CHAPTER **29**

End-Stage Renal Disease and Podiatric Surgery

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End-stage renal disease (ESRD) is becoming an increasing patient population for podiatric physicians and surgeons. According to the CDC, there were 113,000 new cases of ESRD in the United States in 2011 with the likelihood of this number increasing over the next few years (3). With Diabetes Mellitus and hypertension becoming more and more prevalent in the general population, as will patients with ESRD, as these are the two most common causes of ESRD (3). This patient population carries multiple comorbidities, risks, and obstacles when treating their wounds, ischemia, and infections. In fact, according to a study by O'Hare et al "the incidence of non-traumatic lower extremity amputation among the United States end-stage renal disease population is approximately 10 times higher than that among the non-end-stage renal disease patients, even controlling for Diabetes" (4). The purpose of this update chapter is to expand the knowledge base for all physicians treating ESRD patients, specifically, in regards to lower extremity surgical outcomes, morbidity and mortality, as well as the pathophysiology specific to this patient population that may contribute to poor surgical outcomes.

ESRD is defined as total and permanent kidney failure with a glomerular filtration rate of <15 ml/min (2). This is irreversible damage to the kidneys that requires these patients to either remain on dialysis for the rest of their lives or must receive a kidney transplant in order to sustain life. These patients have an inability to excrete metabolic wastes, such as uremic toxins, as well as the inability to regulate their electrolytes and fluid volume. Uremic toxins are any biologically active compounds that are retained due to kidney impairment (1). They eventually will succumb to the build up of these uremic toxins without proper filtration via dialysis whether it be hemodialysis or peritoneal dialysis. ESRD is caused from one or more multiple factors such as Diabetes Mellitus, hypertension, glomerulonephritis, chronic pyelonephritis, polycystic kidney disease, or an idiopathic cause, with Diabetes Mellitus and hypertension being the most common causes at 30% and 24%, respectively (1). Figure 1 demonstrates the distribution of these common causes (1).

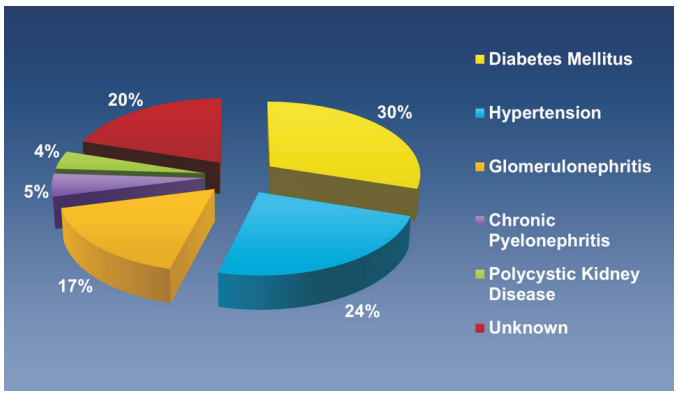

Figure 1. Most Common Causes of End-Stage Renal Disease.

PHYSIOLOGIC ABNORMALITIES

Not only do these patients have a long list of comorbidities in terms of past medical history, but these patients have multiple endocrine, electrolyte, hematologic, and immune abnormalities that need to be considered when treating these patients. Although we might not see these abnormalities when examining the patient, it's important to keep in mind how the difference in their physiologic state compared to the general population can affect lower extremity outcomes in terms of wound healing, limb salvage, morbidity, and mortality.

ENDOCRINE ABNORMALITIES

Patients with ESRD have an innate imbalance of insulin metabolism causing them to have increased insulin resistance as well as decreased clearance of insulin. This increased resistance and decreased clearance of insulin can lead to hypo- or hyperglycemia for the patient (1). This, in turn, leads to a multitude of endocrine imbalances resulting in a vicious cycle of damage to the kidneys and abnormal glucose metabolism. They also have a decreased basal metabolic rate causing them to use more energy to heal any wound or incision site. Given the fact that these patients demonstrate peripheral shunting of blood to their core organs, they have a lower temperature homeostasis causing them to live at a subthermal state. This is considered perfusion hypothermia and can mask a fever as they are starting at a lower baseline core body temperature (1). When these patients are demonstrating a temperature of 99-100° F, although this is not the accepted cut off for a fever at 100.4° F, they perhaps are febrile, but are starting at such a low baseline they are unable to reach the accepted temperature for a fever. It's important to get baseline vital signs and trend their temperature throughout their hospitalization and to be aware of this difference compared to other patients.

ELECTROLYTE ABNORMALITIES

As most know, these patients have a multitude of electrolyte abnormalities that can be detrimental to their health. However, it's crucial to understanding how each of these electrolyte abnormalities can affect our patients in terms of wound healing and mortality. Hypernatremia in the ESRD patient leads to water retention secondary to sodium retention (1). This water retention can lead to edema and possibly cause wound dehiscence post-operatively. One of the most detrimental electrolyte abnormalities these patients face is hyperkalemia. This causes these patients to live in an acidotic state (1). If these patients are not managed appropriately through dialysis and careful awareness of trending their potassium levels they can go into acute respiratory failure and/or experience unwanted cardiac events such as arrhythmias or sudden cardiac arrest. Acute respiratory failure is due to the hypercarbia these patients may experience due to their chronic acidotic state, especially during general anesthesia (1). They also experience hypocalcemia and hyperphosphatemia, which can lead to secondary hyperparathyroidism causing an osteoclastoma. Due to the array of electrolyte abnormalities these patients experience on a daily basis it is optimal for these patients to undergo dialysis 4-6 hours prior to anesthesia (1). If this is not feasible they should receive their dialysis the day prior to any procedure in which anesthesia is required.

HEMATOLOGIC ABNORMALITIES

Due to the build up of uremic toxins in their blood stream and decreased parenchymal erythropoietin production from their irreversible kidney damage patients with ESRD experience decreased red blood cell life span which causes them to live in a chronic hypoxic state. When these patients have decreased oxygenation delivery to their tissue this can lead to poor wound healing whether it be an ulcer or surgical incision. On top of their chronic hypoxic state these patients also experience anemia of chronic disease. They are routinely iron and folate deficient leading them to have micro and macrocytic anemia, respectively. This in turn leads to the release of 2,3 diphosphoglycerate causing the oxyhemoglobin dissociation curve to shift to the right (1). Figure 2 demonstrates how this chronic anemia shifts the oxyhemoglobin curve to the right increasing their chronic hypoxemia (6). This right shift of the oxyhemoglobin curve decreases the affinity hemoglobin has for oxygen. When this happens, there is decreased oxygen being delivered to tissues and organs, which again, results in poor wound healing. ESRD patients have a disorder called functional platelet dysfunction or uremic platelet dysfunction (1). This thrombocytopathy leads to decreased adhesiveness and aggregation of platelets although their coagulation studies are normal. The platelets themselves are not abnormal, but how they behave is abnormal due to increased nitrous oxide production in their blood. This can lead to excessive bleeding and difficulty stopping bleeding intraoperatively. This can be compounded with the inability to apply a tourniquet in some cases due their calcium deposition and peripheral shunting in the arteries causing severe atherosclerosis and non-compressible vessels.

IMMUNE DYSFUNCTION

Sepsis is the leading cause of death in patients with ESRD secondary to superficial infections of hemodialysis sites, as well as, infections in general (3). The build up of uremic toxins leads to uremic immune dysfunction (2). This uremic immune dysfunction causes an inhibition in their innate cell-mediated and humoral immunity (1). This inhibition of both cell-mediated and humoral immunity makes it even more difficult for these patients to fight infections. This can make it even more difficult as a clinician when treating these patients when they present with an infection. Another factor of their immune dysfunction is the increased release of pro-inflammatory cytokines, which, again, leads to poor wound healing.

PHARMACOKINETICS AND ESRD

When treating these patients whether it be in your clinic or in the hospital setting it is of upmost importance to understand the difference in their pharmacokinetics due to their inability to renally excrete medication metabolites. This is also important in the perioperative setting. When administering local anesthetics, most do not take into consideration the multiple physiologic abnormalities these

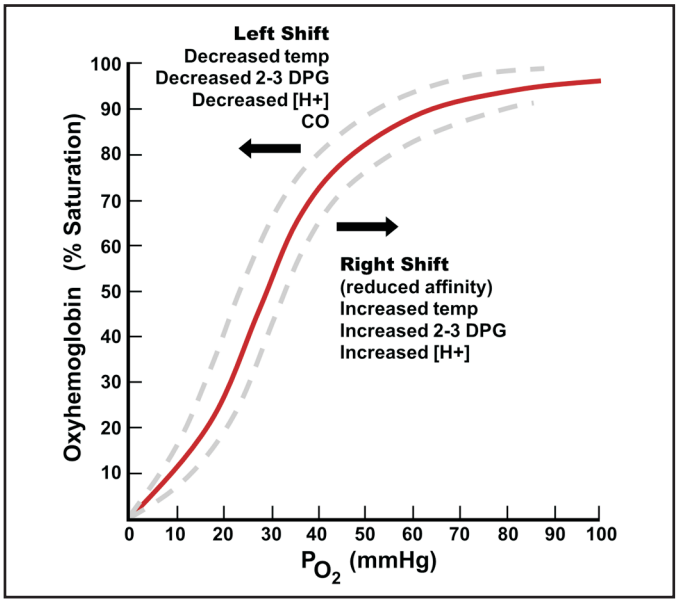

Figure 2. Oxyhemoglobin Dissociation Curve.

patients are living with. Due to their chronic hypoxic and acidotic state these patients have reduced protein binding and lower central nervous system seizure threshold. When administering local anesthetics, such as lidocaine and/or Marcaine it is important to reduce the maximal dose by 25% (1). Another obstacle when treating these patients with an infection, other than their immune dysfunction, is antimicrobial selection and dosing. It is important to use a reliable reference guide when starting these patients on antibiotics and to refer to the renal dosing guidelines. Adjusting the dose of an antibiotic specific to their renal impairment may be the difference between life and death for those with ESRD. It is also important to augment the dose of their antibiotics after dialysis. A useful tool in the hospital setting is consulting infectious disease and pharmacy. Infectious disease can help select the safest and most optimal antibiotic to use for the patient and pharmacy can pks dose the patient and monitor their peaks and troughs when using vancomycin to ensure the patient is being appropriately dosed in a safe manner. When choosing an antibiotic to place these patients on to fight infection trimethoprim-sulfamethoxazole and aminoglycosides should absolutely be avoided due to their potential nephrotoxic side effects (1). If an aminoglycoside must be used, amikacin is the only aminoglycosides that is not renally metabolized or excreted and is the most safe to use. When considering anesthesia for a procedure propofol is actually not renal dependent (7). Figure 3 demonstrates the concentration of propofol in those with ESRD and those without (7). As it is shown, the levels remain fairly equal until 500 minutes of anesthesia with propofol. Another important consideration is the use of benzodiazepines. These are sometimes used in adjunct with the process of obtaining an MRI for a patient who is nervous, claustrophobic, or anxious about the diagnostic study that is to be performed. If prescribing a benzodiazepine, like lorazepam (Ativan) to aid in the patients ability to undergo the diagnostic study decreasing the usual dose by half is recommended. Since these patients are chronically acidotic and experience hypoalbuminemia there is increased free-drug availability of highly protein bound drugs, like benzodiazepines and can lead to benzodiazepine toxicity (1). Another aspect in treating these patients is treating their pain effectively yet safely. It is recommended that morphine, dilaudid, fentanyl, tramadol, and oxycodone are to be used as opiates, however, to decrease the usual dose by 50% (1). Opiates that are to be avoided are codeine, dihydrocodeine, and meperidine as these breakdown into metabolites that are unable to be excreted.

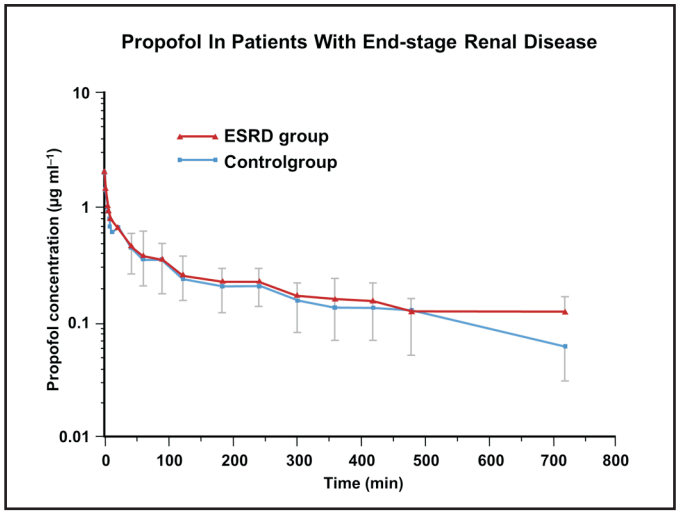

Figure 3. Propofol Concentration in those with ESRD vs. Control.

LIMB SALVAGE AND MORTALITY

When researching this topic, limb salvage and mortality were of upmost importance to the author when assessing lower extremity surgical outcomes in the ESRD population. A study by Leers et al. Examined 34 patients undergoing 41 pedal bypass grafts. Of those 34 patients, 91% had Diabetes Mellitus and 94% had hypertension. The aim of the study was to identify predictive factors of limb salvage failure and mortality. Limb salvage rates at 1 year were 56% with a survival rate of 64%. They found that within the first three months is when the majority of complications and failures were identified due to progressive necrosis despite hemodynamically stable bypass grafts. They observed that heel gangrene, defined as full thickness skin necrosis > 4 cm in diameter was of the strongest predictors to limb loss and mortality. In patients with the defined heel gangrene multiple modalities were attempted including debridement, skin grafts, muscle flaps, and tissue transfers. Despite all of these attempts to heal the gangrene located to the heel all progressed to early limb loss or did not survive. When treating ESRD patients with full thickness skin necrosis >4 cm it is imperative to understand and explain to the patient that this is a very strong predictor of negative outcomes. Primary amputation should be discussed with the patient and offered early as this can save the patient from multiple surgeries and the possibility of ambulating earlier (8). A study by Johnson et all looked at 53 patients undergoing 69 distal arterial reconstruction for gangrene, non-healing ulcers, and ischemic rest pain. They were looking to assess limb loss and mortality rates. Within 30 days post-operatively 9% went on to limb loss and they found a mortality rate of 10% with a two-year survival rate of 38% at 2 years. They observed that failure of foot salvage was due to poor wound healing despite the bypass grafts remaining patent. They stressed the importance of revascularization prior to infection and/or ischemia is present. When seeing these patients in the outpatient setting it is important to constantly assess their vascular status and to refer them to a vascular surgeon for revascularization for early intervention

before complications arise when possible (9). The study by Simsir et al. assessed predictive factors influencing limb salvage and operative mortality rates in 77 patients undergoing 102 operations for ischemia, 50 for amputations and 52 for revascularizations. Similar to the study by Johnson et al., they identified a 30 day limb loss rate of 9%. They demonstrated that atherosclerosis, extensive tissue necrosis, and failed ipsilateral bypass graft were the three most detrimental factors leading to failure of limb salvage. Throughout the course of the study there were 17 patients who passed away with 71% succumbing to sepsis. They found that sepsis was the most common cause of death in their cohort. They also found that poor cardiac function was the second most common cause leading to early mortality. Within the study they stress the absolute importance of a thorough cardiac evaluation prior to surgery. In terms of poor cardiac function, when a patient demonstrated poor ventricular function on echocardiogram and/or reversible defect on stress radionuclide cardiography the mortality rate was much higher than those who did not demonstrate such cardiac abnormalities (10). The last study by Pollard et al. looked at 90 patients undergoing 101 transmetatarsal amputations and observed the most common complications post-operatively. Of the 90 patients in the study, 36 patients had ESRD. The others had co-morbidities and risk factors closely associated with ESRD, such as Diabetes Mellitus, hypertension, and coronary artery disease. Within the entire study, 87% of patients developed post-operative complications with wound dehiscence (52%), stump infarction (31%), chronic stump ulcerations (31%), and post-operative infection (19%) to be the most common. However, when specifically looking at the post-operative success in the ESRD patients, only 44.4% achieved a healed stump. They concluded that the diagnosis of ESRD itself is a statistically strong predictor of non-wound healing (11).

DISCUSSION

As Diabetes Mellitus and hypertension becomes more prevalent in the United States so will the diagnosis and patient population of ESRD. The Diabetes Mellitus epidemic will lead to podiatric physicians treating and managing more ESRD patients in the near future. It is important to remember the various comorbidities these patients experience when treating these patients conservatively and more importantly surgically. Their comorbidities are more than their past medical history and diagnoses they present with. Their endocrine, electrolyte, hematologic, immune, and pharmacokinetic abnormalities must be taken into consideration when treating these patients with the best of our abilities. It must not be forgotten that ESRD patients are at an increased risk for complications in terms of wound healing, infection, ischemia, limb salvage, and mortality. This is critical when assessing the patient and discussing possible outcomes and complications. Due to the complex nature of these patients it is absolutely critical to take a multidisciplinary approach when treating these patients. Consultation of the correct medical services ensures the best treatment for the ESRD patient. Other services that should be considered when treating these patients would be the hospitalist to manage their medications and comorbidities, infectious disease for antibiotic selection, pharmacy for appropriate dosing of medications, vascular for vascular intervention, cardiology for the appropriate risk stratification, and nephrology to manage their dialysis and optimize them for surgery.

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