Peripheral Artery Disease and Chronic Kidney Disease: Clinical Synergy to Improve Outcomes

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Persons with CKD are at a higher risk of developing peripheral artery disease (PAD) and its adverse health outcomes than individuals in the general population who have normal renal function. Classic atherosclerosis risk factors (eg, age, smoking, diabetes, hypertension, and hyperlipidemia) are common in patients with CKD, but CKD also imposes additional unique risk factors that promote arterial disease (eg, chronic inflammation, hypoalbuminemia, and a procalcific state). Current nephrology clinical practice is adversely affected by PAD diagnostic challenges, the complexities of managing 2 serious comorbid diseases, delayed vascular specialist referral, and slow PAD treatment initiation in patients with CKD. Persons with CKD are less likely to be provided recommended "optimal" PAD care. The knowledge that both limb and mortality outcomes are significantly worse in patients with CKD, especially those on dialysis, is not just a biologic fact but can serve as a care delivery call to action. Nephrologists can facilitate positive change. This article proposes that patients with PAD and CKD be strategically comanaged by care teams that encompass the skills to create and use evidence-based care pathways. This proposed collaborative multidisciplinary approach will include vascular medicine specialists, nephrologists, wound specialists, and mid-level providers. Just as clinical care quality metrics have served as the base for ESRD and acute MI quality improvement, it is time that such quality outcomes metrics be initiated for the large PAD-CKD population. This new system will identify and resolve key gaps in the current care model so that clinical outcomes improve within a cost-effective care frame for this vulnerable population.

Key Words: Peripheral artery disease, Kidney disease, Clinical outcomes, Collaborative care, Multidisciplinary teams

Introduction

Cardiovascular disease (CVD)-related ischemic events are more common in individuals with CKD than progression to ESRD and cause significant morbidity and mortality.[1,2] Patients with CKD are more likely to develop atherosclerotic CVD than the general population with preserved kidney function,[3] and of the 3 major CVD syndromes (including both coronary artery disease [CAD] and ischemic stroke), atherosclerotic peripheral artery disease (PAD) is also highly prevalent among persons with CKD.[4] The presence of PAD in patients with CKD markedly increases the short-term risk of heart attack and stroke and serves as the key cause of limb loss and mortality, with such rates being much greater than that of the general population.[5,6] Over the last 10 years, observational studies have contributed significantly to our understanding of how decreased kidney function serves as a risk factor for PAD and its consequent adverse outcomes.[6,7] Despite this large health impact, past randomized clinical trials of PAD therapies have traditionally excluded patients with severe kidney disease, even though such individuals represent the population at highest risk.[8] As a result, current evidence-based guidelines for the evaluation and management of PAD, which might be better applied in CKD and ESRD populations, have necessarily been created by extrapolation of the risk and benefit data observed in the general population. This may contribute to the current lack of enthusiasm to apply this, otherwise strong, evidence base to inform ideal CKD care.

As there is a high CVD and PAD burden in patients with CKD, there is a need for nephrologists, cardiovascular physicians, and primary care clinicians to identify these patients, facilitate the establishment of accurate diagnoses of both CKD and PAD, and then to provide early and appropriate treatment. The objective of this article is to provide an overview of current data, spanning knowledge regarding the epidemiology, risk factors, diagnostic modalities, and potential treatment options that exist for PAD in patients with kidney disease and to apply these data to create a new care paradigm. By highlighting gaps in current practice, we urge the creation of a new, health system-based collaborative care approach that would rely on multidisciplinary care teams dedicated to improve the health and reduce the burden of PAD in persons with kidney disease.

The Epidemiology of PAD in CKD

In a recent meta-analysis, Fowkes and colleagues[9] estimated that as of 2010, nearly 202 million persons had PAD worldwide. This large burden also represents a 25% increase in PAD prevalence over the most recent decade and is attributed, in part, to the aging population and ongoing risk factor exposure internationally. It is likely, therefore, that the "CKD-PAD burden" has comparably increased in both high- and low-middle income nations globally. The prevalence of PAD in the United States is large and affects as much as 4.3% of

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the general adult population older than 40 years.[10] Persons with CKD have higher rates of incident and prevalent PAD because of the aggregation of traditional atherosclerosis risk factors. Population representative data from the National Health and Nutrition Examination Survey (1999-2000) were analyzed by O'Hare and colleagues[4] who reported that 24% of persons with CKD Stage 3 or greater (creatinine clearance of less than 60 mL/min/1.73 m^2) had PAD as objectively defined by an ankle-brachial index (ABI) less than 0.9. This was 6-fold higher prevalence rate compared with persons with a creatinine clearance of greater than 60 mL/min/1.73 m^2 (4%). Other population cohort studies have reported PAD prevalence rates ranging from 12% to 15% in individuals with CKD depending on population characteristics, the degree of kidney dysfunction, and PAD diagnostic modality used.[7,11] The actual PAD prevalence rate is likely significantly higher as the definition of clinically significant PAD has been updated by the intersocietal American College of Cardiology/American Heart Association (ACC/AHA) Scientific Statements and guidelines. A normal ABI (no PAD) is now defined by values between 1.0 and 1.4.[12] Finally, PAD prevalence rates are known to be significantly higher in persons with ESRD requiring dialysis. When PAD is broadly defined by an inclusive set of clinical criteria (including known PAD, symptomatic claudication, signs of critical limb ischemia [CLI] or reduced pulses on examination, limb artery revascularization, or past ischemic amputation), PAD prevalence ranged from 23% to 25%.[13,14] Use of the ABI as the key diagnostic criteria significantly increased prevalence rates to nearly 35%.[15,16] According to recent 2010 claims data from the USRDS, nearly 46% of all dialysis patients in the United States were offered care that was supported by a diagnostic code for PAD.[17] Thus, nephrology training programs must teach, and current nephrology clinicians simply must be adept at applying PAD-related care strategies.

CLINICAL SUMMARY

- CKD patients have a high risk of developing peripheral artery disease (PAD) and related major adverse systemic (heart attack and stroke) and limb outcomes (claudication and amputation).
- Current care standards may not be adequately effective. Nephrologists should be cognizant of the increased risks that exist when PAD and CKD are both present when planning diagnostic or therapeutic interventions.
- Multidisciplinary teams led by nephrologists and vascular physicians should collaborate to improve cardiovascular and amputation outcomes.

Pathophysiology and Risk Factors for PAD in CKD

Traditional risk factors for PAD are similar, but not identical, to those common to other atherosclerotic diseases (eg, coronary and carotid artery diseases). PAD incidence has been studied to a greater extent in dialysis patients, compared with nondialysis patients with CKD to demonstrate that male sex, older age, diabetes, and smoking were all found to be significantly associated with PAD.[14,18] These findings were recently confirmed in persons with CKD stages 3 to 5 not on dialysis using data from the Chronic Renal Insufficiency Cohort study.[19] A number of factors unique to persons with kidney disease may heighten their risk of PAD. CKD itself is strongly and independently associated with PAD. In both the general population and selected patients with CKD, the risk of PAD increases as glomerular filtration rate (GFR) values decrease after adjusting for multiple confounding variables.[19,20] However, a more direct causal association between kidney disease and PAD is yet to be established. It is possible that kidney disease may also be a marker of a metabolic condition associated with progressive vascular dysfunction.[21,22] Evidence for the possibility of a direct arterial impact of CKD is derived from previous studies that have reported associations between albuminuria,[21,22] which is a marker of generalized endothelial dysfunction and which is also a risk factor for atherosclerosis and PAD.[23] Albuminuria is also associated with medial arterial calcification (MAC) that causes elevations in ABI, leading to a "false normal" ABI value or to supranormal, high ABI measurements. It is also important to note that both atherosclerotic PAD and MAC may coexist, thus masking the true PAD burden.[24]

Patients who require dialysis have a unique set of biochemical and endocrine abnormalities that have been shown to be associated with PAD. The chronic uremic state associated with systemic inflammation in dialysis patients leads to hypoalbuminemia and an increased risk of PAD.[25] Hyperphosphatemia is highly prevalent in dialysis patients and has been shown to predict PAD events in a small case-control study.[26] Although vitamin D deficiency[27] and hyperparathyroidism[28] have been associated with a higher risk abnormal ABI, the associations of these less common modifiable risk factors need to be studied on a larger scale in dialysis patients. Hyperhomocystinemia[29] and elevated levels of lipoprotein-a have also been implicated as risk factors for PAD.[18] Results from the Chronic Renal Insufficiency Cohort study have also shown novel associations between markers of inflammation, prothrombotic state, oxidative stress, and insulin resistance with prevalent PAD among persons with CKD.[19]

Establishing the Diagnosis of PAD in CKD

The key rationale that underpins the call for a proactive evaluation of PAD in individuals with CKD is based on the usual assumption that an accurate assessment of cardiovascular risk will permit use of treatments to sustain quality of life (QoL) by lowering this risk, will detect claudication so as to preserve independent function, and will assure that amputations are prevented. We note that a "diagnostic evaluation" is not synonymous with "screening" for PAD. There is currently no defined role for population-based PAD detection efforts in the general