Evaluation of Peripheral Arterial Disease in Prediabetes

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Date of Submission: May 01, 2014

Date of Acceptance: Jun 14, 2014

How to cite this article: Faghihimani E, Darakhshandeh A, Feizi A, Amini M. Evaluation of Peripheral Arterial Disease in Prediabetes. Int J Prev Med 2014;5:1100-6.

Original Article

ABSTRACT

Background: The prevalence of prediabetes in the world continues to increase. These patients have elevated the risk of atherosclerosis. The current study was designed to assess the prevalence of peripheral arterial disease (PAD) and its related risk factors in prediabetes patients.

Methods: This was the case-control study in which 135 adults in three groups: Diabetes, prediabetes, and normal were studied. We evaluated the prevalence of PAD through the measurement of ankle-brachial index (ABI). All the patients were interviewed about demographic and medical data, including age, sex, disease duration, body mass index, hypertension (HTN), fasting blood glucose, hemoglobin A1C (HbA1C), lipid profile, and medication use.

Results: The prevalence of PAD in diabetes patients was higher than the normal group (8.5%vs. 0.0%) ($P < 0.05$), but the differences between prediabetes compared with diabetes and normal group were not significant. The mean level of ABI in normal, prediabetes, and diabetes group was (1.11 ± 0.11), (1.09 ± 0.12), and (1.05 ± 0.03) respectively ($P < 0.1$). There were marginally significant differences of ABI observed between the normal group and the diabetes group. The observed differences between groups in the ABI were significant after adjusting the effects of age and sex ($P < 0.05$). There was an association observed between ABI and HbA1C in diabetes patients ($r = 0.249$, $P < 0.01$) and a significant association seen between PAD and HTN in the prediabetes group ($P < 0.01$).

Conclusions: Peripheral arterial disease is common in asymptomatic diabetes and prediabetes patients. Management of hypertensive prediabetes patients and early detection of PAD in this group as well as in asymptomatic patients is important.

Keywords: Ankle-brachial index, diabetes, peripheral arterial disease, prediabetes

INTRODUCTION

Diabetes mellitus is a public health problem; prevalence of the disease is progressively on the rise. In the year 2000, 171 million (2.8%) people had diabetes, and it is estimated that this number will rise to 366 million (4.4%) in 2030.[1] As the prevalence of diabetes continues to increase, the incidence of diabetes-related complications is also projected to increase. Diabetes foot is one of the most common complications of diabetes. The lifetime risk for foot ulcer in diabetes patients is up to 15%.[2] Diabetes is the most common cause of nontraumatic lower limb amputation in the US[3] and more than 80,000 lower limb amputations in diabetes patients are performed each year in the US alone.[4] Beside the economic burden, diabetes foot is also associated with low quality of life due to associated pain and difficulty walking.[5] Several pathogenic factors are responsible for diabetes foot ulceration among which neuropathy, abnormal foot biomechanics, peripheral arterial disease (PAD), and poor wound healing are the most important. The chief risk factor for PAD is atherosclerosis. The risk factors that favor the development of atherosclerosis consist of advancing age, hyperlipidemia, smoking, hypertension (HTN), and diabetes; these factors are similar to those that promote the development of coronary atherosclerosis.[6] The American College of Cardiology/American Heart Association has recommended screening asymptomatic diabetes patients older than 50 years or who are younger than 50 years old with additional risk factors for cardiovascular disease for PAD.[7] The diagnosis of PAD consists of a brief history, physical examination, and use of noninvasive diagnostic procedure. To evaluate the PAD, a diagnostic procedure should be done because history with or without physical examination alone cannot reliably detect PAD in all patients.[8] Besides, it is common to have asymptomatic PAD.[9] A variety of noninvasive procedures is available to evaluate the PAD. Physiologic tests include measurement of segmental limb pressures and the calculation of pressure index values such as the ankle-brachial index (ABI) and wrist-brachial index, segmental volume plethysmography, exercise testing, transcutaneous oxygen measurements, and photoplethysmography. ABI measurement by B mode Doppler sonography is a simple and nonexpensive method to assess PAD and can be done as an outpatient test.[7] An ABI measurement can not only identify PAD but can also predict the risk of cardiovascular disease.[10,11] A low ABI has a high specificity to predict future cardiovascular events.[12]

In 2003, the Expert Committee on Diagnosis and Classification of Diabetes Mellitus defined an intermediate group of individuals whose blood glucose level did not fall in the criteria for diabetes, but was too high to be considered normal; they are referred to as prediabetes.[13] The risk of development of overt diabetes is high in these people. In 2000, approximately 25% of overweight adults aged 45-74 years (12 million persons) had prediabetes, in the US.[14] Prediabetes patients have elevated the risk of coronary artery disease and atherosclerosis.[15,16] Although several studies have revealed an elevated cardiovascular risk in prediabetes, no study has investigated the risk of PAD in these patients. Atherosclerosis is a systemic condition which affects the cardiovascular system; therefore, PAD may be concomitant with coronary artery disease in people with prediabetes. This study was designed to evaluate the PAD and predict future cardiovascular events in prediabetes people compared with those in asymptomatic diabetes patients. This is the first study done in Iran to evaluate PAD in patients with prediabetes.

METHODS

Study setting and population

This was a case–control study that was done between Octobers and December 2013 at the Isfahan Endocrine and Metabolism Research Center. The patients and first-degree relatives of diabetes patients were recruited between 2003 and 2005 during their participation in the Isfahan diabetes prevention program.[17] Those patients who were between 40 and 55 years and had a history of type 2 diabetes, pre-diabetes or a family history of type 2 diabetes in the first degree relative, were selected randomly to participate in the study; all of them had medical records in the research center.

Diagnostic criteria for diabetes consisted of fasting plasma glucose (FPG) more than 126 mg/dL, 2-h plasma glucose of more than 200 mg/dL after a 75-g challenge, or hemoglobin A1C (HbA1C) level more than 6.4%. FPG: 100-125 mg/dL, 2-h plasma glucose in the 75-g challenge, 140-199 mg/dL, or HbA1C 5.7-6.4% were categorized as prediabetes.[18]

Participants who had a history of symptomatic PAD, diabetes foot ulcer and vascular intervention, valvular heart diseases such as aortic insufficiency and symptomatic atherosclerosis disease such as coronary artery disease, cerebrovascular accident and transient ischemic attack were excluded from the study.

There were 45 patients in the prediabetes group, 45 people in the normal group and 47 patients in the diabetes group. Participants in the normal and prediabetes groups had a family history of type 2 diabetes in the first degree relative. Participants in the groups studied were well matched based on age, sex, and body mass index (BMI).

Procedure

After initial registration and obtaining personal information, including age, sex, and medical and drug history, the methods and purpose of the study were explained to the participants. Symptoms of PAD such as claudication, buttock and hip, thigh, calf, or foot pain at rest and activity, either alone or in combination were enquired from the participants. A cardiovascular examination was done by an internist in all the participants. The weight (by standard scale, Seca, Germany), height (by stadiometer BMI (calculated by dividing body mass [kg] by height [m^2]) and -ABI (by B mode Doppler sonography, Atis, France) were measured. Biochemical parameters such as fasting blood sugar (FBS), HbA1C, cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride were measured at the Isfahan Endocrine and Metabolism Research Center. Participants had the ankle pressure measured after 15 min rest. To obtain the ankle pressure, the systolic pressure was measured in the dorsalispedis and tibialis posterior arteries bilaterally. Then, the brachial pressure was measured in both the arms. ABI for each lower extremity was calculated by dividing the higher of the recorded ankle pressures (dorsalispedis or posterior tibial artery) in each lower extremity by the higher of the two brachial artery systolic pressures.[19] For example in right ABI we used higher of right leg dorsalispedis or posterior tibial artery with higher of arm pressure. An ABI of 0.9-1.3 was considered normal, and an ABI lower than 0.9 in participants was taken as suggestive of peripheral arterial occlusive disease,[20] but the participants who had the ABI value more than 1.3 were exited from the study.

Statistical analysis

Quantitative and qualitative variables were expressed as mean (±standard deviation) and frequency (percent), respectively. Analysis of variance and Chi-square test, were applied, as appropriate, to examine differences in general and clinical characteristics between the three studied groups. Normality of continuous quantitative variables was evaluated using a sample Kolmogorov–Smirnov test and P-P plot. For lipid profile variables that showed positive skewed distribution, a logarithmic transformation was conducted for normalizing. To assess the association between PAD as the dependent variable and diabetes status a predictor variable, multiple linear regression was used in different models. In the fitted regression models, after obtaining the crude effect of diabetes status, its effect on PAD was adjusted for age, gender, and duration of disease, respectively. All statistical analyses were conducted using Statistical Package for Social Sciences (SPSS Inc. version 16.0 Nie, Bent and Hull,1970). $P < 0.05$ were considered as statistically significant.

RESULTS

The demographic and clinical characteristics of the subjects with normal, prediabetes, and diabetes statuses are shown in Table 1. There were no significant differences between the groups in terms of age, sex, and BMI. However, the prevalence of PAD was marginally different between the studied groups ($P < 0.1$). The prevalence of PAD in diabetes patients was more than in normal subjects ($P < 0.05$); however, the observed differences between diabetes patients and prediabetes as well as normal and prediabetes were not statistically significant. The differences of ABI between the groups were marginally significant ($P < 0.1$). The mean level of ABI in normal cases (1.11 ± 0.11) was marginally higher than in patients with diabetes (1.05 ± 0.03) ($P < 0.1$). Although, ABI in normal subjects was higher than in those with prediabetes (1.09 ± 0.12) and higher in prediabetes than in diabetes patients, the observed differences were not statistically significant. Only two patients in the diabetes group had ABI more than 1.3. No significant association was found

Table 1: Demographic and basic clinical characteristics of study participants

Variable	Groups			*P* value
	Normal	Prediabetes	Diabetes	
Age	47.04 (4.00)	46.96 (4.21)	47.21 (4.12)	0.1
Sex (%)				
Male	7 (15)	11 (24)	5 (10)	0.2
Female	38 (85)	34 (76)	42 (90)	
BMI (kg/m^2)	28.99 (4.47)	29.4 (4.10)	30.70 (4.84)	0.16
HTN (%)	8 (17.8)	5 (11.1)	25 (53.2)	<0.001
FBS (mg/dl)	91.4 (6.53)	107.4 (8.71)	146.43 (51.49)	<0.001
HbA1C (%)	4.9 (0.36)	5.3 (0.52)	7.30 (1.60)	<0.001
Cholesterol (mg/dl)	190.2 (42.92)	198.5 (42.3)	174.3 (36.58)	0.016
Triglyceride (mg/dl)	129.5 (62.88)	191.2 (98.22)	156.4 (75.03)	0.002
LDL (mg/dl)	116.9 (35.45)	120.1 (37.68)	99.68 (28.05)	0.009
HDL (mg/dl)	47.1 (12.31)	39.5 (8.89)	41.87 (9.18)	0.002
ABI	1.11 (0.11)	1.09 (0.12)	1.051 (0.13)	0.068
PAD (%)	0	1 (2.2)	1 (2.2)	0.077

BMI=Body mass index, HTN=Hypertension, FBS=Fasting blood sugar, HbA1C=Hemoglobin A1C, LDL=Low density lipoprotein, HDL=High density lipoprotein, ABI=Ankle brachial index, PAD=Peripheral arterial disease

between BMI and ABI in each group as well as in the total studied sample.

The prevalence of HTN in the studied groups was significantly different ($P < 0.001$), significant differences were seen between diabetes patients versus prediabetes and normal subjects ($P < 0.001$).

The difference of FBS level between the studied groups was statistically significant ($P < 0.001$). The results of a *post-hoc* test showed that significant differences were seen between diabetes patients and normal subjects ($P < 0.001$) and prediabetes ($P < 0.001$) as well as prediabetes and normal subjects ($P < 0.001$). The HbA1C levels were statistically different among three studied groups ($P < 0.001$). HbA1C levels in diabetes patients were higher than in prediabetes and normal cases ($P < 0.001$); also, HbA1C levels in prediabetes cases were higher than in normal subjects, but the difference was not statistically significant. The levels of lipid profiles were found to be significantly different between the three groups. In diabetes patients, the lipid profiles were more favorable than the other groups.

The three studied groups were compared in terms of cardiovascular medications including angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blocking agents, calcium channel blockers, diuretics, aspirin, and statins; the results (not shown) showed that among the three studied groups, the use of statins, ACE Inhibitors, ARBs, and aspirin was higher in diabetes patients than in normal and prediabetes (all $P < 0.05$). The use of calcium channel blockers, diuretics, and beta-blockers was not different (all $P > 0.1$). A correlation analysis using Pearson correlation coefficient in the total sample showed a statistically significant positive association between ABI and HbA1C ($r = 0.233$, $P < 0.01$). The results of the correlation analysis between ABI with HbA1C in each group showed only marginal significance in diabetes patients. Other variables, such as FBS, cholesterol, triglyceride, LDL, and HDL did not show a correlation with ABI. Further, a Chi-square test was used to study the association between HTN and PAD in each of the studied groups. The results showed a significant association between HTN and PAD in prediabetes subjects ($P < 0.01$).

Results of linear regression showed that the difference of ABI level was statistically significant between the three studied groups ($P < 0.05$). This observed difference remained significant even after adjusting the effect of age ($P < 0.05$). After further adjustment for sex, the difference was still significant ($P < 0.05$); however, when the adjustment was done for the effect of disease duration, the difference was not significant. A regression analysis was conducted separately for investigating the pairwise group differences in terms of ABI levels. The results for normal and diabetes patients showed that the difference of ABI levels was significant ($P < 0.05$). This observed difference remained significant after adjusting the effect of age ($P < 0.05$). The results of linear regression for prediabetes and diabetes patients, as well as normal subjects, did not show statistically significant differences [Table 2].

DISCUSSION

This study demonstrates that PAD is more prevalent in diabetes patients than in normal people. It also shows that the ABI decreases from normal people to diabetes patients. Another important finding of this study was that there was a significant correlation between HbA1C levels and ABI. The vast majority of previous studies have demonstrated the relationship of glycemic control and PAD. Poor glycemic control, as shown by HbA1C levels, is related to complications of diabetes including polyneuropathy, retinopathy, nephropathy, and also PAD, as was shown in this study. The importance of this finding is that the PAD may be an indicator of cardiovascular disease. According to previous studies, ABI is a good tool to evaluate peripheral artery disease. Individuals with an ABI < 0.5 have a five times greater risk for cardiovascular events, such as MI, ischemic stroke, coronary revascularization, critical leg ischemia, or amputation.[21] A normal ABI is considered to be in the range of 1.1-1.3. When verified by angiography, an ABI < 0.9 has a sensitivity and specificity of 95% for PAD.[6] ABI can also be used as an indicator of PAD severity. In general, an ABI < 0.9 is considered abnormal, and traditional symptoms of claudication are generally seen at levels <0.5. There is some evidence that an ABI of 0.9-1.1, as well as >1.3, may indicate disease. The physiological mechanism resulting in a low ABI is atherosclerosis and narrowing of arteries. Medial calcification of arteries is also common in diabetes patients and is usually assumed to cause mechanical rigidity of the arteries in the lower extremities, and this is known to produce a high ABI value. The vascular effects of diabetes are complex, as this condition is associated with both atherosclerosis and medial calcification of the peripheral arteries. In this study, only two patients had ABI above 1.3, both of them had diabetes for a long time. Previous data has demonstrated that an ABI above 1.30 was associated with significantly higher odds for foot ulcers and several other CVD morbidities. Population-based studies have shown the relation of other cardiovascular risk factors and PAD in diabetes people.[6] These include age, obesity, HTN, and dyslipidemia. In this study, the association was also seen between HTN and PAD in prediabetes person. It is important to prevent PAD, which may be done by controlling HTN before the onset of diabetes. In this study, diabetes people were more hypertensive than prediabetes and normal people. FBS and HbA1C levels were also higher in diabetes people. However, in diabetes patients, the lipid profile was more favorable than in prediabetes and normal persons; this may be related to strict treatment of hyperlipidemia in this group of patients. The implication of this study is that clinicians should consider the importance of both low and a high ABI because an abnormal ABI value is associated with cardiovascular mortality and morbidity. In addition, diabetes and prediabetes patients are at a higher risk of an ABI value out of the normal range. Diabetes patients with signs or symptoms of vascular disease or absent pulses on foot examination should undergo ankle-brachial pressure index testing and be considered for a referral to a vascular specialist. ABI is a simple method of diagnosing vascular insufficiency.[22] The ADA consensus panel on PAD

Table 2: The results of regression analysis for investigating the ABI level across studied groups

Groups	Model	β	SE	*t*	*P* value
Diabetes and prediabetes and normal	Crude (1)	0.030	0.013	2.31	0.020
	Model (1)	0.029	0.014	2.08	0.039
	Model (2)	0.029	0.014	2.05	0.042
	Model (3)	0.022	0.016	1.44	0.160
Diabetes and normal	Crude (1)	0.030	0.013	2.29	0.024
	Model (1)	0.029	0.014	1.99	0.045
	Model (2)	0.028	0.014	1.97	0.051
	Model (3)	0.018	0.016	1.11	0.210
Diabetes and prediabetes	Crude (1)	0.040	0.027	1.45	0.150
	Model (1)	0.040	0.030	1.34	0.183
	Model (2)	0.014	0.030	1.36	0.175
	Model (3)	0.034	0.034	1.00	0.316
Prediabetes and normal	Crude (1)	0.021	0.026	0.818	0.415
	Model (1)	0.021	0.026	0.818	0.416
	Model (2)	0.024	0.026	0.930	0.355
	Model (3)	0.024	0.026	0.912	0.364

ABI=Ankle brachial index, SE=Standard error recommended measurement of ABI in diabetes patients over 50 years of age and in younger patients with multiple PAD risk factors; normal tests should be repeated every 5 years.[23] ABI, may, therefore, be part of the annual comprehensive foot exam in these patients.[6] It is proposed that an abnormal ABI in these patients might increase the risk of cardiovascular events. There are other opinions that ABI be used in people from 50 to 70 years of age with at least one recognized cardiovascular risk factors, such as smoking, low HDL, high total cholesterol, or HTN.[12] In contrast to these recommendations, the U.S. Preventive Services Task Force (USPSTF) advises against ABI screening for asymptomatic PAD, as it is believed that it could lead to unnecessary health-care expenditure.[24] The AHA has asked the USPSTF to reconsider its recommendations.[23]

The low-sample size, absence of information on smoking and level of physical activity, were the limitation of our study.

CONCLUSIONS

In summary, PAD is common in the diabetes and prediabetes population. Physicians should pay special attention to screen PAD in these patients.

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Source of Support: Nil, **Conflict of Interest:** None declared.