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Impact of Renal Failure on Wounds Healing

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Population of patients with the impaired kidney function grows around the world. With the advances of the contemporary medicine people live to the older age, survive cardiac and cerebrovascular events, recover from the complex surgeries, overcome malignancies, infections and autoimmune diseases. That all frequently leads to the development of variable degree of chronic kidney impairment in form of interstitial and/or glomerular injury. Patients with chronic kidney disease (CKD) often share risk factors of hypertension, poorly controlled diabetes mellitus, arterial and venous vascular disease, obesity, malnutrition and chronic inflammatory state. Spectrum of the renal disorders presenting in forms of acute kidney injury (AKI), CKD and End-Stage Renal Disease (ESRD) have complex negative impact on wound development and healing, and therefore provide continuous challenge for the surgeons and wound specialists.

Development of the AKI around the time of the surgery is known to complicate recovery in various surgical specialties. For instance, there is a substantial evidence demonstrating higher rate of AKI related to bariatric surgeries.¹ This mostly influenced by the significant and rapid loss of circulation volume, change in the vascular resistance leading to the development of acute tubular necrosis. Patients, who or at the time of the surgery received angiotensin converting enzyme inhibitors, angiotensin receptor blockers and/or nonsteroidal anti-inflammatory medications, are more prone to the development of kidney dysfunction and delayed wound healing.

Cardiothoracic surgeries predominantly done on patients with the underlying kidney disease and therefore development of AKI is not uncommon. Management of the volume status in postsurgical period may become quite challenging and complicate post-surgical recovery and wound healing.

Burn centers encounter substantial amount of patients with the concomitant AKI from the intravascular volume depletion, inflammatory state and nephrotoxins. Data from the clinical trials supports earlier initiation of renal replacement therapy for better outcomes in this population of patients.

Patients with advanced CKD stage III to V are often characterized by presence of proteinuria, substantial peripheral edema, low serum albumin, electrolytes abnormalities, imbalanced acid-base status and secondary hyperparathyroidism. Animal data demonstrated that CKD effect on wound healing leads to disruption of keratinization kinetics, larger epithelial gap as well as delayed rate of granulation. Ones with CKD has higher rate of wound disruption due to the low rate of revascularization and cell proliferation compared to patients with normal kidney function.²

ESRD patients are known for the development of the unique profile of wounds. Uremic calcific arteriopathy (UCA) or calciphylaxis is a serious condition frequently linked to ESRD. It is mostly described in patients treated with renal replacement therapy including hemodialysis and peritoneal dialysis, but also reported in a kidney transplant recipients. The etiology of this condition until now continues to be a medical enigma. Misbalance of calcium and phosphorus metabolism related to secondary and tertiary hyperparathyroidism is present in almost all patients suffering from calciphylaxis, although it is still unclear why UCA is not affecting all dialysis patients.

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Second-hit theory remains quite popular, with several factors identified as the potential insults: Coumadin based anticoagulation, septic event, surgery etc. Clinical picture frequently is the key in diagnosing the patient with UCA. Presence of characteristic bilateral wounds affecting thighs, buttocks, and lower abdominal wall, associated with unbearable pain from the ongoing necrosis of the soft tissues raises the concern of calciphylaxis. Unfortunately, we are lacking the specific biomarkers for this condition. Pathological finding of calcification affecting medial layer of arteries along with sub-intimal fibrosis and thrombotic occlusion has long been considered the gold standard of diagnosis. Remarkably, majority of ESRD patients will have calcification of medial layer of various arteries in the absence of wounds; consequently this pathological finding is quite nonspecific. On the other hand, presence of bilateral wounds in the proximal distribution in patients treated with renal replacement therapy and clinical diagnosis of UCA may not be always confirmed by the biopsy.³ We are in disparate need for the biomarkers which help to diagnose patients with UC and also identify patients at risk for development of this condition. Partners Calciphylaxis Biobank study is currently recruiting patients in hope to answer some of the questions related to pathophysiology of the disease and risk factors predisposing to it.

While patients without renal pathology also reported to have calciphylaxis, in their instance nonuremic calcific arteriopathy (NUCA), frequency of these cases is quite rare. Presence of autoimmune conditions such as rheumatoid arthritis, sarcoidosis, POEM syndrome, Chron's disease, diabetes mellitus, concurrent use of Coumadin have been reported in the majority of these cases.

Treatment of UCA based on the meticulous wound care, avoidance of excessive trauma and prevention of the secondary infections. Pharmacological treatment options are limited and not validated by the large prospective clinical trials. Current options include use of intravenous and oral sodium thiosulfate,^{4,5} calcimimetics, bisphosphonates, low calcium dialysate, non-calcium based phosphorus binders as Lanthanum Carbohydrate⁶ and longer duration/frequency of dialysis. Several case reports demonstrated successful utilization of hyperbaric oxygen therapy.⁷ In the past years parathyroidectomy has been a leading option for CUA management but later research discouraged it's universal acceptance. Considering substantial cost associated with pharmacological management of tertiary parathyroidism it is still remaining a valid option for selected candidates.⁸ Team-based approach to management of CUA/NUCA is of the paramount importance as patients need expertise from multiple specialties.

Nutritional status of dialysis patients is another important factor to recognize in wound healing. Patients

on renal replacement therapy have ongoing inadvertent protein loss related to hemodialysis or peritoneal dialysis. In addition dialysis therapy depletes the concentration of water-soluble vitamins which need to be replaced appropriately. On the contrary, fat soluble vitamins are not dialyzable and have a tendency to accumulate with a risk of toxicity. Deficiency of microelements like zinc is also known side effect of renal replacement therapy. Use of vitamins specifically designed for patients on dialysis is an important part of the nutritional plan for successful wound healing.⁹

Patients with renal impairment are subject of different pharmacotherapy rules. Metabolism of variable medications as antibiotics and pain medications is different than in patients with preserved glomerular filtration rate. Poor renal clearance predisposes patients to prolong metabolism of medicines and their metabolites, and therefore higher risk of toxicity. Appropriate dosing of medications is very important to prevent harmful side effects.¹⁰

In conclusion, renal impairment may affect make up and rate of wound healing, hospital stay duration and cost of medical care. Management of these patients requires deep expertise and collaboration between surgical and medical teams in order to improve outcomes.

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