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RESEARCH ARTICLE

WOUND HEALING IN RENAL IMPAIRMENT

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ABSTRACT

Renal impairment has long been known to affect woundhealing. 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 woundsand 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, whohave limited physical mobility and predisposition for developing pressure-related wounds. The common risk factors forpoor wound healing, generally observed in patients with CKDand ESRD, include poorly controlled diabetes mellitus, neuropathy, peripheral vascular disease, chronic venous insufficiency and aging.In the present literature review, we discuss the association between different types of renal impairments and their effects on wound healing.

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INTRODUCTION

The last 3 decades have produced more advances in wound repair and tissue regeneration than the previous 2000 years as a result of rapid expansion in the knowledge of the healing process at the cellular and molecular level. (Ibrahim *et al*., 2013) A wound is defined as trauma to any of the tissues of the body, causing disruption of tissue continuity. Two broad categories exist for the classification of wounds: Acute and chronic. An *acute wound* is a wound that has occurred within the past 3 to 4 weeks. Acute wounds undergo a complex interactive process involving a variety of cell types that leads to a healed wound. If the wound persists beyond 4 to 6 weeks it is considered a *chronic wound*, a term that also includes wounds that have been present for months or years. *Non-healing wound* or *delayed healing wounds* are terms used interchangeably to describe chronic wounds. Chronic wounds have proceeded through portions of the repair process without establishing a functional anatomic healing is the effort of injured tissues to restore their normal function and structural integrity after injury.

Phases of wound healing

The normal tissue response to a break in cutaneous defect integrity occurs in three overlapping, but biologically distinct phases. These include inflammation, proliferation, and remodelling phase. The immediate response to injury is the inflammatory phase. This phase includes haemostasis and inflammation. The proliferative phase is the regenerative process and consists of epithelialization, angiogenesis and provisional matrix formation. The final maturational phase is the period of scar contraction with collagen cross linking, scar contraction and loss of edema.

Factors affecting wound healing

Factors that affect physiologic responses and cellular function can potentially influence wound healing. They can be either local or systemic.

Factors that interfere with wound healing

Local

Infection
Foreign bodies
Ischemia
Smoking
Radiation
Trauma
Cancer
Local toxins
Arterial insufficiency

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Venous insufficiency
Hyperthermia

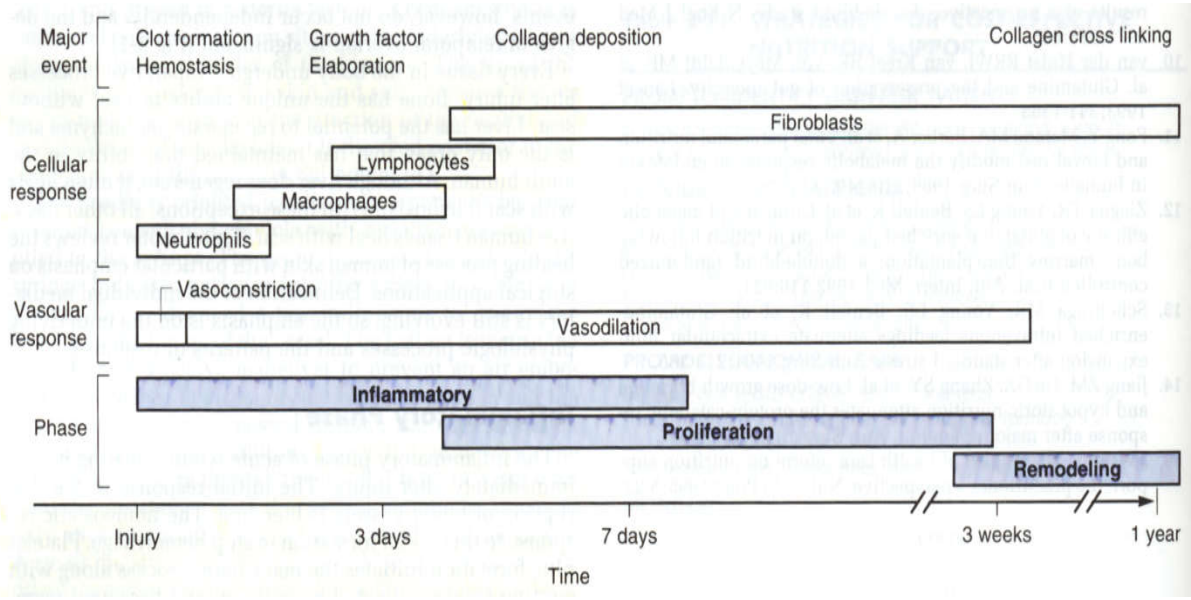
Systemic

Inherited disorders affecting collagen formation
Nutritional deficiencies
Aging
Diabetes
Liver disease
Alcoholism

Uraemia

Medications
Blood transfusions
Jaundice

Modified from Lawrence WT. In: Cohen IK, Diegelmann RF, Lindblad WJ, editors. Wound healing: biochemical and clinical aspects. Philadelphia: Saunders; 1992.



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 .Endothelial dysfunction due to uremia considered to be main culprit for delayed wound healing. (Weingarten *et al*., 2013) Endothelial dysfunction might be characterized by altered basement membrane synthesis, increased vascular tone and permeability-which contributes to increased blood pressure and atherogenesis and loss of antithrombotic and pro-fibrinolytic properties. Such alterations do not necessarily occur simultaneously and may differ according to the nature of the injury.14 However, the mechanisms by which increased uremia might influence endothelial cells, and especially the early responses of endothelial cells to the stimuli present in the serum of patients with CKD, are still not well understood. Systemic exposure of the vasculature to uremic toxins may lead to endothelial activation and to features associated with systemic inflammation like hypertension and atherosclerosis. The uremic state is often associated with breakdown of abdominal wounds. Stein and Wiersum *et al* in a retrospective analysis of 22,389 laparotomies in dogs concluded that renal dysfunction played a significant role in the development and outcome of abdominal wound (Turgeon *et al*., 2012). 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. (Maroz and Segal, 2013) 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. AKI is classified via pre-renal, renal and post-renal forms. 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. (Bihorac *et al*., 2010) The most common etiology of renal impairment in acute settings is acute tubular injury (ATN).6When it is not the sole cause of such renal impairment, ATN often coincides with other variants of renal dysfunction.

Traumatic Wounds

AKI (defined using RIFLE criteria) was common in ICU trauma patients. Recently, Bagshaw *et al*. suggested that trauma admissions to the ICU are frequently complicated by early AKI, with an incidence of about 18% and associated with

mortality rates of 50 to 70%. Wounds related to traumatic crush injuries are often accompanied by AKI caused by pre-renal causes, ATN and rhabdomyolysis. (Bihorac *et al*., 2010) 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 alkalization 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

In burn patients, AKI is a growing health concern as it is associated with both short and long term adverse events.5,6 These frequently lead to extended intensive care unit stays and high mortality rates. (Floege *et al*., 2010; Brodsky *et al*., 2011; Seth *et al*., 2013; Tiong *et al*., 2009; Danovitch, 2009) Although kidney function returns to normal for most burn survivors, a minority require long-term dialysis. Despite decades of research on the etiopathogenesis of AKI in thermal injury, the treatment of this entity is still not well defined. Its management remains supportive, focused on optimizing fluid balance, treating acid-base and other electrolyte disturbances, adjusting the dose of medications, and avoiding secondary hemodynamic and nephrotoxic injury. Despite these conservative measures, renal replacement therapy (RRT) using one or more of the multiple modalities of dialysis and hemofiltration is often required. (Kursh *et al*., 1977) It is unclear, however, whether RRT during the resuscitation period can ameliorate long-term morbidity and mortality. Hence, the key strategy for dealing with AKI is prevention. Multiple conditions contribute to early AKI (first 24h) 16 in the burn patient: hypovolemia, cardiac dysfunction, release of inflammatory mediators and denatured proteins (from extensive tissue destruction), and nephrotoxicdrugs. (Baylis, 2012; Kfoury and Jurdi, 2012; Kuypers, 2009) Late AKI usually falls within the multi-organ dysfunction syndrome (MODS) frequently associated with severe sepsis. (Galperin *et al*., 2014; Margo *et al*., 2010) Hypovolemia and under-resuscitation have classically been thought of as the primary causes of early AKI; however, recent studies suggest that AKI can develop despite adequate resuscitation. Furthermore, recent studies in critically ill patients, including burn patients, have suggested that a positive fluid balance may have a negative influence on kidney function and mortality. (Ross, 2011; Hayashi *et al*., 2012; Hayden and Goldsmith, 2010) All these observations suggest that AKI is more likely dependent on the degree of shock caused by the initial injury, and the subsequent release of injurious inflammatory mediators.

Bariatric Wounds

Postoperative AKI is not infrequent after gastric bypass surgery. Although the overall postoperative mortality is low, AKI is associated with increased duration of hospital stay. Certain co morbid conditions that are unique to this patient population influence the risk for postoperative AKI. In addition, commonly prescribed medications, such as ACE-I and ARB, for treatment of co morbid conditions are independently associated with increased risk for postoperative AKI. (Tiong *et al*., 2009) This suggests that simple strategies, such as avoidance of these classes of drugs, may provide short-term benefits in reducing morbidity and costs of care in patients who undergo gastric bypass surgery. The underlying pathophysiology for postoperative AKI 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 patient population.

Vasculitis

Patients with systemic vasculitis may simultaneously develop necrotizing skin lesions and kidney injury in the form of acute glomerulonephritis. (Floege *et al*., 2010) 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. (Maroz and Segal, 2013) Wound often respond fast to systemic immunosuppressive therapy, but it could be significantly affected by infection.

Drug induced nephropathy

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.11The 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). (Brodsky *et al*., 2011)

CKD and Wound Healing

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR). Chronic kidney disease (CKD) is due to a progressive loss of renal function that may lead to complications such as cardiovascular disease or pericarditis. 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. (Shindo and Kosaki, 1982) 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. (Seth *et al*., 2013) Supporting these animal data, human research has confirmed that patients with CKD have a higher rate of wound disruption than individuals with normal GFR. (Turgeon *et al*., 2012) Although there have been limited human studies on the effects of wound-healing in uremic patients, animal models have clearly shown that the addition of urea or uremic serum inhibits fibroblast growth and delays wound-healing. (Bihorac *et al*., 2010) Rats with renal failure have been shown to form less granulation tissue than those with normal kidney function.6 One study on humansdid show a significant correlation between ESRD and the failure of trans-metatarsal amputations to heal. (Floege *et al*., 2010)

Abnormal levels of zinc have been reported in patients with uremia. (Seth *et al*., 2013) Zinc has been well documented to be imperative in wound-healing by serving as a co-factor in a zinc-dependent enzymesystem that augments auto-debridement and keratinocytemigration. Zinc also confers protection against reactive oxygen species and bacterial toxins that impede wound-healing. Iron repletion commonly used in ESRD patients to optimize erythropoiesis may inadvertently impair wound-healing in these individuals. Iron overload not only will compromise the immune system, but also causes the inhibited synthesis and release of vascular endothelial growth factor (VEGF), which helps maintain angiogenesis.

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. Therefore, in most transplant centers, it is almost never administered immediately after transplantation and is instead introduced only after the surgical wound has healed. 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. (Danovitch, 2009)

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 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. (Kursh *et al*., 1977; Shindo and Kosaki, 1982; Colin *et al*., 1979) Further, the beneficial effect of hemodialysis in uremic dogs was reported in 1966.15It is important to note that hemodialysis in the United States become available to patients with ESRD via the Medicare Waver only in 1971, (Maroz and Segal, 2013) 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 exhibitadverse 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 dimethyl-arginine interferes with L-arginine action and leads to the generation of nitric oxide and impaired endothelial function. (Baylis, 2012) 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

Patients with renal failure, usually end-stage renal disease (ESRD), commonly are affected by severepruritus. Pruritus is a common symptom in patients with end-stage renal disease (ESRD). In older series, up to 90% of patients were affected with pruritus, but now between 20% and 50% are affected. (Ibrahim *et al*., 2013; Weingarten *et al*., 2013; Turgeon *et al*., 2012) Pruritus occurs independent of the cause of the ESRD, and patients on both peritoneal and hemodialysis experience pruritus at similar rates. All races both genders and all ages can develop ESRD pruritus. (Maroz and Segal, 2013) Nephrologists have recognized and documented significant impact of itch on ESRD patients' quality of life. In addition, pruritus is an independent predictor of increased mortality, probably because of effect on a patient's quality of sleep. The pathogenesis of ESRD pruritus is unknown, but improving the quality of dialysiscan reduce the prevalence and severity of ESRD pruritus. Topical and systemic agents as well as broadband ultraviolet phototherapy can be extremely beneficial. Gabapentin has been recently discovered as an effective agent for the patient with ESRD pruritus. Kappa opiate agonists are promising new therapeutic options.

Calciphylaxis

Calciphylaxis, also called calcific uremic arteriolopathy, is a rare disease characterized by medial calcification of the small arteries and ischaemia of the subcutaneous tissue, often leading to necrosis of subcutaneous fat and skin. It affects mainly women with chronic renal insufficiency and obesity. According to recent studies, calciphylaxis seems to occur more frequently than previously believed, with an incidence of 1% per yea. 23 and a prevalence of 4%in dialysis patient. (Hayden and Goldsmith, 2010) The pathogenesis of calciphylaxis is poorly understood and its treatment is largely empirical and somewhat controversial. Recent studies have emphasized crucial role of a multidisciplinary therapeutic approach focusing on the correction of the underlying abnormalities of the calcium and phosphorus plasma concentrations (using non-calcium-containing phosphate binders), local wound care with debridement of necrotic tissues and aggressive treatment of infectious complications (Turgeon *et al*., 2012). The utility of parathyroidectomy, corticosteroid therapy and hyperbaric oxygen therapy remains controversial. However, despite intensive combined treatments, the prognosis of calciphylaxis remains poor: the overall 1 year survival is 45% and the 5 year survival is 35%, with a relative risk of death of 8.5 compared with other dialysis patients (Maroz and Segal, 2013). Calciphylaxis has a dismal prognosis with up to 80-percent mortality. (Vanholder *et al*., 2003)

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. (Foley, 2008) 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. (Brodsky *et al*., 2011) 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. (Cheung and Wong, 2001)

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 CrCl30 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 decisionson 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 CrCl30 mL/min/1.73 m^2 can lead to myoclonus, confusion, lethargy, and other frequently unexplainable neurological symptoms. (Zand *et al*., 2010) 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.

REFERENCES

Ahn ST, Mustoe TA: Effects of ischemia on ulcer wound healing: a new model in the rabbit ear. Ann Plast Surg. 1990;24:17–23.

AlBugami MM, Wilson J-A, Clarke JR, Soroka SD: Oral sodium thiosulfate as maintenance therapy for calcific uremic arteriolopathy: a case series. Am J Nephrol. 2013;37:104–109.

Baylis C: Nitric oxide synthase derangements and hypertension in kidney disease. Curr Opin Nephrol Hypertens. 2012 Jan;21(1):1–6.

Bihorac A, Delano MJ, Schold JD, *et al*: Incidence, clinical predictors, genomics, and outcome of acute kidney injury among trauma patients.Ann Surg. 2010 July;252(1):158–165.

Brodsky S, Nadasdy T, Rovin B, *et al*:Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. Kidney Int. 2011 July;80(2):181–189.

Cheung AH, Wong LM: Surgical infections in patients with chronic renal failure. Infect Dis Clin North Am. 2001;15:775–796.

Colin JF, Elliot P, Ellis H: The effect of uremia upon wound healing:an experimental study. Br J Surg. 1979;66:793–797.

Danovitch GM: Handbook of Kidney Transplantation, 5th ed. Wolters Kluwer &Lippinccott Williams &Wilkins; 2009. p. 228–229.

Daugirdas J, Blake P, Todd S: Handbook of Dialysis, 4th ed. Lippincott Williams & Wilkins Publishers; 2007. p. 462–482.

Floege J, Johnson RJ, Feehally J: Comprehensive Clinical Nephrology, 4th ed. Elsevier; 2010. p. 797–P812.

Floege J, Johnson RJ, Feehally J: Comprehensive Clinical Nephrology, 4th ed. Elsevier; 2010. p. 292–307.

Foley R: Infectious complications in chronic dialysis patients. Perit Dial Int. 2008 Jun;28(suppl 3):167–171.

Galperin T, Cronin A, Leslie K: Cutaneous manifestations of ESRD. Clin J Am Soc Nephrol. 2014 Jan;9(1):201–218.

Hayashi M, Takamatsu I, Kanno Y, Yoshida T, Abe T, Sato Y: A case–control study of calciphylaxis in Japanese end-stage

renal disease patients. Nephrol Dial Transplant. 2012;27:1580–1584.
Hayden M, Goldsmith D: Sodium thiosulfate: new hope for the treatment of calciphylaxis. Semin Dial. 2010;23(3):258–262.
Ibrahim AE, Sarhane KA, and Fagan SP, Goverman J: Renal dysfunction inburns: a review. Ann Burns Fire Disasters. 2013 March 31;26(1):16–25.
Kalantar-Zadeh K, Kopple J: Trace metals and vitamins in maintenance dialysis patients. Adv Ren Replace Ther. 2003;10(3):170–182.
Kfoury LW, Jurdi MA: Uremic pruritis. J Nephrol. 2012;25(5): 644–652.
Kursh ED, Klein L, Schmitt J, Kayal S, Persky L: The effect of uremia on wound tensile strength and collagen formation. J Surg Res. 1977; 23:37–42.
Kuypers DR: Skin problems in chronic kidney disease. Nat Clin PractNephrol2009;5(3):157.
Margo C, Simman R, Jackson S: Calciphylaxis: a review. J Am CollCert Wound Specialits. 2010;2(4):66–72.
Maroz N, Segal MS: Lupus nephritis and end-stage kidney disease. Am J Med Sci. 2013;346:319–323.
Nayman J: Effect of renal failure on wound healing in dogs. Response to hemodialysis following uremia induced by uranium nitrate. Ann Surg. 1966;164:227–235.
Nigwekar SU, Brunelli SM, Meade D, Wang W, Hymes J, Lacson E: Sodium thiosulfate therapy for calcific uremic arteriolopathy. Clin J Am Soc Nephrol. July 03, 2013;8(7):1162–1170.
Ross E: Evolution of treatment strategies for calciphylaxis. Am J Nephrol. 2011;34:460–467.
Seth A, Garza M, Fang R, Hong S, Galiano R: Excisional wound healing is delayed in a Murine model of chronic kidney disease. PLos One. 2013;8(3):e59979. p. 1–10.
Shindo K, Kosaki G: Effects of chronic renal failure on wound healing in rats. II. Microscopic study and hydroxyproline assay. Jpn J Surg. 1982;12:46–51.
Tiong HY, Flechner SM, Zhou L, *et al*: A systematic approach to minimizing wound problems for de novo sirolimus-treated kidney transplant recipients. Transplantation. 2009 Jan 27;87(2):296–302.
Turgeon NA, Perez S, Mondestin M, *et al*: The impact of renal function on outcomes of bariatric surgery. JAm Soc Nephrol. 2012;23:885–894.
Vanholder R, Smet R, Glorieux G, *et al*: Review on uremic toxins: classification, concentration, and interindividual variability. Kidney Int. 2003;63:1934–1943.
Weingarten TN, Gurrieri C, McCaffrey JM, *et al*: Acute kidney injury following bariatric surgery. Obes Surg. 2013 Jan;23(1):64–70.
Zand L, McKian KP, Qian Q: Gabapentin toxicity in patients with chronic kidney disease: a preventable cause of morbidity. Amn J Med. 2010;123(4):367–373.

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