Elevated Ankle Brachial Indices, Incompressible Arteries, and Radiographic Artery Calcifications are Prognostic Indicators for Lower Extremity Amputation

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Statement of Purpose

Medial artery calcification (MAC) or Mönckeberg's arteriosclerosis is calcification of the tunica media in medium sized vessels and affects patients with diabetes mellitus (DM) or end-stage renal disease (ESRD). MAC is associated with an elevated ankle brachial index (ABI) and incompressible vessels.[1] A high ABI is considered abnormal, though not necessarily diagnostic of peripheral arterial disease (PAD).[2] The clinical significance of an elevated ABI is not as well understood as that of a low ABI and its association with PAD. [3] Recent studies suggest patients with elevated ABIs are at a higher risk for cardiovascular (CVD) morbidity and mortality and should be considered PAD equivalents.[1, 3-6] Other studies indicate that an elevated ABI and radiographic MAC are significant risk factors for lower extremity (LE) complications.[5-10] The purpose of this study is to evaluate the prognostic significance of high ABIs, poorly compressible arteries, (PCA) and radiographic artery calcification (RAC) in comparison to low ABI values for lower extremity amputation and morbidity in these patient populations.

Methods and Materials

This is a 13 month retrospective review of LE amputations performed at the Cleveland Clinic between July 1, 2011 and August 31, 2012. Patients were identified utilizing an electronic medical record database. We explored the distribution of ABI's and evaluated variables for an association with ABI level. Patients with PAD, DM, or chronic kidney disease (CKD) were included for review. We excluded amputations resulting from causes not related to arterial disease as well as those with incomplete records or missing arterial evaluation.

Fig. 1 Radiograph demonstrating medial artery calcification involving multiple pedal arteries in a patient with DM and CKD.

Pre-operative ABI exams were categorized into one of three groups: (1) low ABIs (< 0.9); (2) normal ABIs (0.9 - 1.3); and (3) high ABIs (> 1.3) and PCA. The following data was recorded:

- Age and Gender
- Presence of RAC
- Revascularization procedures
- Co-morbidities including: coronary artery disease (CAD), myocardial infarction (MI), hypertension (HTN), dyslipidemia (HLD), polyneuropathy (PN), and tobacco use.
- Complications including: (1) Secondary proximal amputation or (2) Delayed healing as defined as healing time greater than thirty days.

Ischemia and infection were closely evaluated as a primary cause of complications. Each case was reviewed by two investigators (EL and NN). We hypothesize that a high ABI, PCA, and RAC are significant clinical findings associated with high rates of LE amputation and poor healing.

Statistical Analysis

Descriptive statistics were computed comparing the three ABI groups. Categorical data were compared using Chi-square tests for measures of association. The Fisher's exact test was applied for expected cell counts less than five and the Cochran Mantel–Haenszel Chi-square tests were used for ordinal data. Age was non-normal and median comparisons were compared using the Wilcoxon Rank Sum test. A p <0.05 was considered statistically significant.

Literature Review

Elevated Ankle Brachial Index

High ABIs are associated with DM severity, CVD complications, PN, and amputation risk.[5] Several studies reported a correlation of elevated ABIs with all-cause and CVD mortality. [5 11,12] Furthermore, Suominen et al found that elevated ABI mortality predictability was similar to that of low ABI and demonstrated a U-shaped association between ABI and mortality risk.[3] Arain et al found that the prevalence of critical limb ischemia was higher in patients with elevated ABIs than in patients with PAD. This remained a significantly higher independent predictor of mortality than a normal or reduced ABI.[4] Silvestro et al noted increased amputation rates in patients with PCA in a prospective study of 229 patients with chronic critical limb ischemia and diabetes. In a cross-sectional study by Allison et al, patients with a high ABI had an increased risk for foot ulcers and a 1.3-fold increased amputation rate. The association between elevated ABI and amputation was independent of DM and renal insufficiency.[6]

Literature Review

Medial Artery Calcification

Everhart et al studied 4,553 subjects in a 20-year longitudinal study and identified that patients with diabetes who demonstrated radiographic MAC had a 1.5-fold increased mortality rate, 1.6-fold increased rate of CAD, and a 5.5-fold increased rate of amputation when compared to diabetic patients without MAC. They concluded MAC is prognostic for diabetic complications including amputation and mortality in type II patients.[8] Smith et al reviewed 1000 foot x-rays and demonstrated that MAC of the dorsalis pedis artery has a positive predictive value for foot ulceration requiring surgical intervention.[10] Furthermore, Guzman et al demonstrated that a novel tibial artery calcification score is associated with the stage of disease and identifies those at high risk for amputation better than traditional risk factors and an abnormal ABI.[9]

Lehto et al conducted a 7-year longitudinal study and revealed that MAC patients had significantly higher total mortality, CVD mortality, and stroke mortality (p<0.001). MAC patients also had increased LE amputations (p<0.001) than those without MAC. These authors concluded that MAC was an unrecognized powerful predictor of morbidity and mortality in type II patients with diabetes.[13] The pathogenesis of MAC is believed to be multi-factorial, including physical intra-arterial forces, immune stimulating antigens, oxidative stress, elevated serum glucose, calcium, phosphate, pro-inflammatory cytokines, and TGF-β triggering factors.[14] No evidence-based medical therapy was found to address the pathogenesis of MAC.

Results

A total of 155 patients underwent one or more LE amputations at or below-knee level between July 1, 2011 and August 31, 2012 within the Podiatric and Vascular Centers at the Cleveland Clinic. The total number of cases was 168. After applying exclusion criteria, we arrived at a final study sample of 129 patients and 140 LE amputations. Average age was 67 years with 76% men. Average length of follow-up was 14.08 weeks. Of these cases, 31 (22.1%) had a low ABI (< 0.9), 37 (26.4%) had a normal ABI (0.9 - 1.30), and 72 (51.4%) had a high ABI (> 1.3) or PCA. These constituted groups 1, 2, and 3 respectively.

DM was present in 101 (72.1%) cases, PAD in 106 (75.7%), and CKD in 73 (52.1%). RAC (Fig. 1 and Fig. 2) was present in 129 (92.1%) cases (p < .0059). DM was shown to be most prevalent in group 2 at 89.22% with a p < 0.0131. However, DM was also high in groups 1 and 3, 58.1%, and 69.4% respectively. PAD was most prevalent in groups 1 (96.8%) and 3 (86.1%) (p < 0.0001). CKD was significantly higher in groups 1 (54.8%) and 3 (62.5%) (p < 0.001). Perioperative revascularization (p < 0.0001), CAD (p < 0.0119), tobacco usage (p < 0.0075), and increased age (p < 0.0009) occurred most frequently in groups 1 and 3, which is also significant. The prevalence of MI and HLD were highest in groups 1 and 3, although not found to be significant. Full results and baseline characteristics are summarized in Table 1.

Table 1. Baseline Characteristics of Patients According to ABI level

Variable	Low ABI <0.9 n=31 (%)	Normal ABI 0.9- 1.3 n=37 (%)	High ABI >1.3 or PCA‡ n=72 (%)	p value*
Patient Age	70 + 12	59 + 11	59 + 11	.0069***
Female	10 (32.3)	4 (10.8)	21 (29.2)	0.036
Diabetes Mellitus	18 (58.1)	33 (89.2)	50 (69.4)	0.0131
Peripheral Artery Disease	30 (96.8)	14(37.8)	62 (86.1)	<0.0001
Radiographic Artery Calcification	25 (80.6)	33 (89.2)	71 (98.6)	0.0059
Revascularization	23 (74.2)	7 (18.9)	49 (68.1)	<0.0001
Coronary Artery Disease	16 (51.6)	12 (32.4)	45 (62.5)	0.0119
Chronic Kidney Disease	17 (54.8)	11 (29.7)	47 (65.3)	0.002
Myocardial Infarction	9 (29)	6 (16.2)	23 (31.9)	0.209
Hypertension	28 (90.3)	30 (81.1)	64 (88.9)	0.43
Dyslipidemia	21 (67.7)	21 (56.8)	50 (69.4)	0.403
Polyneuropathy	14 (45.2)	26 (70.3)	46 (63.9)	0.0877
Prior Amputation	12 (41.9)	19 (51.4)	30 (41.7)	0.601
History of Tobacco Use	20 (4.5)	12 (32.4)	44 (61.1)	0.0075
Charcot Neuroarthropathy	0 (0)	3 (8.11)	1 (1.39)	0.1111**

We detected advanced age in groups 1 and 3 among the different ABI groups (p < 0.009). DM was highest in group 2. (p < 0.0131) PAD and CKD was highest in groups 1 and 3 (p < 0.0001 and 0.002 respectively). RAC was prevalent in all three groups, especially group 3(p < 0.0059). The following co-morbid variables were also found to be significantly higher in groups 1 and 3: CAD (p < 0.119), LE intervention (p < 0.0001), and tobacco history (p < 0.0075).
‡Poorly Compressible Arteries. * Chi-Square test for significance unless otherwise indicated. ** Fisher's exact test. *** Wilcoxon Rank-Sum test

Results

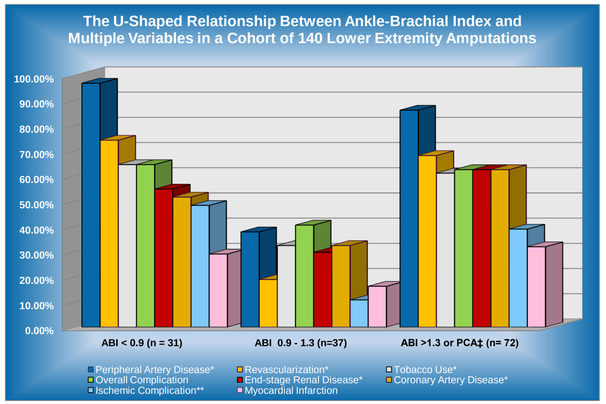

Fig. 2 The U-shaped relationship between the ABI and PAD, CAD, MI, HLD, ischemic complications, advanced age, and tobacco use, suggests that a high ABI or PCA are equally prognostic as having a low ABI. * Chi-Square test for significance unless otherwise indicated. ** Fisher's exact test. ‡Poorly Compressible Arteries

The overall complication rate was 80 (57.1%) and highest in groups 1 (64.5%) and 3 (62.5%). This was considered borderline significant (p < 0.58). Complications observed were secondary amputation and delayed healing. Statistical significance was detected for ischemia as a contributing factor in groups 1 (48.3%) and 3 (38.9%) (p < 0.0011). Infections were observed to be highest in group 3 (45.8%) which was borderline significant (p < 0.0577). There was no detected significant association between these two complications with ABI level. The number of patients who were deceased and lost to follow up was 12. Table II summarizes the complications by ABI level. There was no association detected for the type of amputation and ABI level.

Table 2. Complications by ABI level

	Low ABI (n = 31)	Normal ABI (n = 37)	High ABI or PCA‡ (n = 72)	p value*
Overall Complication	20(64.5)	15(40.5)	45(62.5)	0.058
Secondary Amputation	8(25.8)	5(13.5)	12(16.7)	
Delayed Healing	7(22.6)	9(24.3)	26(36.1)	
Death	4(12.9)	1(2.7)	7(9.72)	
Ischemia	14(48.3)	4(10.8)	28(38.9)	0.0011**
Infection	6(20.7)	13(35.1)	33(45.8)	0.0577

Two complications recorded were secondary amputation and delayed healing. There was no detected significant association to ABI level. Statistical significance was detected for ischemia as a contributing factor in groups 1 and 3 (p < 0.0011). Infections were observed to be highest in group 3 which is borderline significant . * Chi-Square test for significance unless otherwise indicated ** Fisher's exact test

Analysis and Discussion

High ABIs, PCA, and RAC are common in patients with DM and ESRD and are independent risk factors for CVD morbidity.[1, 3-6] Results of our study reaffirm this. Our data reveals a high percentage of patients with high ABIs or PCA receiving LE amputations. This has also been observed in other cohorts.[6, 7] Interestingly, a very high percentage (92.1% overall) of all 3 groups exhibited RAC. Our data supports the notion that RAC should be considered as a limb-at-risk for amputation.[10, 12, 13] Co-morbidities and other factors found to be significantly associated with both low and high ABIs include PAD, CKD, CAD, revascularization, tobacco usage, and advanced age. There was a U-shaped relationship between the ABI and these variables (Figure 2). MI and HLD also displayed this U-shaped relationship, although not significant. This data suggests that patients with low and high ABIs are equally associated with CAD, PAD, and CKD.

Analysis and Discussion

Although group 2 had 89.2% cases with diabetes, the majority were found to have ABIs in the upper limit of normal (> 1.1). Another risk factor contributing to the prevalence of LE amputations despite a normal ABI could be due to PN which was 70.3% in group 2, the highest percentage of all groups.

In our study, patients with high ABIs received LE revascularization at a comparable rate to those with low ABIs, likely attributed to co-existing intimal calcification. Our cohort had 79 cases (56.4%) of perioperative revascularization, 46 (58.2%) of which had complications. Analysis of this relationship is beyond the scope of our review. The relationship of CAD and tobacco use and its association with intimal atherosclerosis and low ABIs is well understood. [15, 16] We are not aware of any studies directly correlating MAC with CAD and tobacco use.

We found borderline significance of higher complication rates in the low and high ABI groups. Ischemia was a significant factor contributing to increased re-amputation rates and delayed wound healing. In our review of the literature, we found that a clear pathogenesis of medial artery calcification is likely multifactorial and no recommended evidence-based treatment options have emerged to address this pathology.

Fig. 2 Radiograph demonstrating intimal and medial artery calcification in tibial arteries in a patient with end-stage renal disease.

Limitations of this study include the retrospective nature which consequently had incomplete or missing records. Our study also lacks a control group where multivariate analysis could be utilized to further assess our findings as risk factors. All of the cases occurred within the last year and many of these are still under observation for final outcomes (n=21). Thus, the true complication rates could be underestimated. We also did not account for the presence of LE edema as a possible factor on complications. In addition, we found that toe brachial indices (TBI) were not readily performed on many of the cases. Therefore, we were unable to accurately assess if there was a correlation of abnormal TBIs and PAD in the setting of high ABIs. Future studies evaluating ABIs, PCA, and RAC and its association to primary LE wounds is also necessary to appraise their significance on the full breadth of LE morbidity. This study provides preliminary data in further establishing elevated ABIs, PCA, and RAC as significant risk factors for LE amputation.

In conclusion, results of our study reveal the following:

1. Elevated ABI's, PCA, and RAC are significant clinical findings associated with a high prevalence of LE amputation and delayed wound healing in patients with DM, PAD or CKD.
2. The U-shaped relationship between ABI level and PAD, CKD, CAD, MI, HLD, ischemic complications, advanced age, and tobacco use, suggests that a high ABI or PCA are equally prognostic as having a low ABI.
3. Radiographic artery calcification in the setting of PAD, DM, or CKD is a significant finding which ought to be considered an individual risk factor for LE amputation.

Since few if any medical or therapeutic measures exist to address MAC, these findings underscore the critical importance of prevention and protection in this challenging patient population.

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