RESEARCH

THE RELATIONSHIP BETWEEN ACUTE ARTERIAL OCCLUSIONS AND THE STAGE OF PERIPHERAL ARTERIAL DISEASE ACCORDING TO THE FONTAINE CLASSIFICATION

Turkish Journal of Geriatrics
DOI: 10.31086/tjgeri.2019.95
2019;22 (2):214-221

- İbrahim Murat ÖZGÜLER[1]
- Latif ÜSTÜNEL[1]
- Ayhan UYSAL[1]

CORRESPONDANCE
İbrahim Murat ÖZGÜLER
Fırat University Hospital, Cardiovascular Surgery, Elazığ, Turkey.

Phone: +904242333555
e-mail: drmuratozg@hotmail.com

Received: 17/04/2019
Accepted: 30/05/2019

[1] Fırat University Hospital, Cardiovascular Surgery, Elazığ, Turkey.

Abstract

Introduction: Peripheral vascular disease is defined as narrowing of blood vessels that restricts blood flow. Atherosclerosis is the most common etiology followed by vasculitis, dysplastic syndromes, degenerative diseases, thrombosis, and thromboembolism. The mortality rate at diagnosis is 4%–6%. Atherosclerotic peripheral vascular disease and leg amputation from such condition increase the mortality rate to 30%, and the 5-year survival rate is less than 30%. Thus, disease severity and extent of peripheral vascular disease must be evaluated and presented.

Materials and Method: Between January 2005 and March 2018,98 patients underwent surgery for acute arterial occlusion owing to chronic peripheral arterial disease were evaluated according to the Fontaine Classification, demographic characteristics, concomitant disease, physical examination findings, type of surgery and amputation and mortality rates, and its causes were analyzed.

Results: None of the patients (n=98) presented with Fontaine stage I disease. Because peripheral arterial disease is usually observed in the elderly population, elderly patients with several health problems at advanced age are more likely to undergo extremity amputation. It can be reduced by including the ankle brachial index examination in any outpatient clinic. Other stages of the disease were also evaluated in detail.

Conclusion: ABI examination should be included in the systemic examination for patients aged>70 years. Currently, lumbar hernia, osteoporosis or osteoarthritis are also observed in such patients, and the clinical signs of peripheral arterial disease are masked. Due to these diseases, the diagnosis of peripheral arterial disease is delayed.

Keywords: Peripheral arterial disease; Ankle Brachial Index; Amputation

ARAŞTIRMA

AKUT ARTERİYEL TIKANIKLIKLAR VE PERİFERİK ARTER HASTALIĞININ FONTAİNE SINIFLAMASI'NA GÖRE EVRESİ ARASINDAKİ İLİŞKİ

Öz

Giriş: Periferik vasküler hastalık, kan akışını kısıtlayacak şekilde damarların daralması olarak tanımlanır. Ateroskleroz en sık görülen etiyolojik etken olup bunu vaskülit, displastik sendromlar, dejeneratif hastalıklar, tromboz ve tromboembolizm izlemektedir. Hastalığın mortalite oranı %4-6 arasındadır. Aterosklerotik periferik vasküler hastalıkta bacak amputasyonu mortalite oranını % 30'a yükseltir ve 5 yıllık sağkalım oranı da %30'dan azdır. Bu nedenle, hastalığın şiddeti ve periferikvasküler hastalığın kapsamı iyi değerlendirilmeli ve ortaya çıkarılmalıdır.

Gereç ve Yöntem: Ocak 2005-Mart 2018 tarihleri arasında periferik arter hastalığı nedeniyle akut arter tıkanıklığı nedeniyle tedavi gören 98 hasta Fontaine Sınıflandırması, demografik özellikler, eşlik eden hastalık, fizik muayene bulguları, cerrahi tip, amputasyon ve mortalite açısından değerlendirildi, oranları ve nedenleri analiz edildi.

Bulgular: Hastaların hiçbiri (n=98) Fontaine evre I hastalığı ile başvurmadı. Periferik arter hastalığı genellikle yaşlı popülasyonda gözlendiğinden, ileri yaşta birçok sağlık problemi olan yaşlı hastaların ekstremite amputasyonu geçirme olasılığı daha yüksektir. Bu durum herhangi bir poliklinik muayenesine anklebrakiyal indeks muayenesinin de eklenmesi ile azaltılabilir. Hastalığın diğer evreleri de bu çalışmada detaylı olarak değerlendirildi.

Sonuç: Anklebrakiyal indeks muayenesi, 70 yaş üstü hastalar için sistemik muayeneye dahil edilmelidir. Hali hazırda, bu hastaların çoğunda lomber herni, osteoporoz veya osteoartrit de sık gözlendiğinden periferik arter hastalığının klinik bulguları maskelenmekte ve tanısı gecikmektedir.

Anahtar sözcükler: Periferik arter hastalığı; Ankle Brakiyal İndeks; Amputasyon

INTRODUCTION

Peripheral vascular disease (PAD) is defined as narrowing of blood vessels that restricts blood flow. It mostly occurs in the legs, but is sometimes seen in the arms. Atherosclerosis is the most frequently encountered etiology followed by vasculitis, dysplastic syndromes, degenerative diseases, thrombosis, and thromboembolism. The mortality rate at diagnosis is 4%–6% (1).

Atherosclerotic PAD and related leg amputations increase the mortality rate to 30%, and the 5-year survival rate is less than 30% (2,3). It is important to evaluate and delineate the severity of disease and extent of PAD in the management of these patients.

The incidence of PAD in developed countries ranges from 15% to 30% according to increasing age groups (4-7). In young individuals, the incidence rate is 12% (3). Male patients are more commonly affected, and the incidence in men increases with age (8). According to the results of the Global Burden of Disease Study 2013, the prevalence of the disease increased to 155% since 1990 (9). Hiatt et al. reported that PAD is a significant prognostic indicator of mortality related to myocardial infarction and stroke. In severe chronic PAD, the 1-year mortality rate is 45% (10,11).

The risk factors of PAD include smoking, hypertension, hyperlipidemia, diabetes, obesity, and history of familial vascular disease. According to the survey by the National Health and Nutrition Examination, 95% of the patients exhibit at least one of the risk factors. Approximately 70% of patients are reported to have two or more risk factors (12). Diabetes and smoking cause a 2.5-fold increase in the risk of developing PAD. A linear relationship between the number of cigarettes smoked per day and risk of developing PAD was observed (2,13). Uncontrolled diabetes is a prominent risk factor in rapidly progressing atherosclerosis and coronary artery disease (14). The forms of PAD are more severe in individuals with diabetes that progresses to insulin resistance, and such individuals are 5–10 times more at risk of limb amputation than those without diabetes. Dyslipidemia is also one of the factors correlated to PAD. Elevated serum levels of cholesterol, low-density lipoproteins (LDL), triglycerides, and lipoprotein A are independent risk factors for the development of PAD. Moreover, age is a significant risk factor that increases the risk of developing PAD (15).In patients aged ≥70 years, PAD is a common health concern (2,3). Men are more frequently affected in younger individuals with PAD. The number of affected men and women is equal in patients aged ≥60 years or older (2,3).

Currently, a notable association was observed between PAD and atrial fibrillation, congestive heart failure, obstructive sleep apnea syndrome, chronic renal failure, and other diseases (16). PAD increases the risk of atrial fibrillation, and atrial fibrillation increases the incidence of PAD (15,17).

Acute arterial obstruction in individuals with chronic vascular diseases is a rare phenomenon, and only a limited number of studies have investigated individuals with such disease. The current study aimed to evaluate acute peripheral arterial occlusion that developed as a result of chronic PAD in patients at our institution and to discuss these results in the context of the existing literature.

MATERIALS AND METHOD

Study patients

Between January 2005 and March 2018, 98 patients underwent surgery for acute arterial occlusion due to chronic peripheral arterial disease at our cardiovascular surgery department. These patients were evaluated according to the Fontaine classification as summarized in Table 1. All the patients were evaluated and demographic characteristics, concomitant disease, physical examination findings, type of surgery, and amputation and mortality rates and its causes were analyzed in the present study.The data were taken from the hospital records. Patient and ethic board approvals were obtained.

Table 1. Fontaine classification.

Stage 1	Asymptomatic patients
Stage 2a	Intermittent claudication more than 200 m
Stage 2b	Intermittent claudication less than 200 m
Stage 3	Resting pain
Stage 4	Necrosis and gangrene

Treatment protocols for PAD

The treatment options for PAD are as follows: in newly evolved clinical practice, patients undergo embolectomy with Fogarty catheter and in case of failed embolectomy, revascularization by bypass surgery on suitable segments using autologous (saphenous vein) and synthetic grafts is conducted. In patients who are not eligible for all endovascular procedures and surgical procedures, PGE2 analogue iloprost (1.5mcg/kg/min) is administered for 7 days. After medical therapy, close surveillance of possible complications is conducted. In the present study, all these therapeutic options are performed in the indicated order in majority of the patients.

Statistical analysis

All discrete variables are expressed in percentage. Continuous variables were presented as mean and standard deviation. Descriptive statistical analysis were performed using the Statistical Package for the Social Sciences software version 20 (SPSS v.20, IBM, the USA).

RESULTS

A total of 98 patients were evaluated in the present study. None of the patients presented with Fontaine stage I disease. In the following subsections, we evaluated other stages of the disease in detail.

Stage 2a Disease

A total of 6 patients presented with stage 2a disease. Of these, four (66%) were men, and two (34%) were women. The mean ages of the male and female patients were 69 and 61.5 years, respectively. One (16%) patient had a history of peripheral vascular intervention (PVI). This patient underwent leg amputation. The amputation rate was 16%. No comorbidities were observed in this group. Moreover, none of the patients died.

Stage 2b Disease

A total of 20 patients were included in this group. Fifteen (71%) patients were men and five (29%) patients were women. The mean ages of the male and female patients were 67.8 and 74.1 years, respectively. Twelve (57%) patients underwent PVI. The comorbidities were hypertension (HT) (n=5, 23%), congestive heart failure (CHF)(n=2, 9%), type 2 diabetes mellitus (DM) (n=1, 9%), chronic obstructive pulmonary disease (COPD) (n=1, 4%), chronic renal failure (CRF) (n=1, 4%), and atrial fibrillation (AF) (n=7, 33%). The characteristics of the patients are summarized in Table 2. None of the patients underwent amputation. PVI included embolectomy (n=15, 71%), femoro-femoral extra-anatomic bypass (n=1, 4%), femoropopliteal bypass with saphenous vein graft (n=1, 4%), and axillofemoral extra-anatomic bypass (n=1, 4%). Five (23%) patients who received medical treatment with iloprost were chosen. Data of the patients are summarized in Table 3. Two (8%) patients died, of which one (4%) died due to acute renal failure and the other patient (4%) died due to gastrointestinal system hemorrhage (GIB). The causes and mortality rates are summarized in Table 4.

Stage 3 Disease

A total of 50 patients were included in this group, of which 25(50%) were men and 25 (25%) were women. The mean ages of the male and female patients were 68.3 and 75.6 years, respectively. Twenty-five (50%) patients underwent PVI. The comorbidities were HT (n=24, 48%), CHF (n=26, 52%), DM (n=5, 10%), COPD (n=12, 24%), CRF (n=1, 2%), and AF (n=16, 32%). The comorbidities are summarized in Table 2. A total of eight (38%) patients underwent amputation, of which 2 (6%), 3

Table 2. Summary of comorbidities.

Fontaine	Stage 2a	Stage 2b	Stage 3	Stage 4
History of previous vascular intervention	1 (16%)	12 (57%)	25 (50%)	9 (42%)
Hypertension	-	5 (23%)	24 (48%)	2 (9%)
Heart failure	-	2 (9%)	26 (52%)	2 (9%)
Diabetes mellitus	-	2 (9%)	5 (10%)	3 (14%)
Chronic obstructive pulmonary disease	-	1 (4%)	12 (24%)	-
Chronic renal insufficiency	-	1 (4%)	1 (2%)	-
Atrial fibrillation	-	7 (33%)	16 (32%)	5 (23%)
Previous coronary artery bypass grafting	-	-	4 (8%)	-

(6%), and 2 (4%) patients underwent below-the-knee, ankle-level, and finger amputations, respectively. The distribution of the PVI is as follows:34 (68%) femoral embolectomy, 1 (2%) femoro-femoral extra-anatomic bypass, and 1 (4%) aortobifemoral bypass. Three(16%) patients received medical therapy with iloprost. The summary of the interventions are summarized in Table 3.Two (4%) patients died, of which one died due to metabolic acidosis (2%) and another patient (2%) died due to acute respiratory insufficiency caused by COPD (Table 4).

Stage 4 Disease

A total of 21 patients were included in this group, of which10 (47%) were men and 11 (53%) were women. The mean ages of the male and female patients were 67.2 and 76.3 years, respectively. Nine (42%) patients underwent PVI. The distribution of comorbidities is as follows: HT (n=2, 9%), CHF(n=2, 9%), DM (n=3, 14%),and AF (n=5, 23%). The distribution of comorbidities is summarized in Table 2. Eight (38%) patients underwent amputation, of which 2 (9%), 1 (4%),3 (14%), and 2 (9%) underwent knee-level, above-the-knee-level, ankle-level, and finger amputation, respectively. The distribution of the PVI is as follows: 11 (52%) femoral embolectomy, 1 (4%) femoro-femoral extra-anatomic bypass, 1 (2%) axillofemoral extra-anatomic bypass, 3 (6%) femoropopliteal bypass with saphenous graft, 2 (4%) aortobifemoral bypass, and 1 (2%) iliofemoral bypass. Three (14%) patients received medical therapy with iloprost. The summary of the interventions are summarized in Table 3. Two (9%) patients died, of which one (5%) died due to acute renal insufficiency and another patient died due to dissection of the iliac artery (Table 4).

DISCUSSION

Cardiovascular diseases have underlying causes that are preventable and treatable in most cases. Chronic PAD is considered one of these cardiovascular diseases. To manage these cardiovascular diseases, physicians should be aware of these risk factors. The diagnosis of PAD is simple, and it can be usually performed on bed side during physical examination. In the current study, among the 98 patients treated in the past 13 years, we did not encounter any stage 1 disease. These patients were likely admitted to different departments, such as orthopedics or physical medicine, for extremity and joint pains. Majority of the patients are present with uncertain

intermittent claudication. These patients have an inadequate vascular system, and this is associated with numerous diseases. In relation to this, the diagnosis of PAD will lead to the development of preventive measures to treat other cardiovascular diseases. The primary treatment plan is based on life style changes and reduction of risk factors. This approach will prevent individuals from developing medical problems in the future. Early diagnosis and treatment is important in such patients.

Our study showed that the average ages of patients with stage 2b disease were67.8 in men and 74.1 years in women. The symptomatic stage of PADis commonly observed in the advanced age group. This can be explained more clearly in patients with stage 3 disease, with a mean age of 68.3 years in men and 75.6 years in women. Therefore, stage 3 disease is extremely critical for limb loss. With revascularization, limb salvage can be achieved in this age group. In clinical practice, numerous patients lose time of several weeks owing to leg pain and difficulty in walking at the physical therapy and orthopedic clinics for the diagnosis and treatment of PAD. Therefore, they waste time for the transition to stage 4, which is irreversible for revascularization. However, this diagnosis will be easier if the ankle brachial index (ABI) examination is conducted, which is extremely easy to perform and does not require a long time to perform in outpatient clinics. The ABI is calculated by dividing the systolic pressure at the ankle by the systolic pressure at the arm. It is considered a specific and sensitive metric for the diagnosis of PAD. In addition, ABI is used to predict mortality and adverse cardiovascular events independent of traditional risk factors of CV. The major cardiovascular societies advice measuring the ABI of smokers aged>50 years, individuals with DM who are aged>50 years, and all patients aged >70 years. ABI examination should be included in the systemic examination of patients aged >70 years. Currently, lumbar hernia, osteoporosis or osteoarthritis are also observed in these patients, and the clinical signs of peripheral arterial disease are masked. Due to these diseases, the diagnosis of peripheral arterial disease is delayed. In this way, patients with stage 2b or stage 3 peripheral arterial disease could be diagnosed at an earlier stage and progression to stage 4 can be prevented. The fact that the mean age of male and female participants with stage 4 disease were 67.2 and 76.3 years, respectively, supports this view. We concluded that elderly patients who present with health problems

Table 3. Summary of patient therapies.

Fontaine	Stage 2a	Stage 2b	Stage 3	Stage 4
Amputation	1 (16%)	-	8 (16%)	8 (38%)
Femoral embolectomy	1 (16%)	15 (71%)	34 (68%)	11 (52%)
Femoro-femoral extra-anatomic bypass	-	1 (4%)	1 (2%)	1 (4%)
Axillofemoral extra-anatomic bypass	-	1 (4%)	1 (2%)	1 (4%)
Femoro popliteal bypass with saphenous vein	-	1 (4%)	3 (6%)	-
Aorto-bifemoral bypass	-	-	2 (4%)	1 (4%)
Iliofemoral bypass	-	-	1 (2%)	-
Ilomedin therapy	-	5 (23%)	8 (16%)	3 (14%)

Table 3. Summary of patient therapies.

Fontaine	Stage 2a	Stage 2b	Stage 3	Stage 4
Acute renal failure	1 (4%)	1 (4%)	-	1 (5%)
Gastrointestinal bleeding	1 (4%)	1 (4%)	-	-
Metabolic acidosis	-	-	1 (2%)	-
Pulmonary disease	-	-	1 (2%)	-
Dissection of the iliac artery	-	-	-	1 (5%)

at an advanced age can undergo amputation of the extremity due to this mechanism.

PAD should be considered as an expression of atherosclerotic vascular disease. Asymptomatic or subclinical disease reduces functional capacity and patient's quality of life. After the diagnosis of PAD, the incidence of cardiovascular disorder significantly increases. As critical limb ischemia occurs, cardiovascular disease-related mortality and the risk of morbidity begin to exponentially increase. The mortality rates in these conditions are comparable to that of aggressive malignancies when the population is considered. In the aging population, the prevalence of PAD and critical limb ischemia is progressively increasing. The results of the present study indicate that disease progression is observed in older female population. The treatment options include surgical, endovascular, or medical treatments.

Smoking is the main risk factor both in PAD-related mortality and the development of cardiovascular diseases. Reduced physical activity also plays an important role in increased mortality in these patients. Reduced ABI and the presence of DM-associated PAD have a direct relationship with increased mortality observed in these patients. In the present study, the incidence of comorbidities increased with increasing stages of the disease. The incidence of comorbidities in stage 2a, 2b, 3, and 4 disease is 16%, 71%, 94% and 90%, respectively. These findings indicate that the number of factors affecting the prevalence of cardiovascular diseases increase with the increase in disease stage. This indicates that PAD is a component of multisystemic diseases.

Cessation of smoking positively affects clinical outcome. This is more prominent in younger patients. The international guidelines recommend that physicians should offer patients counseling regarding cessation of smoking (18,19).

DM and ABI are indicators of cardiovascular disease-related mortality. Moreover, the severity and duration of DM affect the development of PAD (20). In the present study, 10 (10.2%) of 98 patients had DM. Studies regarding ABI have conflicting results (21-23). An ABI of <0.5 is significantlyassociated with the risk of mortality from cardiovascular diseases. In the present study, we have found that cardiovascular diseases became more prevalent with the progression of the disease. The incidence of cardiovascular diseases in stages 2b, 3, and 4 disease were 23%, 44%, and 23%, respectively. These patients are significantly at risk of critical extremity ischemia. We have found that the amputation rate and the rate of a proximal level of amputation increased as the disease progressed. The amputation rates in disease at stages 2a, 2b, 3, and 4 were 16%, 0%, 16%, and 38%, respectively.

AF is a significant risk factor in acute arterial occlusion, and it is the most frequently encountered comorbidity in our study. Its incidence among the stages of the disease was similar. AF may be the main factor affecting the evolution of the disease; however, its adverse effects are preventable with appropriate treatment. The rate of PVI increased with AF in our study.

Hyperlipidemia increases all causes of mortality in PAD. Statins used in hyperlipidemia treatment increase walking distance and reduce claudication in patients with PAD (24). In chronic occlusive vascular diseases, we routinely use treatment for anti-hyperlipidemia and monitor LDL and try to maintain the serum levels of LDL at <120 mg/dL.

In conclusion, smoking cessation and increased physical activity reduce cardiovascular disease-related mortality in patients with PAD. The presence of DM and reduced ABI are correlated to cardiovascular disease-related mortality. Surveillance for stage 1 disease must be conducted for an early diagnosis and treatment of these patients. ABI examination should be included in the systemic examination for patients aged >70 years. Currently, osteoporosis or osteoarthritis is also observed in such patients, and the clinical signs of peripheral arterial disease are masked. Due to these diseases, the diagnosis of peripheral arterial disease is delayed. In this way, patients with stage 2b or 3 peripheral arterial disease will be diagnosed earlier and progression to stage 4 disease will be prevented. Patients who are not eligible for any invasive interventions should be listed for medical therapy, and every treatment measure should be considered. In stage 4 disease, amputation should only be considered as treatment option after all other treatments have been performed.

REFERENCES

1. Malyar NM, Freisinger E, Meyborg M, et al. Lowrates of revascularization and high in-hospital mortality in patients with ischemic lower limb amputation: Morbidity and mortality of ischemic amputation. Angiology 2016;67(9):860-69. (PMID:26764367)
2. Hirsch AT, Haskal ZJ, Hertzer NR, et al. American Association for Vascular Surgery; Society for Vascular Surgery; Society for Cardio- vascular Angiography and Interventions; Society for Vascular Medicine and Biology; Society of Interventional Radiology; ACC/AHA Task Force on Practice Guidelines Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease; American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; Vascular Disease Foundation. ACC/AHA 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American association for vascular surgery/society for vascular surgery, society for cardiovascular angiography and interventions, society for vascular medicine and biology, society of interventional radiology, and the acc/aha task force on practice guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease): endorsed by the American association of cardiovascular and pulmonary rehabilitation; national heart, lung, and blood institute; society for vascular nursing; trans atlantic inter-society consensus; and vascular disease foundation. Circulation 2006;113:463-654. (PMID:16990459).
3. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45:(S)65-67. (PMID:17223489).
4. Newman AB, Sutton-Tyrrell K, Rutan GH, Locher J, Kuller LH. Lower extremity arterial disease in elderly subjects with systolic hypertension. J Clin Epidemiol 1991;44:1520. (PMID:1986053).
5. Hiatt WR, Hoag S, Hamman RF. Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. Circulation 1995;91:147279. (PMID:7867189).
6. Australian Institute of Health and Welfare. Cardiovascular disease: Australian facts 2011. Cardiovascular disease series. Cat. no. CVD 53.Chapter 8: Peripheral vascular disease. Dir:D. Kalisch 2011;117-24. (ISSN 1323-9236,ISBN 978-1-74249-130-1).

7. Fowler B, Jamrozik K, Norman P, Allen Y. Prevalence of peripheral arterial disease: persistence of excess risk in formersmokers. Aust NZ J Public Health 2002;26(3):21924. (PMID:12141616).

8. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. J Am Med Assoc 2001;286:1317-24. (PMID:11560536).

9. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause–specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385(9963):117-71. (PMID:25530442).

10. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. NEJM 2001;344:1608-21. (PMID:11372014).

11. Newman AB, Shemanski L, Manolio TA, et al.Ankle-armindex as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol 1999;19:538-45. (PMID:10073955).

12. 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;110:738-43. (PMID:15262830).

13. Kinlay S. Management of critical limb ischemia. Circ Cardiovasc Interv 9. 2016;e001946. (PMID:26858079).

14. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004;141:42131. (PMID:15381515).

15. Haring R, Travison TG, Bhasin S, et al. Relation between sex hormone concentrations, peripheral arterial disease, and change in ankle-brachial index: Findings from the Framingham Heart Study. J Clin Endocrinol Metab 2011;96:3724-32. (PMID:21937625).

16. Kullo IJ, Bailey KR, Kardia SL, Mosley TH, Boerwinkle E, Turner ST. Ethnic differences in peripheral arterial disease in the NHLBI Genetic Epidemiology Network of Arteriopathy (GENOA) study. Vasc Med 2003;8:237-42. (PMID:15125483).

17. Dhaliwal G, Mukherjee D. Peripheral arterial disease: Epidemiology, natural history, diagnosis and treatment. Int J Angiol 2007;16:36-44. (PMID:22477268).

18. Conen D, Everett BM, Kurth T, et al. Smoking, smoking cessation, [corrected] and risk for symptomatic peripheral artery disease in women: a cohort study. Ann Intern Med 2011;154:719-26.(PMID:21646555).

19. Jonason T, Bergstrom R. Cessation of smoking in patients with intermittent claudication. Effects on the risk of peripheral vascular complications, myocardial infarction and mortality. Acta Med Scand 1987;221:253-60. (PMID:3591463).

20. Al-Delaimy WK, Merchant AT, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Effect of type 2 diabetes and its duration on the risk of peripheral arterial disease among men. Am J Med 2004;116:236-40. (PMID:14969651).

21. Diehm C, Lange S, Darius H, et al. Association of low ankle brachial index with high mortality in primary care. Eur Heart J2006;27: 1743-49. (PMID:16782720).

22. McDermott MM, Feinglass J, Slavensky R, Pearce WH. The ankle brachial index as a predictor of survival in patients with peripheral vascular disease. J Gen Intern Med 1994;9:44549. (PMID:7965239).

23. O'Hare AM, Katz R, Shlipak MG, Cushman M, Newman AB. Mortality and cardiovascular risk across the ankle-arm index spectrum: results from the Cardiovascular Health Study. Circulation 2006;113:388-93. (PMID:16432070).

24. Mohler ER 3rd, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. Circulation2003;108:148186. (PMID:12952839).