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Wound Healing in Patients With Impaired Kidney Function

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Abstract

Renal impairment has long been known to affect wound healing. However, information on differences in the spectrum of wound healing depending on the type of renal insufficiency is limited. Acute kidney injury (AKI) may be observed with different wound types. On one hand, it follows acute traumatic conditions such as crush injury, burns, and post-surgical wounds, and on the other hand, it arises as simultaneous targeting of skin and kidneys by autoimmune-mediated vasculitis. Chronic kidney disease (CKD) and end-stage renal disease (ESRD) often occur in older people, who have limited physical mobility and predisposition for developing pressure-related wounds. The common risk factors for poor wound healing, generally observed in patients with CKD and ESRD, include poorly controlled diabetes mellitus, neuropathy, peripheral vascular disease, chronic venous insufficiency, and aging. ESRD patients have a unique spectrum of wounds related to impaired calcium–phosphorus metabolism, including calciphylaxis, in addition to having the risk factors presented by CKD patients. Overall, there is a wide range of uremic toxins: they may affect local mechanisms of wound healing and also adversely affect the functioning of multiple systems. In the present literature review, we discuss the association between different types of renal impairments and their effects on wound healing and examine this association from different aspects related to the management of wounds in renal impairment patients.

Keywords: Wound healing, Renal impairment, Calciphylaxis, Uremic toxins

Introduction

Renal impairment has long been known to affect wound healing. However, information on differences in the spectrum of wound healing depending on the type of renal insufficiency is limited.

Acute kidney injury (AKI) may be observed with different wound types. On one hand, it follows acute traumatic conditions such as crush injury, burns, and post-surgical wounds,[1–3] and on the other hand, it arises as simultaneous targeting of skin and kidneys by autoimmune-mediated vasculitis.[4] Chronic kidney disease (CKD) and end-stage renal disease (ESRD) often occur in older people, who have limited physical mobility and predisposition for developing pressure-related wounds. The common risk factors for poor wound healing, generally observed in patients with

CKD and ESRD, include poorly controlled diabetes mellitus, neuropathy, peripheral vascular disease, chronic venous insufficiency, and aging. ESRD patients have a unique spectrum of wounds related to impaired calcium–phosphorus metabolism, including calciphylaxis, in addition to having the risk factors presented by CKD patients. Overall, there is a wide range of uremic toxins: they may affect local mechanisms of wound healing and also adversely affect the functioning of multiple systems.

In the present literature review, we discuss the association between different types of renal impairments and their effects on wound healing and examine this association from different aspects related to the management of wounds in renal impairment patients.

AKI and Wound Healing

AKI is a clinical syndrome defined as an increase in the serum creatinine level to >0.3 mg/dL (or an increase by 50%) or the development of oliguria within 48 h. In the traditional approach, AKI is classified via pre-renal, renal, and post-renal algorithms. However, classification in clinical practice needs to consider various inter-related reasons for AKI diagnosis. Renal problems in surgical patients commonly fall into the category of multiple organ failure and the development of AKI in hospital settings is a known predictor of poor patient outcome.[5]

By far, the most common etiology of renal impairment in acute settings is acute tubular injury (ATN).[6] When it is not the sole cause of such renal impairment, ATN often coincides with other variants of renal dysfunction.

Traumatic Wounds

Wounds related to traumatic crush injuries are often accompanied by AKI caused by pre-renal etiology, ATN and rhabdomyolysis.[5] The extent of kidney injury can vary from minor impairment to complete failure with the need for renal replacement therapy (RRT). Initial management of AKI from rhabdomyolysis involves aggressive intravascular volume resuscitation and alkalinization of urine to prevent intra-tubular precipitation of myoglobin. Although most patients tend to fully recover, some develop irreversible damage with life-long dialysis dependency.

Burns

Patients with thermal injury may develop AKI either early after sustaining the injury or after a delay. Early AKI develops within the first several days of burn injury as a result of the decreased effective intravascular volume, hemodynamic instability with cardiac dysfunction, cytokine injury resulting from the inflammatory response, and the effect of denatured proteins from tissue destruction. On the other hand, delayed-onset of AKI is observed after the first 72 h of thermal injury and is often associated with more extensive burns (25% or more of the total body surface area), drug toxicity, sepsis, and multiorgan dysfunction. Patients with AKI suffer impairment of the acid-base balance, electrolyte abnormalities, volume impairment, and further amplification of the inflammatory cascade, all of which lead to a high mortality risk.[1] Healing of the thermal injury in patients

with concurrent AKI is delayed because of multiple factors including delayed wound closure from the inability to recruit the interstitial third-spaced volume to the intravascular compartment. Timely initiation of RRT in patients with severe AKI has been shown to improve burn patient survival and wound healing.[1]

Bariatric Wounds

The development of AKI in morbidly obese patients who have undergone panniculectomy is quite common. The underlying pathophysiology can be explained by the abrupt changes in circulation demand occurring after the surgery. The loss of a substantial segment from circulation leads to a rapid drop in vascular resistance, resulting in hypotension. In these patients, the factor contributing to the development of AKI is the frequently observed hypertension requiring antihypertensive medications. Careful planning of hypertension management in the pre-surgical period can prevent significant alterations in hemodynamics and in turn, the severity of AKI. Wound healing in bariatric patients with wounds and AKI is delayed because of poor electrolyte volume. Additionally, high rate of post-surgical complications and prolonged hospital stay has been reported in such patients.[2,3]

Vasculitis

Patients with systemic vasculitis may simultaneously develop necrotizing skin lesions and kidney injury in the form of acute glomerulonephritis.[7] A broad spectrum of autoimmune disorders may be responsible for the above manifestations, including systemic lupus erythematosus, anti-neutrophil cytoplasmic antibody (ANCA)-vasculitis, cryoglobulinemia, cryofibrinogenemia, and polyarteritis nodosa. In such cases, pathological diagnosis must be established early via skin or/and kidney biopsy in order to initiate the appropriate immunosuppression therapy in time.[4] Wound often respond fast to systemic immunosuppressive therapy, but it could be significantly affected by infection.

Pharmacotoxicity

Wound patients can also develop AKI secondary to medication or agents administered during management of wound care, e.g., antibiotics (gentamicin, vancomycin, trimethoprim-sulfamethoxazole, etc.), nonsteroidal anti-inflammatory drugs (NSAIDs) (indomethacin, meloxicam, and naproxen), and iodinated radio-contrast agents used in medical imaging.

Warfarin-related skin necrosis is a rare but devastating condition often accompanied by the development of AKI. The etiology of AKI under conditions of warfarin exposure may be related to multiple factors including the development of ATN from shock, lower urinary tract obstruction due to large blood clots, renal infarct, and warfarin-related nephropathy (glomerular hemorrhage leading to tubular obstruction with red blood cell casts).[8]

CKD and Wound Healing

CKD is defined as a persistent reduction in glomerular filtration rate (GFR) to below 60 mL/min/1.73 m^2 for three months or the presence of proteinuria, microalbuminuria, hematuria, and radiologic/histologic changes in the kidneys.

Diabetes mellitus is by far the most common cause of CKD, followed by hypertension. The manifestations of CKD depend on the disease stage. In the early stages of CKD (stages 1–3), impairment of renal function can manifest as proteinuria and variable edema, while in stage 4–5 CKD, substantial edema, electrolyte abnormalities, acid-base disorders, and secondary hyperparathyroidism often develop. All these factors are important considerations with regard to wound healing.

Research data on mice suggest that the effect of CKD on wound healing is mediated by the disruption of keratinization kinetics, the delayed rate of granulation, and a large epithelial gap. The underlying chronic inflammatory state and low rate of vascularization and cell proliferation were also identified as mechanisms that lead to poor wound healing.[9] Supporting these animal data, human research has confirmed that patients with CKD have a higher rate of wound disruption than individuals with normal GFR.[3]

Kidney Transplantation and Wound Healing

Patients receiving renal transplants require considerably stronger immunosuppressive regimens than those receiving other solid organ transplants. Because they are often administered 2–3 immunosuppressive agents to prevent rejection of the kidney allograft, they are at risk of developing infectious complications and malignancies.

With regard to a specific immunosuppressive agent, it is important to mention that poor wound healing is a characteristic side-effect of sirolimus (Rapamune®). Therefore, in most transplant centers, it is almost never administered immediately after transplantation and is instead introduced only after the surgical wound has healed. Some centers have reported good wound healing outcomes in selected populations of patients with BMI <32 kg/m^2 who were not administered the loading dose of sirolimus.[10]

In cases in which wounds develop in patients who have received renal transplants and require surgical intervention, temporary changing of the immunosuppression regimen to an agent other than sirolimus is advised to ensure optimal wound healing.

In kidney transplant recipients, any wound that shows delayed healing should be managed with suspicion of the development of de novo malignancy, including melanoma, basal and squamous cell carcinoma, cutaneous lymphoproliferative disorder, and Kaposi sarcoma. For this reason, kidney transplant patients are routinely advised to undergo dermatological surveillance examination at least once a year.[11]

ESRD and Wound Healing

Patients who experience progressive loss of kidney function and develop renal failure requiring renal replacement therapy (RRT) or those with AKI who are RRT dependent for >90 days fall in the category of ESRD patients.

Uremia

For long, animal research and clinical medicine have recognized the negative effect of uremia on wound healing. The adverse effects of uremia on fibroblast proliferation, hydroxyproline level, and collagen production in wounds were identified as early as the 1960s and 1970s.[12–14] Further, the beneficial effect of hemodialysis in uremic dogs was reported in 1966.[15] It is important to note that hemodialysis in the United States become available to patients with ESRD via the Medicare Waver only in 1971,[4] which is when clinical observations of wound healing outcomes became possible in this population of patients.

In the uremic process, compounds vital for normal physiological processes accumulate in excess because of impaired renal function and thereby become toxic. At present, close to 100 uremic toxins have been recognized,[16] and these solutes have different physical properties. Some are water soluble and easily removed via dialysis, while others are strongly protein bound or have a high molecular weight and therefore cannot be removed using dialysis. One specifically interesting uremic toxin is beta-2 microglobulin, which is a large and poorly dialyzable molecule. Accumulation of beta-2 microglobulin leads to the development of systemic amyloidosis in dialysis patients, which in turn has a wide spectrum of manifestations, including bone fractures, carpal tunnel syndrome, frozen shoulder, spontaneous spleen rupture, and polyneuropathy. Although blood urea nitrogen is universally recognized as a toxic solute, it is in fact merely a surrogate quantitative marker of uremia. In terms of mechanism of action, some toxins exhibit adverse effects on wound healing via platelet dysfunction and impaired hemostasis, while others, such as IL-6, contribute to the chronic inflammatory state. Accumulation of asymmetric dimethylarginine interferes with L-arginine action and leads to the generation of nitric oxide and impaired endothelial function.[17] Further excess 3-deoxyglucosone (a precursor for advanced glycosylation products) contributes to impaired collagen function, among other abnormalities.

Preservation of residual renal function (ability to urinate) in dialysis patients is very important for the clearance of large molecules, and it should be taken into strong consideration while prescribing nephrotoxic pharmacological agents.

Uremic Pruritus

Uremic pruritus is a term defining symptom of itching due to ESRD. Renal impairment makes patients susceptible to the development of skin dryness (xerosis), probably because of its negative effect on microcirculation and sweat gland atrophy. Superimposed uremic pruritus can easily lead to mechanical skin trauma, lichenification, prurigo nodularis, and acquired perforating dermatosis.

Uremic pruritus is a very common and distressing symptom in ESRD patients. It can manifest in a form of generalized itching as well as localized to the particular area. Itching is present in up to 52% of patients with renal impairment but is frequently disregarded by health care providers. The underlying physiological mechanism of uremic pruritus is complex and poorly understood. It is believed to be the result of chronic systemic inflammation, hyperparathyroidism, poor dialysis quality, and an imbalance in opioid receptor expression. The itching disrupts the patient's daily life and sleep, impairs skin integrity, and is a strong risk factor for the development of infection, and kidney transplantation is the only definitive treatment for uremic pruritus.[18]

Uremic pruritus is also a risk factor for wound development and poor wound healing because of the repetitive trauma it induces. For wound management in affected patients, the use of topical emollients in combination with pharmacological antipruritic agents (e.g., gabapentin, pregabalin, cromolyn, and sertraline) should be the routine practice. In rare cases, the use of phototherapy with ultraviolet B irradiation can be prescribed.[19,20]

Calcific Uremic Arteriolopathy (Calciphylaxis)

Calcific uremic arteriolopathy (CUA), also known as calciphylaxis, refers to the calcification of the medial layer of small vessels. This disorder mostly affects patients with ESRD, with a prevalence close to 4% in this population, although it has also been described in patients with preserved renal function (those with multiple myeloma; rheumatoid arthritis; liver cirrhosis; and polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome).[21]

CUA leads to skin necrosis and extremely painful non-healing wounds. The clinical presentation is frequently characterized by the development of proximal (and often symmetrical) lesions on the buttocks, thighs, and abdomen with less common involvement of the acral regions. Non-healing wounds present provide an opportunity for infection with multiple microorganisms and sepsis.[22]

Recognized risk factors for CUA include diabetes mellitus, poorly controlled secondary hyperparathyroidism along with the use of calcium-based phosphorus binders, obesity, female gender, history of RRT, white ethnicity,[3] low albumin level, and impairment of the vitamin K pathway because of warfarin use.[23] CUA leads to substantial morbidity, prolonged hospitalization, and mortality rates as high as 80%.

Because of the complexity of CUA, its management strongly depends on the multispecialty team approach. Biopsy examination for a definite diagnosis is challenging considering the poor wound healing. Although CUA has many well-recognized clinical features, pathological examination (biopsy) is essential for a definitive diagnosis, which will support further management and treatment. Further, CUA treatment remains rather subjective, as no large prospective clinical trials that could recommend a strong evidence-based approach have been conducted to date. Meticulous wound care, avoidance of unnecessary trauma and ischemia (e.g., via vasopressor use), optimization of hematocrit, and possibly hyperbaric oxygen therapy are some of the steps in CUA management. Pharmacological options mostly target the calcium–phosphorus balance, for example, avoidance of calcium-based phosphorus binders and vitamin D analogs, reduction of the calcium concentration in the dialysate, discontinuation of warfarin, and administration of bisphosphonates.

Intravenous administration of sodium thiosulfate has shown some beneficial effects in terms of pain reduction and wound regression. Sodium thiosulfate increases the solubility of calcium deposits and possesses anti-oxidant and chelating properties, which alleviate systemic inflammation and increase the synthesis of inhibitors of extra-osseous calcification.[22,24] Several retrospective observational studies have investigated the use of intravenous infusion of sodium thiosulfate. The largest such study reported encouraging results for the use of this therapy: it found a significant improvement in as many as 80% patients after 18 months of therapy.[25] One disadvantage however is that the cost of intravenous sodium thiosulfate is substantially higher than that of its oral form (CAD 12,000 per month of therapy versus CAD 45). However, a case series including 4 patients treated with oral sodium thiosulfate showed positive responses, and therefore this therapeutic mode may be considered as a promising alternative to intravenous sodium thiosulfate infusion.[26]

Overall, a better understanding of the pathophysiology of CUA and the development of novel pharmacological strategies are necessary.

Loss of Proteins and Important Nutrients

Not many non-nephrologist health care providers are aware that RRT in the form of hemodialysis or peritoneal dialysis predisposes patients to significant protein loss. It has been reported that hemodialysis patients lose 6–8 g of amino acids per procedure, while peritoneal dialysis patients lose 8–20 g of protein per day from the peritoneal cavity. This loss of protein and the ensuing protein-deficient state have a significant negative impact on wound healing.[27]

Nutritional supplementation of protein in dialysis patients is very important. Several protein-containing supplemental products have been designed specifically for patients with kidney disease, such as Nepro®, Re/Gen®, Novasource® Renal, LiquiCel®, Pro-Stat®, and pure protein bars. A distinct feature of these products is their low potassium content (≤200 mg) and phosphorus (≤150 mg), which is essential in patients who have impaired renal exertion of these electrolytes.

While fat-soluble vitamins (A, E, K, and D) are poorly removed by any form of dialysis and carry the risk of accumulation, water-soluble vitamins (B group) are highly dialyzable. Minerals such as zinc, selenium, and iron can also be removed with dialysis. Zinc deficiency is recognized to be related to poor wound healing and has been reported in 40–78% of hemodialysis patients.[28]

In renal impairment patients, supplementation of vitamins and minerals should be administered keeping in mind that renal mechanisms to prevent hypervitaminosis are hampered, and specific renal doses must be considered. The use of multivitamin complexes designed specifically for patients with renal failure should improve the general health of this population and promote good wound healing.

Postsurgical Infections

Although it is known that patients with renal failure have an impaired immune system and are predisposed to infections, little is known about the mechanism of this immune imbalance. The effect of uremic toxins, chronic inflammation, and immune system activation has been reported to be the main underlying causes. A study reported that the septicemia-related mortality was 100–300 times higher in dialysis patients than in a matched cohort from the general population.[29] Additionally, the presence of the hemodialysis catheter or a synthetic vascular graft is a risk factor for systemic infection.

Unfortunately, clinical trials providing information on the outcomes of post-surgical infection in patients with renal failure are scarce. Animal research on mice with surgically induced CKD showed that these mice had a similar rate of post-surgical wound infection as a control group with preserved renal function, although wound healing was delayed in the former group.[8] Importantly, patients with CKD or ESRD usually suffer the disease burden for extended time periods and have other than just acute uremia conditions that impair wound healing, such as microcirculation impairment and ischemia.[30] Animal models of ischemia have been reported to show an increased rate of post-surgical infections (20% vs. 2% in a non-ischemic control).[31]

Collectively, the findings seem to indicate that clinicians should consider the risk of development of systemic infection as well as local wound infection to be higher in patients with renal impairment.

Drug Metabolism in Patients With Renal Disease

The pharmacokinetics of multiple medications is affected by impaired renal clearance. Therefore, during wound management in patients with renal disease, the dosage of antibiotics and pain medications must be taken into consideration, on the basis of creatinine clearance (CrCl). Most antibiotics have prolonged metabolism in patients with CrCl <30 mL/min/1.73 m^2. Most clinical laboratories calculate the GFR as part of the routine metabolic panel. Although GFR provides a less accurate estimation of renal function than CrCl, it is a good starting point for decisions on drug dosage. Patients with CKD or ESRD frequently require low doses of drugs because of impaired renal clearance, and if feasible, the antibiotic levels should be frequently monitored in these patients.

Pain management is an important aspect of wound management, and it is a very challenging task in the case of patients with impaired renal function. The use of NSAIDs is not advisable for patients with CKD as these drugs can significantly hamper renal function. Administration of pain medication in patients with renal insufficiency also needs to account for prolonged drug metabolism and the consequent longer half-lives of the drugs. For instance, gabapentin and pregabalin are often prescribed for the management of peripheral neuropathic pain. However, overdosing of these medications in patients with CrCl <30 mL/min/1.73 m^2 can lead to myoclonus, confusion, lethargy, and other frequently unexplainable neurological symptoms.[32] Careful dose adjustment will minimize the occurrence of dangerous side-effects and prevent unnecessary expensive workup.

Conclusion

Impaired renal function has multiple implications on wound healing. Therefore, a multi-disciplinary approach should be ideally used to achieve favorable outcomes in wound healing and to improve the general health of patients with impaired renal function.

Footnotes

Conflicts of interest: none.

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