Noninvasive Screening and Testing for PAD in CKD Patients

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6.1 Introduction

Cardiovascular disease (CVD) is the cause of death in nearly half of end-stage renal disease (ESRD) patients [1]. An individual with ESRD has a CVD mortality rate 15 times that found in the general population. Moreover, CVD is the leading cause of death in patients with chronic kidney disease (CKD), and a patient even with early-stage CKD is five to ten times more likely to die from a cardiovascular event than progress to ESRD [2]. As nephrologists we are aware of the importance of CVD risk factor detection and modification. We are instructed by a multitude of guidelines to evaluate our ESRD and CKD patients for atherosclerotic coronary artery disease (CAD) with cardiologic referral, lipid management, and stress testing.

The prevalence of PAD increases significantly with age and is high regardless of age in patients with diabetes or tobacco abuse [14]. Previous studies have shown that peripheral arterial disease (PAD) is associated with a significantly elevated risk of cardiovascular disease morbidity and mortality and is generally regarded as a CVD equivalent in terms of mortality risk [3–5]. Despite these facts, PAD remains underdiagnosed and undertreated [14]. Patients with PAD are often asymptomatic or present with atypical symptoms, and although the severe complications of PAD are devastating and should be aggressively prevented, the benefits of detection and treatment of PAD beyond the recommended guidelines for its associated comorbid conditions remain somewhat uncertain. This may be especially true for the subset of CKD patients with PAD. The purpose of this chapter is to describe an approach to PAD screening in CKD patients.

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6.2 Pathophysiology of PAD in CKD Patients

The pathophysiology of vascular disease in the CKD population differs from the nonrenal disease population. Vascular disease associated with traditional atherosclerotic disease risk factors such as diabetes, dyslipidemia, hypertension, tobacco abuse, and aging is characterized by intimal disease with lipid-rich plaques producing focal stenoses and the potential for plaque rupture and subsequent thrombosis. In CKD, on the other hand, plaques are characterized by intense medial calcification, which tends toward chronic stenotic disease rather than acute plaque rupture [6]. Although medial calcification does occur in the aging population, the form seen in the CKD population occurs at a much earlier age and with much greater severity [7–9].

The most evident factors in the development of medial arterial calcification are serum levels of calcium and phosphate. Relatively early in the progression of CKD, the kidneys retain phosphate. The tissue most exposed to the serum is the vascular endothelium. Recent epidemiologic data suggest that there is a direct correlation between serum phosphate levels and all-cause and cardiovascular mortality in CKD and ESRD [10]. Vascular smooth muscle cells (VSMC) also appear central to the process of medial calcification. Vascular smooth muscle cells may undergo trans-differentiation into phenotypically distinct cells that are capable of generating calcification in the presence of inflammation [11].

A.S. Yevzlin et al. (eds.), *Interventional Nephrology*,
DOI 10.1007/978-1-4614-8803-3_6,

6.3 Epidemiology of PAD in CKD Population

Prior estimates of PAD prevalence in the USA have ranged from 3 to 30 % in US adult populations [12–15]. A study by Selvin et al. analyzed data from 2,174 participants aged 40 years and older from the 1999–2000 National Health and Nutrition Examination Survey [16]. PAD was defined as an ankle-brachial index less than 0.90 in either leg. The prevalence of PAD among adults aged 40 years and over in the USA was 4.3 %, which corresponds to approximately five million individuals. Among those aged 70 years or over, the prevalence was 14.5 %. Among the risk factors identified, CKD (OR 2.00, 95 % CI 1.08–3.70) conferred a twofold increased risk of PAD. Interestingly, fibrinogen and C-reactive protein levels, which are known to be disproportionately elevated in CKD patients, are also associated with PAD [16]. In an updated analysis of NHANES including data from 1999 to 2004, the estimated prevalence of PAD among US adults over 40 years of age was 5.9 %, or approximately 7.1 million individuals.

Our understanding of PAD prevalence is further enhanced by two epidemiological studies in at-risk individuals followed in community-based primary care practices. The peripheral arterial disease detection, awareness, and treatment in primary care (PARTNERS) trial assessed the prevalence of PAD in 6,979 American adults aged 70 years and older and 50 years of age or older with diabetes or tobacco abuse [14]. PAD was defined by questionnaire and ankle-brachial index testing. The study found that 29 % of all patients had PAD based on an abnormal ABI (<0.9) but that only 9 % of these patients reported typical claudication symptoms [14]. The German epidemiological trial on ankle brachial index (GETABI) determined the prevalence of PAD in 6,821 German adults by practitioner history and ankle-brachial index testing. Unlike in PARTNERS, the only inclusion criterion in the GETABI trial was that patients were aged 65 years and older. The study found that 21 % of patients had either symptomatic or asymptomatic PAD (ABI <0.9).

Most studies of cardiovascular disease in patients with CKD have not examined lower-extremity PAD per se [17–19], despite exceedingly high amputation rates in this patient population [20]. A study by O'Hare et al. examined the cross-sectional association of PAD, defined as an ankle-brachial index (ABI) <0.9, and CKD stage 3–5, defined as an estimated creatinine clearance (CRCL) <60 mL per min, among 2,229 eligible participants in the National Health and Nutrition Examination Survey (NHANES) 1999–2000 [22]. Univariate logistic regression analysis showed that compared with their counterparts with CKD stage 2 or higher kidney function, patients with moderate to severe CKD were at ninefold increased risk to have an ABI <0.9 (versus an ABI of 1–1.3). The authors developed two multivariable models to adjust sequentially for demographic characteristics and comorbid conditions that might confound the association between renal insufficiency and ABI. After adjustment for age, gender, and race, moderate to severe CKD remained strongly associated with an ABI <0.9 (OR 3.0, 95 % CI 1.7–5.3, $P < 0.001$). This association persisted after further adjustment for comorbid conditions including diabetes, coronary artery disease, and history of stroke; measures of diabetes severity (glycosylated hemoglobin, self-reported retinopathy, and insulin use); history of diagnosed hypertension; and measured blood pressure, total cholesterol, BMI, and smoking history. The authors concluded that clinicians should be aware of the remarkably high prevalence of PAD among patients with CKD. Moreover, they argued that accurate identification of patients with CKD combined with routine ABI measurement in this group would greatly enhance efforts to detect subclinical PAD.

Given the increased incidence of PAD in CKD, the K/DOQI guidelines recommend screening all patients upon initiation of dialysis [21]. The K/DOQI guidelines, however, in this particular area, must be taken with caution given the weakness in evidence supporting them. In addition, the guidelines address only dialysis patients and do not make specific recommendations for those with CKD. The issue is further complicated by the fact that there is no consensus regarding optimal treatment strategies. The issues regarding cardiovascular mortality, lower limb mortality, patient's functional status, and candidacy for available medical and interventional therapies must be weighed when making the decision to screen for PAD in CKD. Put simply, patients with CKD and ESRD may not be candidates for revascularization, which would be an argument against screening in these situations in the first place.

Therefore, before screening methods are discussed, it is important to determine risk factors for the presence of PAD. Data from waves 1, 3, and 4 of the US Renal Data System Dialysis Morbidity and Mortality Study were used to examine cross-sectional associations of a range of conventional cardiovascular risk factors and uremia- or dialysis-related variables with PAD in a recent study [22]. PAD was positively associated with the duration of dialysis (vintage) and malnourished status and was negatively associated with serum albumin and parathyroid hormone levels and predialysis diastolic BP. Kt/V was negatively associated with PVD in waves 3 and 4 but not in wave 1. PAD was associated with increasing age, white (versus nonwhite) race, male gender, diabetes mellitus, coronary artery disease, cerebrovascular disease, smoking, and left ventricular hypertrophy, as for the general population, but not with hypertension or hyperlipidemia [23].

6.4 Noninvasive Screening Methods

6.4.1 Physical Exam and History

Diagnosis begins with a detailed medical history and exam in patients who are at risk for PAD, which in our patient population includes all CKD stage 3–5 patients. The medical history should focus on symptoms of claudication, rest pain, impaired ability to walk, and nonhealing lower-extremity ulcerations. Claudication, the symptom classically associated with PAD, usually presents as reproducible muscle pain that occurs with activity and improves with rest. It results from a mismatch between oxygen supply to and demand of muscle group during exercise. Conditions other than lower-extremity atherosclerosis can result in claudication-like symptoms, such as compartment syndromes, deep venous thrombosis, and spinal stenosis. Therefore, an astute clinician should distinguish between these various diagnoses, looking for signs of trauma, edema, or back problems in addition to PAD. Although claudication is classically associated with PAD, most patients (up to 90 %) are asymptomatic or present with atypical leg symptoms [14, 24]. At more advanced stages, PAD may manifest as rest pain, nonhealing leg ulcers, or gangrene. Physical examination should focus on skin integrity (e.g., hair loss, presence of wounds or ulcers) and assessment of peripheral pulses with accurate documentation of all pulses at each visit. Diminished bilateral peripheral pulses, femoral bruits, and prolonged capillary refill are very specific for PAD [25, 26].

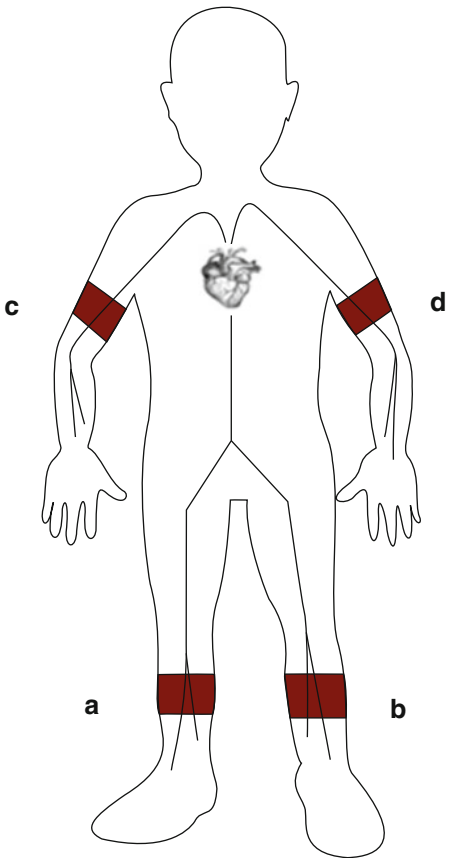

Fig. 6.1 ABI methodology. *Right ABI* right ankle systolic BP (*a*)/higher upper extremity systolic BP (left (*c*) or right (*d*)). *Left ABI* left ankle systolic BP (*b*)/higher upper extremity systolic BP (left (*c*) or right (*d*))

6.4.2 Noninvasive Testing

The ankle-brachial BP index is a simple, noninvasive, and reliable test for the detection of PAD and assessment of its severity. Clinical guidelines for PAD recommend ABI as a screening test for asymptomatic PAD of the lower extremities [27, 28]. ABI has also been reported to correlate well with PAD severity and angiographic findings [29]. One method of measurement uses a 10–12 cm sphygmomanometer cuff placed just above the ankle and a Doppler instrument used to measure the systolic pressure of the posterior tibial and dorsalis pedis arteries of each leg (Fig. 6.1). These pressures are then divided by the higher brachial pressure of either arm to form the ankle-brachial ratio or "index." A reduced ABI in symptomatic patients confirms the existence of hemodynamically significant occlusive disease between the heart and the ankle, with a lower ABI (<0.9) indicating a greater degree of hemodynamic significance of the occlusive disease. The reproducibility of the ABI varies in the literature, but it is significant enough that reporting standards require a change of 0.15 in an isolated measurement for it to be considered clinically relevant or >0.10 if associated with a change in clinical status. The typical cutoff point for diagnosing PAD is ≤0.90 at rest. However, patients with borderline reduced values (0.9–1.0) are also at increased risk of adverse cardiovascular events and mortality and should be considered for further testing and/or treatment.

In patients with PAD who do not have classic claudication (asymptomatic patients), a reduced ABI is highly associated with cardiovascular events [30]. This risk is related to the degree of reduction of the ABI (lower ABI predicts higher risk) and is independent of other standard risk factors. The purpose of screening asymptomatic patients in the general population is to attempt to modify their CVD risk by prescribing aspirin, lipid medications, diet, etc., if they are discovered to have PAD. For this reason, ABI testing is recommended in a variety of "at-risk" patient subgroups frequent to primary care practices (Table 6.1) [31]. In CKD patients, the presence of CKD alone is an independent risk factor for CVD. Thus, by virtue of CKD alone, independent of PAD diagnosis, patients should be treated with an aggressive CVD risk reduction regimen. For this reason, screening of asymptomatic CKD patients for PAD is not recommended (Tables 6.1 and 6.2). For a detailed algorithmic approach to PAD screening in the CKD population, see Fig. 6.2.

Table 6.1 Recommendations for ankle-brachial index (ABI) screening to detect PAD in the general population and in CKD population

An ABI should be measured in a non-CKD patient:	An ABI should be measured in a CKD patient:
All patients who have exertional leg symptoms	All patients who have exertional leg symptoms
All patients between the age of 50 and 69 and who have a cardiovascular risk factor (particularly diabetes or smoking)	
All patients age ≥70 years regardless of risk factor status	
All patients with a Framingham risk score 10–20 %	

Table 6.2 The value of a reduced ABI in the general population differs from that in CKD population

General population	CKD
Confirms the diagnosis of PAD	Confirms the diagnosis of PAD
Detects significant PAD in (sedentary) asymptomatic patients	Used in the differential diagnosis of leg symptoms to identify a vascular etiology
Used in the differential diagnosis of leg symptoms to identify a vascular etiology	Identifies patients with reduced limb function (inability to walk defined distances or at usual walking speed)
Identifies patients with reduced limb function (inability to walk defined distances or at usual walking speed)	
Provides key information on long-term prognosis, with an ABI ≤0.90 associated with a three- to sixfold increased risk of cardiovascular mortality	
Provides further risk stratification, with a lower ABI indicating worse prognosis	
Highly associated with coronary and cerebral artery disease	
Can be used for further risk stratification in patients with a Framingham risk score between 10 and 20 %	

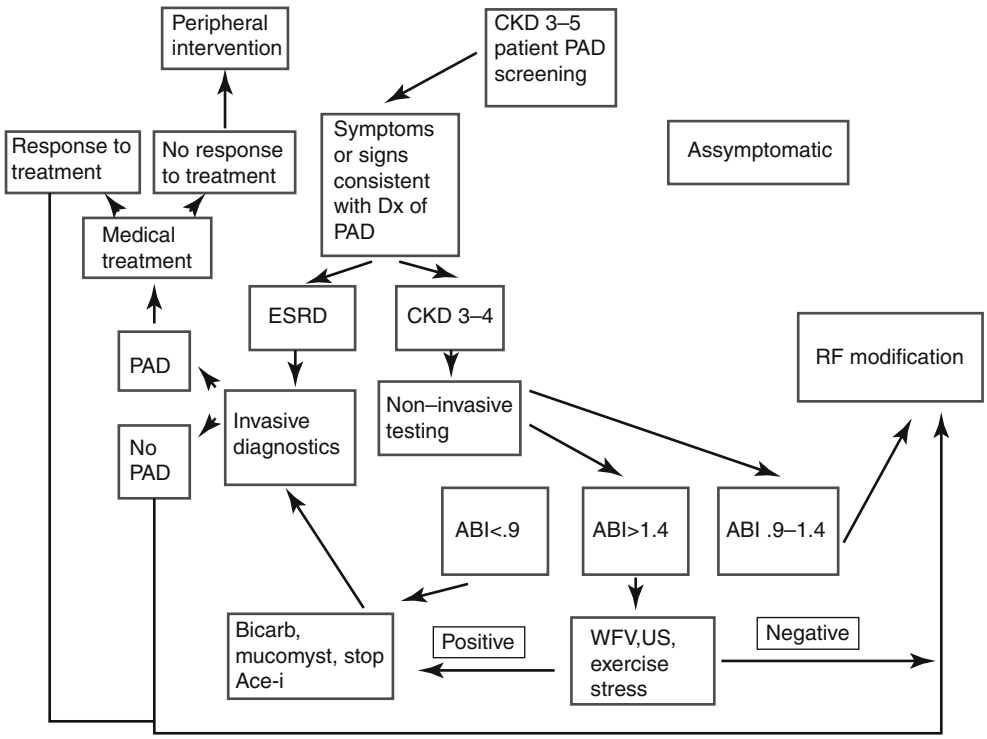

Fig. 6.2 Diagnostic approach to the CKD patient with suspected PAD. Patients with symptoms and borderline reduced ABI (0.9–1.0) values should be considered for additional testing (e.g., exercise ABI/PVR, CTA/MRA, or arterial duplex). Hemodynamically significant inflow (e.g., aortoiliac) disease may not cause a significant resting pressure gradient but will cause symptoms and can be detected with a postexercise ABI or vascular imaging study. Patients with borderline reduced ABI (0.9–1.0) regardless of symptoms are known to be at increased risk of all-cause mortality and CVD morbidity and mortality and should also be targeted for aggressive risk factor modification

However, ABI has been suggested to be unsuitable for assessing PAD in patients with diabetes, older age, history of intervention for PAD, or advanced chronic kidney disease (CKD) [18, 32, 33]. In particular, increased arterial stiffness might interfere with ABI measurements and affect the sensitivity of ABI for detecting PAD among dialysis patients. These patients typically have an ABI >1.40. In some of these patients, the Doppler signal at the ankle cannot be obliterated even at cuff pressures above 300 mmHg [31]. In these patients additional noninvasive diagnostic testing should be performed to evaluate the patient for PAD (Fig. 6.2).

In an attempt to establish a screening test for PAD that has sufficient diagnostic value and is safe and inexpen-

sive, Ogata et al. attempted to use duplex ultrasound [34]. Of the 315 patients evaluated in their study, 23.8 % had PAD. The receiver operating characteristic analysis (area under the receiver operating characteristic curve = 0.846) showed that sensitivity and specificity of ABI values for PAD were 49.0 and 94.8 %, respectively. As a result of the limitations of ABI and ultrasonographic studies in PAD screening, alternative diagnostic strategies have been employed, including magnetic resonance (MR) angiography and computed tomographic (CT) angiography. While both of these modalities have been shown to be reliably accurate in providing information regarding the presence and extent of vascular disease, they are not without limitations. Alternative tests include toe systolic pressures, pulse volume recordings, transcutaneous oxygen measurements, or vascular imaging (most commonly with duplex ultrasound).

6.4.3 Invasive Testing

Unfortunately, CT and MR, once thought to be noninvasive in nature due to their safety profile, are fraught with potential problems for the CKD population. CT uses ionizing radiation and requires the use of iodinated contrast, which is nephrotoxic and could potentially exacerbate CKD. Contrast MR angiography of the lower extremities is a highly accurate modality, which does not utilize ionizing radiation or iodinated contrast. The emergence of nephrogenic systemic fibrosis (NSF) as a complication of gadolinium use in patients with compromised renal failure has limited the continued use of MRA in the CKD population [35].

As a result, conventional angiography remains the gold standard for diagnosis of PAD in CKD patients with multiple risk factors. Angiography is a highly accurate method for evaluation of PAD. Although invasive, it offers the distinct advantage of allowing for treatment with percutaneous transluminal angioplasty (PTA) or stenting of significant lesions discovered at the time of assessment. The disadvantages of angiography include the use of iodinated contrast and ionizing radiation, relative cost, need for patient sedation and monitoring, and the potential occurrence of associated complications. The potential complications of arterial angiography include bleeding, infection, and vascular injury. Patients with CKD not yet on dialysis, and even those on dialysis in whom residual renal function is an issue, may not be able to safely undergo conventional angiography. However, the use of various preparatory methods prior to angiography seems to diminish the risk of acute kidney injury in the setting of CKD [36]. Furthermore, contrast dose can be very strictly managed in these patients by a careful and deliberate approach to diagnostic evaluation in the CKD population (Fig. 6.2).

Conclusion

PAD is a problem that affects CKD patients out of proportion to the general population and mirrors CVD outcomes very closely. Unlike the general population, PAD in CKD occurs in association with traditional atherosclerotic disease risk factors and in combination with the process of medial calcification. Screening for PAD should be performed in symptomatic patients, and CVD risk factor modification should occur in all CKD patients, regardless of the presence of PAD.

References

1. USRDS: United States Renal Data System Annual Data Report, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney Urologic and Hematologic Diseases. 2000. p. 339–48.
2. Foley RN, Murray AM, Li S, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States medicare population, 1998 to 1999. J Am Soc Nephrol. 2005;16(2):489–95.
3. Murabito JM, Evans JC, Larson MG, et al. The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: the Framingham study. Arch Intern Med. 2003;163(16):1939–42.
4. Newman AB, Shemanski L, Manolio TA, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the cardiovascular health study: the cardiovascular health study group. Arterioscler Thromb Vasc Biol. 1999;19(3):538–45.
5. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med. 1992;326(6):381–6.
6. Kerr PG, Guérin AP. Arterial calcification and stiffness in chronic kidney disease. Clin Exp Pharmacol Physiol. 2007;34(7):683–7.
7. Robinson RF, Nahata MC, Sparks E, et al. Abnormal left ventricular mass and aortic distensibility in pediatric dialysis patients. Pediatr Nephrol. 2005;20(1):64–8.
8. Goodman WG, Goldin J, Kuizon BD, et al. Coronary artery calcification in young adults with end-stage renal disease who are undergoing hemodialysis. N Engl J Med. 2000;342(20):1478–83.
9. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004;15:2208–18.
10. Young EW, Akiba T, Albert JM, et al. Magnitude and impact of abnormal mineral metabolism in hemodialysis patients in the dialysis outcomes and practice patterns study (DOPPS). Am J Kidney Dis. 2004;44(5 Suppl 2):34–8.
11. Cooper BA, Penne EL, Bartlett LH, Pollack CA. Protein malnutrition and hypoalbuminemia as predictors of vascular events and mortality in ESRD. Am J Kidney Dis. 2004;43(1):61–6.
12. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med. 2001;344(21):1608–21.
13. Braunwald E, Zipes DP, Libby P. Heart disease: a textbook of cardiovascular medicine. Philadelphia: Saunders; 2001.
14. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA. 2001;286(11):1317–24.
15. Hirsch AT, Hiatt WR, PARTNERS Steering Committee. PAD awareness, risk, and treatment: new resources for survival–the USA PARTNERS program. Vasc Med. 2001;6(3 Suppl):9–12.

16. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. Circulation. 2004;110(6):738–43.
17. Lamar Welch VL, Casper M, Greenlund K, Zheng ZJ, Giles W, Rith-Najarian S. Prevalence of lower extremity arterial disease defined by the ankle-brachial index among American Indians: the Inter-Tribal Heart Project. Ethn Dis. 2002;12:S1-63-S7.
18. Leskinen Y, Salenius JP, Lehtimäki T, Huhtala H, Saha H. The prevalence of peripheral arterial disease and medial arterial calcification in patients with chronic renal failure: requirements for diagnostics. Am J Kidney Dis. 2002;40(3):472–9.
19. Newman AB, Siscovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the cardiovascular health study: cardiovascular heart study (CHS) collaborative research group. Circulation. 1993;88(3):837–45.
20. Eggers PW, Gohdes D, Pugh J. Nontraumatic lower extremity amputations in the Medicare end-stage renal disease population. Kidney Int. 1999;56:1524–33.
21. DeLoach SS, Mohler 3rd ER. Peripheral arterial disease: a guide for nephrologists. Clin J Am Soc Nephrol. 2007;2(4):839–46.
22. O'Hare AM, Glidden DV, Fox CS, Hsu CY. High prevalence of peripheral arterial disease in persons with renal insufficiency. Circulation. 2004;109(3):320–3.
23. O'Hare AM, Hsu CY, Bacchetti P, Johansen KL. Peripheral vascular disease risk factors among patients undergoing hemodialysis. J Am Soc Nephrol. 2002;13(2):497–503.
24. Mcdermott MM, Greenland P, Liu K, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. JAMA. 2001;286(13):1599–606.
25. McGee SR, Boyko EJ. Physical examination and chronic lower-extremity ischemia: a critical review. Arch Intern Med. 1998;158(12):1357–64.
26. McDermott MM, Criqui MH, Liu K, et al. Lower ankle/brachial index, as calculated by averaging the dorsalis pedis and posterior tibial arterial pressures, and association with leg functioning in peripheral arterial disease. J Vasc Surg. 2000;32(6):1164–71.
27. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). Eur J Vasc Endovasc Surg. 2007;33 Suppl 1:S1–75.
28. K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45 (4 Supple 3):S1–153.
29. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997;26(3):517–38.
30. Heald CL, Fowkes FG, Murray GD, Price JF. Ankle brachial index collaboration: risk of mortality and cardiovascular disease associated with the ankle-brachial index: systematic review. Atherosclerosis. 2006;189(1):61–9.
31. Steffen LM, Duprez DA, Boucher JL, Ershow AG, Hirsch AT. Management of peripheral arterial disease. Diabetes Spectrum. 2008;21(3):171.
32. McLafferty RB, Moneta GL, Taylor Jr LM, Porter JM. Ability of ankle-brachial index to detect lower-extremity atherosclerotic disease progression. Arch Surg. 1997;132(8):836–40.
33. Okamoto K, Oka M, Maesato K, et al. Peripheral arterial occlusive disease is more prevalent in patients with hemodialysis: comparison with the findings of multidetector-row computed tomography. Am J Kidney Dis. 2006;48(2):269–76.
34. Ogata H, Kumata-Maeta C, Shishido K, et al. Detection of peripheral artery disease by duplex ultrasonography among hemodialysis patients. Clin J Am Soc Nephrol. 2010;5(12):2199–206.
35. Haemel AK, Sadowski EA, Shafer MM, Djamali A. Update on nephrogenic systemic fibrosis: are we making progress? Int J Dermatol. 2011;50(6):659–66.
36. Li JH, He NS. Prevention of iodinated contrast-induced nephropathy. Chin Med J (Engl). 2011;124(23):4079–82.