia, caused by extensive fluid losses from burn wounds and shifts into the interstitial space, leads to critically reduced intravascular volume and renal hypoperfusion. Simultaneously, the burn injury unleashes a potent systemic inflammatory response, characterized by a surge in cytokines like IL-1β, IL-6, and TNF-α, which promotes widespread endothelial dysfunction and exacerbates renal microvascular damage. This inflammatory cascade can directly injure renal cells and is implicated in both acute and later phases of kidney dysfunction. Furthermore, extensive tissue damage and muscle breakdown release nephrotoxic substances such as myoglobin and free hemoglobin. These denatured proteins can directly obstruct renal tubules and induce oxidative stress, leading to acute tubular necrosis. The toxic effects of these proteins are amplified under conditions of hypovolemia and acidosis. Finally, sepsis frequently complicates the clinical course, particularly in later stages, profoundly intensifying inflammation and multiorgan dysfunction, including the kidneys. Sepsis-induced AKI is strongly associated with poor outcomes and accounts for a significant portion of mortality in burn patients. Hence, fluid resuscitation tailored to individual needs, continuous monitoring with advanced biomarkers like neutrophil gelatinase-associated lipocalin and cystatin C for early detection of kidney injury, prompt recognition and aggressive treatment of infections to prevent sepsis, and the judicious application of renal replacement therapies are also necessary.

Acknowledgments

We would like to express our gratitude to the (Clinical Research Development Unit, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran) for sharing their pearls of wisdom with us during the course of this research.

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Conflicts of interest
The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process
During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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

Funding/Support
This is a self-funded study.

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