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END-STAGE RENAL DISEASE AND LIMB SALVAGE

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Abstract

The prevalence of peripheral arterial disease and both traditional and nontraditional vascular risk factors are more common in patients with end-stage renal disease who are undergoing hemodialysis than the general population. Patients undergoing hemodialysis may also be at risk for peripheral arterial disease via nonvascular risk factors and the hemodialysis treatment itself. Unfortunately, because peripheral arterial disease and its risk factors in hemodialysis patients have not been thoroughly ascertained, evaluation of potential treatments has been limited. Given the high potential of morbidity and impaired quality-of-life related to peripheral arterial disease in patients with end-stage renal disease, additional studies are needed to evaluate both quality of life and potential screening for peripheral arterial disease, its risk factors, and treatments to identify areas for improvement in this vulnerable population.

Cardiovascular Disease in End-Stage Renal Disease

According to the National Kidney Foundation Disease Outcomes Quality Initiative (DOQI) clinical practice guidelines for cardiovascular disease (CVD) in dialysis patients, treatment of patients with CVD who are on dialysis is suboptimal based on insufficient evidence of treatment efficacy, exclusion of this population from most major CVD-related trials, and a clinician attitude of therapeutic nihilism towards these patients.[1] All patients with end-stage renal disease (ESRD) on dialysis are at increased risk for CVD.[2] In fact, CVD in its various manifestations (e.g., myocardial infarction, heart failure, stroke, lower extremity occlusive disease, amputations, etc.) is the leading cause of death in patients with ESRD, accounting for nearly 50% of deaths.[3] After adjusting for age, gender, race, and diagnosis of diabetes, mortality from CVD is far higher in patients with ESRD compared to the general population.[4-7]

ESRD and CVD have interlocking relationships and do not act as wholly independent processes. A synergy exists whereby CVD can precipitate ESRD by virtue of damage to the blood vessels and kidneys from high blood pressure, circulating inflammatory factors, etc. Conversely, ESRD can be seen as a harbinger of CVD since it is accompanied by accelerated atherosclerosis and the effects of its associated treatment, renal replacement therapy, or hemodialysis (HD). Some of the potential mechanisms for enhanced atherogenesis in patients with ESRD are lipid abnormalities, increased prevalence of hypertension and diabetes, increased inflammation and oxidative stress, elevated fibrinogen, impaired nitric oxide bioavailability, and hyperhomocysteinemia due to decreased clearance.[2] In addition to unbalanced metabolite removal, the dialysis procedure can introduce endotoxin and nonphysiological chemicals along with nonphysiological particles present in the air and water. Futhermore, the process may impose blood trauma; the damaged blood cells and their degraded end-products, together with the tissue degeneration resulting from the original disease, may further alter the immunological processes of the patients. Typically, chronic HD patients exhibit immunodeficiency syndrome, and thus they are more prone to development of atherosclerotic lesions. The degenerating processes of tissues from blood trauma induced by the procedure and the original disease process may include fibrin and fat degeneration and dystrophic calcifications. Atherosclerosis and amyloidosis would subsequently occur.[8] This relationship is highly complex, involving both traditional (e.g., high blood pressure, high cholesterol, diabetes) and nontraditional (e.g., endothelial dysfunction, inflammatory activity) CVD risk factors,[9] and is a controversial topic of investigation ranging from the level of genomics to clinical risk factor treatment research.

The 2005 report of the National Kidney Foundation DOQI guidelines stresses the interactions between CVD and ESRD and recommends aggressive CVD screening and treatment for all ESRD patients receiving hemodialysis (HD).[1] Several recent large-scale registry studies estimate that up to 60% of new ESRD patients have some manifestation of CVD.[10-12] Likewise, the American Heart Association issued a statement in 2003 that recommended patients with ESRD be considered a "highest risk group" for subsequent CVD events.[13]

Like coronary causes of CVD, noncoronary causes of CVD (e.g., lower extremity occlusive disease, cerebrovascular disease) are thought to be more prevalent in the ESRD population than among the general population, with estimates ranging from 4-45% (depending on the definition and population studied); these noncoronary causes are responsible for significant morbidity, disability, decrements in quality of life, and death.[7, 10, 14-17] Even so, noncoronary causes of CVD in ESRD are not usually evaluated nor suitably addressed in these patients. In fact, noncoronary causes of CVD (herein referred to collectively as peripheral arterial disease, or PAD) have often been overlooked by practitioners and clinical researchers such that limited information is available to guide screening, treatment, and preventive strategies.[16]

Peripheral Arterial Disease and Medical Treatment

As PAD is a strong predictor of cardiovascular mortality in both the general and dialysis populations, early diagnosis of PAD and aggressive medical therapy might improve cardiovascular survival

in dialysis patients; however, there are no randomized controlled trials available to dialysis patients of any therapeutic interventions for PAD. Data is limited, as until 2011 most trials of CVD treatments (e.g., lipid-lowering medications) did not include people with chronic kidney disease or ESRD for concerns of safety or altered outcome.[18] The impact of this problem can be seen in studies based on data collected from the Dialysis Outcomes Practice Population Study (DOPPS) registry[19] and in comprehensive reviews of literature[18] indicating that medical treatments for CVD (aspirin, statins, and beta blockers) are underused in patients with ESRD/HD and chronic kidney disease. In our own unpublished PAD screening study of almost 400 dialysis patients, we found a 60% incidence of PAD and 17% with foot wounds when a careful foot exam was performed. Only 33% of patients were on statins.

This issue had been addressed in June 2011 by the Study of Heart and Renal Protection (SHARP), in which a combination of simvastatin/ezetimibe showed a 17% overall reduction in major adverse cardiac events in CKD patients. Moreover, the Swedish Web-system for Enhancement and Development of Evidence-Based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) investigators published observational data on the beneficial effect of statins on mortality in CKD stages I-IV. Nevertheless, ESRD patients have not been shown to benefit from statins in trial data to date; the A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: an Assessment of Survival and Cardiovascular Events (AURORA) trial yielded a nonsignificant 4% reduction of myocardial infarction, stroke, cardiovascular death, or all-cause mortality despite a mean 43% low-density lipoprotein cholesterol (LDL-C) reduction.[20]

PAD Treatment Modalities

Infrainguinal Bypass Surgery

Lower extremity revascularization in ESRD patients follows the same standard interventions as those of non-ESRD patients, with the gold standards continuing to be controversial. Historically, infrainguinal bypass surgery, also referred to as "open" surgery, was considered the first-line therapy for revascularization; however, this was based on studies of optimal surgical candidates with favorable anatomy and adequate autogenous conduits. To accommodate the challenges presented by "real life" patients, researchers developed creative techniques using alternative conduits including heparin-bonded prosthetic grafts, distal vein patch grafts, composite grafts, or cryopreserved veins, but they all have reported inferior outcomes to autogenous veins. On the other hand, the minimally invasive nature of endovascular therapy, especially given the advanced age and multiple comorbidities of the majority of patients, led to a trend towards its use as first-line therapy.

Endovascular Therapy

Excellent results have been reported for endovascular therapy over the last decade, and it has continued to gain popularity as more novel technologies have become available. These include excimer laser, plaque excisional atherectomy, orbital atherectomy, cryoplasty, specialty balloon angioplasty (Figure 1), infrainguinal stents (Figure 2), stent grafts, chronic total occlusion crossing and re-entry devices, and specialty wires. Multiple trials comparing open and endovascular treatments have concluded that both approaches have similar limb salvage rates; however, open repair was associated with higher morbidity, longer intensive care unit and hospital stays, and higher costs.[21] With the complexity of PAD in critical limb ischemia (CLI), it is hard to separate the complimentary roles of open and endovascular therapies. The best approach is always individualized therapy—be it a combined "hybrid" approach, an open approach after exhaustion of endovascular approaches, or an endovascular salvage after open repair.[22] Nevertheless, amputation should still be "first-line" therapy in debilitated, bedridden patients with advanced CLI when there is major tissue loss, advanced osteomyelitis, or a need to control infection.

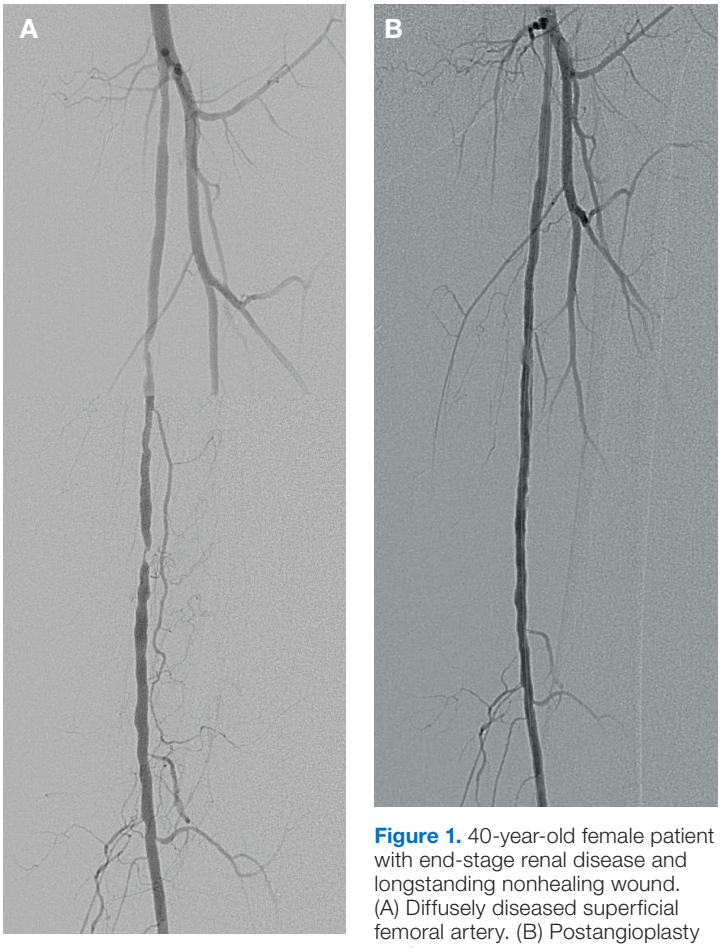

Figure 1. 40-year-old female patient with end-stage renal disease and longstanding nonhealing wound. (A) Diffusely diseased superficial femoral artery. (B) Postangioplasty angiogram.

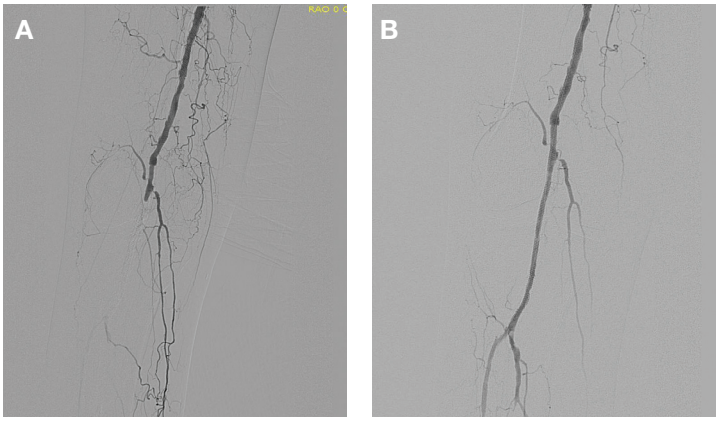

Figure 2. 60-year-old male patient with end-stage renal disease who presented with acute onset right foot rest pain. (A) Occluded right popliteal artery stent. (B) Successful recanalization and angioplasty of occluded segment with restoration of runoff.

Limb Salvage

Lower limb revascularization for CLI in ESRD patients is associated with rather favorable limb salvage rates. In one large series, a 61% limb salvage rate was reported at 4 years follow-up.[23] Similarly, two meta-analyses reported pooled limb salvage rates of 74.7% at 2 years[24] and 69.7% at 5 years.[23] However, patients with ESRD had a higher amputation rate than non-ESRD patients despite patent grafts accounting for 10% of revascularized limbs. At the same time, the perioperative mortality risk is high after limb revascularization and increases proportionately with the degree of renal insufficiency. Biancari and colleagues reported a combined (open and endovascular) 3-year survival of 27.1% vs. 59.7% in ESRD and non-ESRD patients, respectively,[23] and demonstrated that ESRD was an independent predictor of all-cause mortality. In patients with ESRD, age ≥75 years and bypass surgery for leg ulcer or gangrene were associated with higher 1-year all-cause mortality,[23] whereas a smaller series reported an immediate mortality of 10% after endovascular therapy.[25] A meta-analysis of surgical series showed a 30-day perioperative mortality of 5% in ESRD patients. Moreover, the late 3-year survival of patients undergoing bypass surgery was 41%,[24] which is comparable to patients with ESRD undergoing on-pump CABG (42%).[26]

Quality of Life

The quality of life (QoL) of patients with ESRD is substantially lower than that of the general population. In addition, studies such as DOPPS II have demonstrated that the QoL of ESRD patients with PAD is even more compromised compared to non-PAD patients in that it is equivalent to patients with terminal malignancies or heart failure. Unfortunately, studies have failed to demonstrate considerable differences in QoL even after infrainguinal revascularization compared to primary amputations in ESRD patients with PAD[27, 28] Therefore, limb salvage as the endpoint of revascularization should be interpreted with care and in light of functional outcome in the ESRD population. Salvaged limbs may still have residual symptoms of critical ischemia, including neuropathy and nonhealing wounds, that interfere with daily activities or extensive infection that will lead to amputation despite patent bypass grafts. For instance, Nicholas et al. reported significant differences in the rates of independent ambulation at 1 year for patients with and without ESRD (10% vs. 56%, respectively).[27] Therefore, functional outcome of revascularization including living independently, being fully mobile, and having all wounds healed at 6 months should be considered when evaluating limb salvage outcome.[29] For more postrevascularization issues, including nonhealing wounds after amputation and free-flap failures, refer to the article by Klebuc and Menn in this issue.

Conclusion

In the general population, programs designed for early detection and treatment to delay disease progression have improved cardiovascular health, prolonged life, and diminished the risk of myocardial infarction, stroke, and amputation. While lower limb revascularization in ESRD patients has favorable limb salvage outcomes, the mortality rates are high in this group. Early referral, adequate treatment of tissue loss, and complete revascularization are essentials in the management of these patients.[30] Further research is needed to enhance detection and awareness of these conditions in the ESRD/HD population and to evaluate whether early detection and treatment results in prevention, or at least mitigation, of disease.

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