ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 03 | March - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ASSOCIATION OF ANKLE BRACHIAL INDEX WITH CARDIOVASCULAR AND SOCIODEMOGRAPHIC RISK FACTORS IN DIABETIC POPULATION

Diabetology

Sejal Bheda — Post graduate Student, PT School and Center, Seth GS Medical College and KEM hospital, Parel, Mumbai.

Mariya P Jiandani* — Associate Professor,PT School and Center, Seth GS Medical College and KEM hospital, Parel, Mumbai.*Corresponding Author

Amita Mehta — Professor & Head, PT School and Center, Seth GS Medical College and KEM hospital, Parel, Mumbai.

ABSTRACT

Lower-extremity arterial occlusive disease is much more likely to occur in patients with type II diabetes. Due to rapidly increasing prevalence of Diabetes and its dreadful complications like amputation and associated mortality, it is crucial to screen symptomatic as well as asymptomatic diabetic patients for peripheral arterial disease (PAD) at an early stage. There is immense evidence stating increased risk of coronary vascular disease(CVD) and PAD in diabetics. The risk factors being similar to that of CVD, there is less information available regarding association of Ankle brachial index with individual cardiovascular risk factors in diabetic population. This study was done with the objective to evaluate association of Ankle Brachial Index (ABI) with Physical activity level, chronicity of Diabetes Mellitus ,cardiovascular risk factors and sociodemographic factors.

Methods: Type 2 diabetic patients coming to diabetic-endocrinology OPD of tertiary care hospital were evaluated for Fasting Blood Sugar, Serum Total cholesterol and Serum Triglycerides, International Physical Activity Questionnaire- long form (IPAQ LF). ABI was evaluated and interpreted as per guidelines of American Heart Association. Data was analyzed using SPSS for windows version 16 software.

Results: Total 500 patients (male=271, female=229) with mean age 57.85 (± 9.66) years participated in the study. The association of ABI was statistically significant with Physical activity level (p= 0.005), chronicity of Diabetes Mellitus (p< 0.001), Glycemic control (p= 0.02), Serum Total Cholesterol (p <0.001) and Serum Triglycerides (p = 0.032). The association of ABI with Waist circumference (p=0.307) and Smoking (p= 0.380) was statistically not significant. The study also revealed significant association of ABI with age (<0.001), gender (<0.001), weekly sitting time (p= 0.002), presence of claudication symptom (0.019), annual family income (p= 0.021)and family history of diabetes mellitus (p= <0.001).

Conclusions: This study revealed significant association of Ankle Brachial Index with cardiovascular risk factors and socio-demographic parameters.

KEYWORDS

Ankle Brachial Index (ABI), Cardiovascular Risk Factors, Diabetes, Physical Activity, Peripheral Arterial Disease.

Diabetes is a considered to be health-threatening concomitant disease all over the globe. The world prevalence of diabetes today are 425 million and this is expected to increase to 629 million by the year 2045.[1] India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "diabetes capital of the world" .[2] The number of patients with diabetes in India currently are 72.9 million. This is said to increase to 134.3 million by the year 2045 .[3]

Diabetes is a serious, common, costly and controllable disease. Controlling diabetes is easier and cheaper than managing its complications. The data from several epidemiological, experimental - human and animal studies and more recently the data from several mega trials like the Diabetes control and complications trial (DCCT), Kumomoto study and the UK prospective diabetes study (UKPDS) have convincingly proved the importance of tight metabolic control in arresting the progression and prevention of microvascular disease. Hyperglycemia contributes to the increased incidence of macrovascular disease but dyslipidemia, hypertension, central obesity, decreased physical activity, and smoking play a major role in accelerated atherosclerosis seen in diabetics.[4]

Few Indian studies have assessed peripheral arterial disease (PAD) in diabetics. Two large studies from South India, namely, by Mohan et. al.[5] (n=4941) and Chennai urban population study (CUPS)[6] (n=1262) found a prevalence of PAD in diabetics to be 3.9% and 6.3%, respectively. Two recent studies from North India, one by Agrawal et al[7] (n=4400) and the other by Madhu et al[8] (n=364) found the prevalence of PAD in diabetics to be 18.1% and 13.73%, respectively.
Peripheral arterial disease (PAD) is characterized by atherosclerotic occlusive disease of the lower extremities and is a marker for atherothrombotic disease in other vascular beds.[9] While PAD is a major risk factor for lower-extremity amputation, it is also accompanied by a high likelihood for symptomatic cardiovascular and cerebrovascular disease. Diabetic patients with Intermittent claudication have a 35% risk of sudden ischaemia and a 21% risk of major amputation, compared with 19% and 3%, respectively, in non-diabetic patients.[10] The risk of PAD is inversely related to previous levels of physical activity suggesting a protective effect of exercise.[11] The major risk factors in diabetic PAD leading to amputation have been reported as hyperlipidemia, obesity, abnormal glucose tolerance, smoking, and hypertension.[12]Due to rapidly increasing prevalence of Diabetes and its dreadful complications like amputation, CVD and mortality, it has become very crucial to screen symptomatic as well as asymptomatic diabetic patients for PAD at an early stage. There is immense evidence stating increased risk of CVD and PAD in diabetics. But, there is less information available regarding association of Ankle brachial index with individual risk factors like physical activity, glycemic control, lipid profile, waist circumference and smoking in diabetic population. Also, there is disparity in the results in the available data from the literature about the association on ankle brachial index with cardiovascular risk factors like physical activity, lipid levels and obesity.

This study was undertaken to evaluate the association of a cardiovascular risk factors with ABI so that primary prevention and risk factor modification can be implemented at an earlier stage. The association of Ankle Brachial Index with cardiovascular risk factors namely-Physical activity and chronicity of Diabetes Mellitus, Glycemic control, Waist circumference, Serum Total Cholesterol (Sr. TC) and Serum Triglycerides (Sr. TG), Smoking were studied.

MATERIALS & METHODS:

A Cross-sectional study was carried out in Diabetic OPD at Endocrinology department of a Tertiary health care hospital. Ethical approval was obtained from institutional ethics committee. Sample size was calculated using the formula given below **n=4pqNe2 (N-1)+4pq** (Where, n= desired sample size, N= Available subjects = 750, p= prevalence of Abnormal ABI (ABI ≤ 0.9) = 21% from pilot study on 50 subjects, q= 100-p = 79, e= error (~10% p)= 4.41).Approximately 720 patients were screened and 500 Patients in age group between 30 and 80 years both males and females diagnosed with Diabetes Mellitus by the physician based on Criteria for diagnosis of diabetes by American Diabetes Association 2012and having necessary blood reports (Fasting blood sugar and Sr. TC, Sr. TG reports) were included.

Patients with Diabetes Mellitus other than Type 2, patients with amputation of both lower limbs, Patients having Ulcers and swelling in lower limbs, Patients on Vasodilator drug therapy, Patients not willing to participate, Patients not willing to sign their consent were excluded. Demographic details including name, age, residence, occupation, annual family income, were noted. Duration and treatment of diabetes, symptoms of vascular claudication, smoking and/or alcohol intake, hypertension, symptoms of coronary artery disease or intervention and family history of diabetes for the same was also noted.

Glycemic control was measured by taking mean of 3 readings of Fasting blood sugar test done within previous 6 months. Fasting blood sugars between 70-130 mg/dl was considered good glycemic control for adults and between 90-130mg/dl for elderly population as per American Diabetes Association guidelines 2014. Fasting blood sugar levels were taken as all patients do not have Glycosylated Haemoglobin values. Values of Serum total cholesterol and serum triglycerides were noted from the filed reports done within previous 6 months of the study. Anthropometric measurements like body mass index and waist circumference was measured by standard methods. The WHO STEPS protocol for measuring waist circumference was followed (WHO, 2008b).

Physical activity was measured using international physical activity questionnaire. (IPAQ). It includes multiple domains of physical activity like job related, transportation, household, recreation/ sports and sitting. The scoring was done in MET* MIN / WEEK .

Resting parameters of ABI were measured with patient in supine position after 5 minutes of rest, as per standard guidelines given by American heart association (Circulation 2012)using Portable Doppler Unit (Emco Mini dop D 500 Pocket Doppler).ABI was calculated and interpreted according to the American Heart Association definition by dividing the higher systolic pressure of the right and left ankle by the higher systolic pressure of both the arms. Lower ABI of the two was considered. (ABI=SBP of Ankle/ SBP of Arm)

- ABI <0.9 – Abnormal low
- ABI 0.91-0.99 – Borderline abnormal
- ABI- 1-1.4 – Normal
- ABI >1.4- High, Non compressible arteries.

RESULTS :

Total 500 (271 males and 229 females) subjects participated in the study. Baseline characteristics are as given in the table 1. 24.45 % females had abnormal ABI as compared to 18.81% males . Association of Ankle brachial index was assessed with categorical variables like Physical activity, chronicity of Diabetes Mellitus, Glycemic control (mean of 3 FBS), Waist circumference, Serum Total Cholesterol (Sr. TC), Serum Triglycerides (Sr. TG) and Smoking by applying Chi square test and ANOVA test for continuous variable like 'sitting time per week'; Association of ABI with sociodemographic variables like age, sex, annual family income, family history of diabetes were also analyzed by chi square test using Statistical package for social sciences (SPSS) for windows version 16 Software. Statistical significance was defined by p value ≤0.05

Table 2 highlights the proportion of patients with abnormal ABI and Table 3 shows the association with various factors. The association of ABI was statistically significant with duration of diabetes (p value <0.005) ,Glycemic control (p= 0.020), Serum Total cholesterol(p value <0.001) and triglycerides (p value = 0.032). The association of ABI with glycemic control ,when analysed with only two categories of ABI , that is ≤0.9 and >0.9 , was statistically not significant (p =0.066). There was significant association with physical activity. On comparing the mean sitting time values with respect to ABI categories using One way ANOVA test, it was found that at least one of these categories of mean sitting time differ significantly from others (p=0.002) (Table 4).Hence, multiple comparison test was performed to confirm the results .Significant difference between the mean sitting time of Low and normal ABI categories (p = 0.019) was found.

Although, more number of subjects with abnormal waist circumference had ABI ≤ 0.9, the association of ABI with waist circumference was statistically insignificant (p = 0.143). Similarly the association of ABI with Smoking was statistically insignificant (p = 0.380) with a Risk ratio= 1.12 (0.87-1.4) and Odds ratio= 1.222 (0.759-1.914) at 95% CI

On evaluation of the association between ABI and socioeconomic factors there was a statistically significant association with income (p = 0.021). ABI ≤ 0.9 was seen to be significantly more in subjects having family history of diabetes (p <0.001).

Table . 1:Mean Demographic Variables Of Participants

Variable	Mean	Range
Age (years)	57.85 (± 9.66)	30-80
BMI (Kg/ m2)	26.21 (± 0.08)	16.27-44.44
Waist circumference (centimeters)	90.63 (± 10.43)	65-133
Mean Fasting blood sugar (mg/dl)	143.57 (± 62.33)	52-584
Serum total cholesterol (mg/dl)	164.34 (± 40.96)	70-311

Table . 2: Association Of ABI With Cardiovascular And Sociodemo graphic Factors

Variable	Chi 2 Value	P Value
Gender	43.044	<0.001[c]
Age	25.868	<0.001[c]
Physical activity level	10.688	0.005[c]
Duration of diabetes	20.562	<0.001[c]
Glycemic Control	9.836	0.020c
Serum Total cholesterol	17.690	<0.001[c]
Serum Triglycerides	8.839	0.032[c]
Waist circumference	2.141	0.143 [c]
Smoking	0.769	0.380 [c]
Sitting time		0.002[(a)]
Annual family income	13.234	0.021
Claudication	5.519	0.019[c]
Family history of diabetes	14.971	<0.001[c]

Table 3 :Proportion Of Participants With Abnormal ABI

Variable	Abnormal ABI (%)	
AGE (YEARS)	30-40	18.8
	40-50	13.8
	50-60	19
	60-70	19.3
	70-80	48.9
Gender	Male	18.81
	Female	24.45
BMI (Kg/Meter2)	< 25	19.47
	≥ 25	22.99
Waist Circumference	NORMAL	17.6
	HIGH	23.3
Duration Of Diabetes Mellitus	0-1 YEAR	14.1
	1-3 YEARS	24.2
	3-10 YEARS	21.8
	>10 YEARS	23
Family Annual Income	Rs. 0-50,000	26
	Rs.50,000-1 Lakh	15.2
	Rs.1 Lakh-3Lakhs	9.1
	>Rs.3 Lakhs	13.95
Glycemic Control	Good	18
	Poor	24.7
Serum Total Cholesterol	< 200(mg/dl) (Normal)	19.8
	>200 (mg/dl) (High)	31
Serum Triglycerides	<150 (mg/dl) (Normal)	18.13
	>150(mg/dl) (High)	30.147
Physical Activity	Low (<600 MET-minutes/week)	24.2
	Moderate (600-3000 MET-min/week)	22.9
	High (>3000 MET-in/week)	8.1
	Low (<600 MET-minutes/week)	24.2
Claudication	Present	29.8
	Absent	19.2
Smoking/ Tobacco Use	Present	45
	Absent	40.9
Family History Of Diabetes Mellitus	Present	28.13
	Absent	13.92

Table 4: Association Of ABI With Sitting Time

	ABI Category	mean	Std dev	95% CI for mean		min	max	P value
				Lower bound	Upper bound			
Sitting time (min)	Low	3870.2804	1093.68	3660.65	4079.90	840.00	5040.00	0.002
	Borderline Low	3288.40	1244.97	3024.62	3552.19	1260.00	5040.00	
	Normal	3429.15	1426.50	3265.41	3592.89	252.00	13440.00	
	High	4276.36	770.28	3758.87	4793.85	2940.00	5040.00	
	Total	3517.42	1335.77	3400.05	3634.79	252.00	13440.00	

DISCUSSION

Diabetes is a dreadful condition due to the associated complications leading to increased rate of comorbidity and mortality. [13] Uncontrolled diabetes worsens prognosis in any medical and surgical conditions.[14] This study aimed to find association of ankle brachial index with cardiovascular risk factors viz. physical activity level, chronicity of diabetes, diabetes control, obesity, serum total cholesterol & triglyceride levels, and smoking; and we found significant association with all the above except obesity and smoking. We also assessed its association with weekly sitting time, family history of diabetes, gender and age and it was significant with weekly sitting time, presence of positive family history of diabetes, female gender and older age.

Simillar to study done by Agarwal et. al. [15] and Tavintharanet. al[16] greater proportion of females had abnormal ABI. It has been shown that there is a sex difference in the degree of calcification between coronary artery and peripheral arteries (e.g. thoracic aorta), with men having greater coronary calcification and women having greater calcification of the thoracic aorta. This raises the possibility that the associations between sex and atherosclerosis may differ between vascular beds, and in part may explain why, compared with men, women are more likely to develop PAD but less likely to develop CAD. As seen in Table 2 and 3 there is a significant association between physical activity & ABI and between weekly sitting time & ABI suggesting that more number of diabetic patients with high physical activity and less sitting time had normal ABI scores as compared to sedentary patients. The mechanism by which sedentary state may predispose to PAD cannot be determined from present study, but there are several physiological possibilities. Exercise may enhance endothelial function, by upregulating vasoprotective pathways such as hemeoxygenase, superoxide dismutase and nitric oxide synthase, and by down-regulating the expression of proteins mediating vascular inflammation and thrombosis. [17] In patients with PAD, regular activity has been associated with improvements in endogenous fibrinolysis, improved microcirculatory function and reduced mortality . [18]It has also been shown that patients with PAD who walk regularly, experience less functional decline over time. We cannot determine the cause – effect relationship but physical activity is associated with better disease state as well as outcome in diabetic patients.

Studies done by Walters et al [19] showed that PAD is closely associated with glycemic control and duration of diabetes. In patients with diabetes, hyperglycemia has been postulated as being responsible for the non-enzymatic glycation of proteins such as elastin and collagen. Nitric oxide (NO) is a potent stimulus for vasodilatation and limits inflammation via its modulation of leukocyte-vascular wall interaction. Furthermore, NO inhibits vascular smooth muscle cell (VSMC) migration and proliferation and limits platelet activation. Therefore, the loss of normal NO homeostasis can result in a cascade of events in the vasculature leading to atherosclerosis and its consequent complications.

It is known that platelets play an integral role in the connection between vascular function and thrombosis. Therefore, abnormalities in platelet biology may not only promote the progression of atherosclerosis, but also influence the consequence of plaque disruption and atherothrombosis leading to dangerous [20] complications. As in the endothelial cell, platelet uptake of glucose is unchecked in the setting of hyperglycemia and results in increased oxidative stress. Consequently, platelet aggregation is enhanced in patients with diabetes.

Platelets in diabetic patients also have increased expression of glycoprotein Ib and IIb/IIIa receptors, which are important in thrombosis via their role in adhesion and aggregation. Lipid modifications noted in diabetic patients, such as glycated oxidized low-density lipoprotein, can promote apoptosis of VSMC.[21] DM and hyperglycemic states promote hypercoagulability via upregulation of tissue factor by endothelial cells and VSMCs These conditions also increase coagulation factor VIIA production and decrease anticoagulants, such as antithrombin and protein C production. The overall effect of hyperglycaemia on vascular endothelium is detrimental, leading to occlusive arterial disease. Chronic diabetes is strongly associated with the severity of these changes.

The lipid abnormalities are generally associated with lower extremity PAD. The association of ABI was statistically significant with Sr.TC and Sr.TG owing to higher proportion of patients having abnormal ABI having raised lipid levels in the present study. These findings were supported by a study done by Mohan et al[22]

High TG levels are markers for atherogenic lipoproteins, particularly important in patients with insulin resistant syndromes such as type 2 DM. Patients with type 2 DM commonly present with combined dyslipidemia which is characterized by fasting and postprandial hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C) levels, small LDL and HDL particles, and accumulation of partially metabolized chylomicrons (CMs) and very low density lipoproteins (VLDLs), the so-called remnant particles rich in apolipoprotein (apo) C-III and cholesterol. Lipids play a key role in the initiation and progression of atherosclerosis in large vessels, which is the major cause of lower extremity PAD.

The association of ABI with waist circumference was not statistically significant in present study. Planas et al [23] found in their study that abdominal fatness but not total body fatness was predictor of peripheral occlusive arterial disease in elderly men. However, in other studies, association between ABI and obesity was not significant.

In this study the association of ABI with smoking was not found to be statistically significant Although these results were similar to some of the studies many other studies have found significant association between these two variables. In spite of these findings, given the known health benefits of smoking cessation, it is advisable that efforts to cease smoking should be considered.

The association of ABI was found to be significant with family annual income with higher proportion of patietns with abnormal ABI in lower income group (< 50000/ year) . Studies from different populations have demonstrated that cardiovascular risk factors and disease disproportionately affects those of lower socioeconomic status. [24] R. Pande and M. Creager analyzed data from the National Health and Nutrition Examination Survey 1999–2004 to determine whether there was a higher prevalence of peripheral artery disease (PAD) in individuals with lower socioeconomic status. They found that the PAD prevalence was significantly higher in individuals in lower income categories and there was no significant difference in the findings even after adjusting for differences in use of cardiovascular risk modifying medications, such as anti-platelet therapy, statins, beta-blockers, and ACE inhibitors or angiotensin receptor blockers. [25] Awareness of healthy lifestyle and compliance to treatment could be considered to mediate the SES–atherosclerosis relationship.

The association of ankle brachial index with family history of diabetes was observed to be statistically significant in the diabetic population. It was also observed that the proportion of abnormal ABI in subjects with family history of diabetes was 28.13 % as compared to only 13.92 % in those without family history. The possible reason for this association could be the genetic predisposition to diabetes and hypercholesterolemia which are known risk factors of PAD.

The study being cross sectional, the causal relationship of ABI and cardiovascular risk factors could not be determined. Ideal methods like Glycosylated heamoglobin (HBA1C) for assessing glycemic control, Accelerometry for physical activity level assessment and Arterial colour Doppler for diagnosing peripheral arterial disease were not feasible considering the cost involved . Therefore, mean of 3 Fasting blood glucose values, International physical activity questionnaire and Ankle brachial index were used respectively. This was a single centre study and hence there could be a population bias.

The study showed association of Ankle Brachial Index with modifiable cardiovascular risk factors like reduced physical activity, sedentary lifestyle, poor glycemic control and abnormal lipid levels and non-modifiable risk factors like increasing age, female sex, chronicity of diabetes mellitus and family history of diabetes mellitus.

Therefore, it is advisable that all the diabetics attending Medical or Endocrine OPD should be screened for peripheral arterial disease irrespective of presence or absence of claudication symptoms, using quick, simple, and reliable test - Ankle Brachial Index. Also, Lifestyle modification should be initiated at the earlier stages to prevent and control the complications related to Diabetes Mellitus and to achieve better prognosis.

Acknowledgements: Dr Ujwal Yeole, Associate Professor & Principal, Dept. of Physiotherapy, Tilak Maharashtra Vidyapeeth, Pune; Dr Tushar Bandgar, Prof & Head, Department of Endocrinology, Seth GS Medical College and KEM hospital, Parel, Mumbai.

REFERENCES :

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care. 1998 Sep;21(9):1414–31.
2. Joshi SR, Parikh RM. India--diabetes capital of the world: now heading towards hypertension. J Assoc Physicians India. 2007 May;55:323–4.
3. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes: Indian scenario. The Indian journal of medical research. 2007
4. Ramachandran A, Snehalatha C, Latha E, Manoharan M, Vijay V. Impacts of urbanisation on the lifestyle and on the prevalence of diabetes in native Asian Indian population. Diabetes Res ClinPract. 1999 Jun;44(3):207–13.
5. Eshcol J, Jebarani S, Anjana RM, Mohan V, Pradeepa R. Prevalence, incidence and progression of peripheral arterial disease in Asian Indian type 2 diabetic patients. J Diabetes Complications. Elsevier; 2014 Jan 9;28(5):627–31.
6. Premalatha G, Shanthirani S, Deepa R, Markovitz J, Mohan V. Prevalence and risk factors of peripheral vascular disease in a selected South Indian population: The Chennai urban population study. Diabetes Care. 2000;23(9):1295–300.
7. Agrawal R, Ranka M, Beniwal R. Prevalence of micro and macro vascular complications in type 2 diabetes and their risk factors. Int J Diabetes DevCtries. 2004;24:11–6.
8. S. V. Madhu SK, Department. Preclinical evaluation of athrosclerosis.Int J Diabetes DevCtries. 2006;26(3):105–11.
9. Sheehan P. Peripheral Arterial Disease in People With Diabetes: Consensus Statement Recommends Screening. Clin Diabetes. 2004 Oct 1;22(4):179–80.
10. McDaniel MD, Cronenwett JL. Basic data related to the natural history of intermittent claudication. Ann Vasc Surg. 1989 Jul;3(3):273–7.
11. Housley E, Leng GC, Donnan PT, Fowkes FG. Physical activity and risk of peripheral arterial disease in the general population: Edinburgh Artery Study. J Epidemiol Community Health. 1993 Dec;47(6):475–80.
12. Beach KW, Brunzell JD, Strandness DE. Prevalence of severe arteriosclerosis obliterans in patients with diabetes mellitus.Relation to smoking and form of therapy.Arteriosclerosis. Jan;2(4):275–80.
13. American College of Endocrinology and American Diabetes Association Consensus statement on inpatient diabetes and glycemic control. Diabetes Care. 2006 Aug;29(8):1955–62.
14. Ouattara A, Lecomte P, Le Manach Y, Landi M, Jacqueminet S, Platonov I, et al. Poor intraoperative blood glucose control is associated with a worsened hospital outcome after cardiac surgery in diabetic patients. Anesthesiology. 2005;103(4):687–94.
15. Agarwal AK, Singh M, Arya V, Garg U, Singh VP, Jain V. Prevalence of peripheral arterial disease in type 2 diabetes mellitus and its correlation with coronary artery disease and its risk factors. J Assoc Physicians India. 2012 Jul;60:28–32.
16. Subramaniam T, Nang EEK, Lim SC, Wu Y, Khoo CM, Lee J, et al. Distribution of ankle--brachial index and the risk factors of peripheral artery disease in a multi-ethnic Asian population. Vasc Med. 2011 Apr;16(2):87–95.
17. Cooke JP. Flow, NO, and atherogenesis. ProcNatlAcadSci U S A. 2003 Feb 4;100(3):768–70.
18. Garg PK, Tian L, Criqui MH, Liu K, Ferrucci L, Guralnik JM, et al. Physical activity during daily life and mortality in patients with peripheral arterial disease. Circulation. 2006;114(3):242–8.
19. Walters DP, Gatling W, Mullee MA, Hill RD. The prevalence, detection, and epidemiological correlates of peripheral vascular disease: a comparison of diabetic and non-diabetic subjects in an English community. Diabet Med. 1992 Oct;9(8):710–5.
20. Brownlee M, Vlassara H, Cerami A. Nonenzymatic glycosylationand the pathogenesis of diabetic complications. Ann Intern Med. 1984 Oct;101(4):527–37.
21. Suzuki LA, Poot M, Gerrity RG, Bornfeldt KE. Diabetes accelerates smooth muscle accumulation in lesions of atherosclerosis: lack of direct growth-promoting effects of high glucose levels. Diabetes. 2001 Apr;50(4):851–60.
22. Mohan V, Premalatha G, Sastry NG. Peripheral vascular disease in non-insulin-dependent diabetes mellitus in south India.Diabetes Res ClinPract. 1995 Mar;27(3):235–40.
23. Planas A, Clará A, Pou JM, Vidal-Barraquer F, Gasol A, de Moner A, et al. Relationship of obesity distribution and peripheral arterial occlusive disease in elderly men. Int J Obes Relat Metab Disord. 2001 Jul;25(7):1068–70.
24. Subherwal S, Patel MR, Tang F, Smolderen KG, Jones WS, Tsai TT, et al. Socioeconomic disparities in the use of cardioprotective medications among patients with peripheral artery disease: an analysis of the American College of Cardiology's NCDR PINNACLE Registry. J Am CollCardiol. Journal of the American College of Cardiology; 2013 Jul 2;62(1):51–7.
25. Pande RL, Creager MA. Socioeconomic inequality and peripheral artery disease prevalence in US adults.Circ Cardiovasc Qual Outcomes. 2014 Jul 1;7(4):532–9.