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The Relationship between Abnormal Ankle-brachial Index and Micro-vascular Complications of Diabetes Type II

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Abstract

Background: The prevalence of diabetes mellitus is increasing worldwide and the relationship between peripheral vascular involvement and the complications of diabetes disease, such as retinopathy, has been reported in some studies but has not yet been fully proven. The aim of this study was to investigate the relationship between diabetes complications and peripheral and central vascular involvement.

Method: A number of 150 patients with diabetes type II aged 30 to 70 years old were entered into this cross- sectional study. Ankle-brachial index (ABI), carotid intima media thickness and diabetes complications were investigated in them.

Results: Abnormal ABI was more prevalent (79%) in Female patients. Furthermore, diabetes disease duration (P=0.005), systolic blood pressure (P=0.005) and retinopathy (P=0.003) were higher in females. Based on regression model, the highest relation of abnormal ABI incidence was observed with female gender (OR=2.4). Moreover, only blood pressure was among the abnormal ABI effective risk factors.

Conclusion: Female gender, duration of diabetes disease, systolic blood pressure and retinopathy incidence were among the effective factors in the incidence of abnormal ABI and abnormal ABI had a direct and reverse relationship with causing vascular diseases in diabetic type II patients.

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Introduction

Overall prevalence of diabetes type II is increasing worldwide (1, 2) and diabetes disease is the sixth cause of diseases-related deaths (3, 4). Diabetes worldwide prevalence will reach to 7.7 percent or 439 million adults until 2030, so that, a 69 percent increase in diabetes incidence will be between the years of 2010 to 2030 (5-7). There are 4 million people with diabetes in Iran with an average increase of 500,000 people

annually (8-10). Complications due to diabetes are very divers and numerous, so, disease correct treatment and preventing its complications are very vital. Diabetes is the most common cause of chronic renal failure, blindness, and amputation in adults due to advanced atherosclerosis (10). High blood pressure, impaired fat metabolism and obesity cause metabolic syndrome that exacerbates these complications (11).

There are various tools to predict the incidence of such complications but the best of them are non-invasive methods. Using ankle-brachial index (ABI) is an easy and non-invasive method to investigate atherosclerosis. The relationship between ABI and coronary, cerebral and peripheral vascular involvement has been proven (12).

Ankle brachial pressure index has a reverse relationship with the incidence of cardiovascular diseases (13) and can be a marker for the incidence of general atherosclerotic diseases (14). Furthermore, since diabetes is considered as an indirect factor for the incidence of carotid artery stenosis in normal population (15), diabetes type 2 is also a main risk factor for atherosclerosis progress. One of the indicators of coronary vessels atherosclerosis severity is carotid artery intima-media thickness (CIMT). Since CIMT measuring is easier and more repeatable than other peripheral vessels, nowadays, atherosclerotic diseases incidence risk is measured by using ultrasound machine with high resolution as another valuable tool (16). CIMT is one of the strongest predictors of rising deaths from CVD (17). Finally, the evidence suggests a clear relationship between arterial hypertension, hypercholesteremia and inflammatory factors as predictors of carotid atherosclerosis in patients with type 2 diabetes (18). The aim of conducting this study was to investigate the relationship between abnormal ABI and micro-vascular complications of diabetes and carotid intima-media thickness.

Materials and Method

A number of 150 patients with diabetes type 2 and in the age range of 30 to 70 years referred to Diabetes Clinic of Bahonar Hospital affiliated to Kerman University of Medical Sciences were selected through using simple random sampling method in this cross-sectional study. Patients with diabetes type 2, who had been diagnosed with diabetes for more than 6 months according to ADA 2017 index, were included in the study (19). Exclusion criteria were cervical deformity, foot amputation and diabetes type 1. After obtaining informed consent, the patients who had the inclusion criteria were investigated for the thickness of intima-media, carotid artery and ankle-brachial index, simultaneously. In the following, the demographic data were recorded by the researcher in the checklist.

ABI determination

Initially, the systolic blood pressure was respectively measured in the right arm, right ankle, left ankle and left arm in supine mode and after ten minutes rest. In this method, the ankle and arm pressures were measured by inflating 20 to 30 mm Hg above systolic pressure and discharge rate of 1 to 2 mm Hg by using barometer cuff and Doppler sonography probe that was placed on foot back artery in the ankle and Brachial artery in the arm. Instead of stethoscope, Doppler sonography probe was used to observe the first blood flow. Then, the ratio of the maximum systolic ankle pressure to the maximum systolic

pressure of the right or left arm was calculated and recorded for each limb. Index between 0.9 and 1.4 was considered normal and more or less than these amounts was considered as abnormal.

Carotid sonography

Carotid sonography was conducted by an experienced radiologist in sonography blinded to the experiments on the participants in the project. Right and left carotid sonography was conducted by high resolution B mode ultrasound (Philips Lu 22). Joint carotid artery, carotid bulba and internal carotid artery were investigated and echo distance between the edges of adventitia Media and Lumen intima was considered as intima-media thickness and finally, mean right and left intima-media thickness was considered as the intima-media thickness.

Fatty liver

Disease grading was conducted by a radiology expert and using Philips Lu 22 mark sonography. Disease grading was based on the conditions of the liver echo and its comparison with the adjacent kidney, as well as its comparison with the spleen echo and the appearance of the diaphragm and the margin of the intrathecal vessels and accordingly, the disease was classified into three groups: grade 1 or mild fatty liver, grade 2 or medium fatty liver and grade 3 or sever fatty liver (20).

Retinopathy determination

The patients were investigated by an ophthalmologist and visual acuity and the anterior part of eye were examined then, retina with dilated pupil was investigated and diabetic retinopathy severity was obtained.

Nephropathy determination

Early morning urine was taken from patients and then, urine albumin and creatinine rates were determined by auto-analyzer. In the absence of false positive causes of proteinuria, the ratio of albumin to creatinine upper than or equal to 30 mg/g was considered as micro-albuminuria.

Blood sample was taken after 12 to 14 hours fasting and fasting blood sugar, creatinine and blood fats profile experiments were taken. LDL, HDL, TG and cholesterol were checked and tested by Pars Test Kit (Selectra XL system), HbA1C, FBS and Cr were checked and tested by the Biurex Fox Kit (Selectra XL system). Furthermore, height was measured by a measuring tape and weight measured by the OMRAN scale. Checklist data were then collected and finally, all of the data were analyzed through SPSS22 software.

Data analysis

The frequency, relative frequency and central index were used for descriptive statistics and Chi-Square or Fisher test, t-test, Pearson coefficient and regression for analytical statistics. According to Kolmogorov test, distribution of variables was not normal. Therefore, we benefited from non-parametric tests such as Chi-square and Kruskal-Wallis.

Ethical considerations

An informed consent was taken from all patients and all stages and objectives of the research were explained to them. Patients' unwillingness to participate in the study had no effect on their normal course of treatment. In addition, necessary licenses and the ethics code (No. 95000447) for conducting the study was obtained from the Ethics Committee of Kerman University of Medical Sciences.

Results

A total of 150 patients with the mean age of 57.3 + 8.6 years were investigated of whom, 57% were men and 43% were women. In whole, 50 patients (30%) had abnormal ABI. The basic characteristics of the patients with normal and abnormal ABI have been shown in table 1.

Table 1. Comparison of basic characteristics in patients with normal and abnormal ABI

Characteristic	All patients (n=150)	Normal ABI group (n=100) 1.3>ABI>0.9 (N±100)	Abnormal ABI group (n=50) 1.3<ABI<0.9	P
Age (year)	57.3+8.6	57.2+8.3	57.5+9.2	0.3
male	57	78.9	21.1	0.01
Diabetes duration (year)	10.7+7.5	9.6±7.2	13±7.6	0.005
Body mass index	28.1±4.4	27.9±4.1	28.5±4.8	0.3
Systolic blood pressure (mmHg)	145.2±21.8	141.3±18.9	153±25.2	0.005
Diastolic blood pressure (mmHg)	85±8	84.5±7.2	86±9.4	0.2
Fasting blood sugar (mg/dl)	162.3±61.4	165±60.6	157.1±63.3	0.3
Hb A1c	8.1±1.6	8.2±1.7	7.8±1.6	0.09
Cholesterol (mg/dl)	162.4±42.7	164.2±44.8	158.8±38.4	0.6
TG (mg/dl)	157.4±67.8	160.4±68.3	151.5±67.2	0.2
Urea (mg/dl)	133.7±12.5	33.1±11.5	34.8±14.4	0.5
Cr (mg/dl)	1.0±0.3	1.0±0.3	1.0±0.4	0.6
LDL (mg/dl)	90.1±32.1	90.3±32.1	89.7±32.5	0.9
HDL (mg/dl)	45.7±16.5	44.4±11.9	48.2±23	0.9
Diabetes FH	70	66.7	33.3	1.0
Smoking	10.7	56.3	44.8	0.3
Fatty Liver	53.3	66.3	33.8	0.9
Retinopathy	40	56.7	43.3	0.30
Nephropathy	18	74.1	25.9	0.3
CIMT	0.73±0.11	0.73±0.11	0.74±0.12	0.7
GFR	82.3±28.7	82.7±26.2	81.3±33.3	0.5

Female gender was more prevalent in patients with abnormal ABI (79%). Furthermore, diabetes duration (P=0.005), systolic blood pressure (P=0.005) and retinopathy were higher in them.

Multivariate logistic regression model was used in order to determine abnormal ABI risk factors that its results have been shown in table 2 and accordingly, the highest relationship was observed with female gender (OR=2.4). Furthermore, blood pressure was the only risk factor of abnormal ABI.

Table 2. Abnormal ABI risk factors according to univariate and multivariate models

Characteristic	Univariate OR (95%CI)	P	Multivariate OR (95%CI)	P
Age (year)	1 (1.04-0.96)	0.8	-	-
Male gender	0.3 (0.8-0.1)	0.01	2.4 (5.3-1.09)	0.03
Diabetes duration	1.04 (1.11-0.01)	0.01	1.03 (1.09-0.9)	0.1
Body mass index (Kg/m^2)	1.03 (1.11-0.95)	0.4	-	-
Systolic blood pressure (mmHg)	1.02 (1.04-1)	0.003	1.02 (1.03-1)	-
Diastolic blood pressure (mmHg)	1.02 (1.06-0.95)	0.2	-	-
Fasting blood sugar (mg/dl)	0.9 (1-0.9)	0.4	-	-
Hb A1c	0.8 (1-0.6)	0.1	-	-
Cholesterol (mg/dl)	0.99 (1-0.98)	0.4	-	-
TG (mg/dl)	0.9 (1-0.9)	0.4	-	-
Urea (mg/dl)	1.01 (1.03-0.98)	0.4	-	-
Cr (mg/dl)	1.2 (2.9-0.5)	0.5	-	-
LDL (mg/dl)	0.9 (1-0.9)	0.9	-	-
HDL (mg/dl)	1.01 (1.03-0.9)	0.1	-	-
FH	1 (2-0.4)	1	-	-
Smoking	1.6 (4.7-0.5)	0.3	-	-
Fatty Liver	1.40 (2.05-0.5)	1	-	-
Retinopathy	1.2 (4.2-1.05)	0.03	1.5 (3.4-7.0)	0.2
Nephropathy	0.6 (0.6-0.2)	0.3	-	-
CIMT	2.8 (5.5-0.1)	0.4	-	-
GFR	0.9 (1-0.9)	0.7	-	-

Discussion

Diabetes type 2 is a kind of prevalent metabolic disorder that is known with a defect in glucose homeostasis and impaired insulin secretion and function (21). Type 2 diabetes, which accounts for more than 90% of diabetes cases, causes many long-term complications in patients including vascular complications that, in addition to affecting life quality and imposing medical costs, increase mortality risk in these people by 2 -4 times (22, 23). In the present study that was conducted in order to investigate ABI index and risk factors of atherosclerosis incidence in patients with diabetes type 2, the results showed the relationship of abnormal ABI with variables of female gender, diabetes duration, systolic blood pressure and retinopathy incidence. Furthermore, eye involvement (retinopathy) was more prevalent in patients with abnormal ABI that, itself, shows that when there is peripheral vascular involvement, according to high or low ABI (>1.3 or >0.9), the risk of retinopathy incidence is higher. This finding has been reported in some other studies too (24, 25).

ABI is a good marker for atherosclerosis and ABI<0.9 is useful for diagnosing peripheral arterial occlusive diseases (26); ABI>1.3 is also the symptom of arterial calcification (27) and both of them are observed in diabetic people, prevalently. Additionally, abnormal ABI in diabetic patients is the predictor

of cardiovascular mortality and morbidity (28). Although the relationship between retinopathy and abnormal ABI has been observed in cross-sectional studies, the mechanism of the relationship between atherosclerosis and diabetic retinopathy has not been specified yet and possibly the mechanisms involved in the development of atherosclerosis and diabetic retinopathy should be similar because the mechanisms of developing complications of macro and micro-vascular diabetes type II include obesity, insulin resistance and hypertension. In our study, CIM thickness was used as a marker that its increase could be a sign of early atherosclerosis and its effect on abnormal ABI was investigated and no relationship was observed. Although CIMT and ABI are atherosclerosis indicators, it has been shown in Hayashi study that ABI alone has a poor relationship with atherosclerosis and simultaneous measuring of both has the power to offer the prognosis (29) and since no significant relationship has been reported between CIMT and abnormal ABI, possibly other factors are also effective in it. According to the regression model, abnormal ABI showed relationship with female gender and systolic blood pressure. Female gender has been reported as one of the abnormal ABI risk factors in other studies too (30) that is consistent with our study finding. Furthermore, high systolic blood pressure has been reported as an effective factor in developing abnormal ABI but diastolic blood pressure has had no effect (30). The effect of hypertension, especially systolic, in causing atherosclerosis has been proven (12,30, 31). In our study, no relationship was observed between serum level of lipids and abnormal ABI, while in Li j study, abnormal ABI had relationship with cholesterol (30), in Chen *et al.* study, this relationship was observed only with triglyceride level (25) and in Lee *et al.* study only with HDL level(24). Lipid lowering drugs may be helpful in preventing coronary arteries disease (32) but in a meta-analysis on patients with PAD, there has been no evidence that these drugs are effective in preventing and treating peripheral arterial disease (PAD), improving pain, ABI and skin necrosis.

No relationship was observed between BMI and abnormal ABI in our study that is consistent with some other studies (31, 33). One of the other effective factors in abnormal ABI was diabetes duration that has been reported in recent studies too (11, 31, 33, 34).

In our study, sonography showed no significant relationship between fatty liver and abnormal ABI and we found no similar study done to investigate this relationship. In Lv *et al.* study, fatty liver showed no relationship with nephropathy and retinopathy but had relationship with diabetic peripheral neuropathy (35), but in Kim *et al.* study, there was a reverse relationship between fatty liver and nephropathy and retinopathy (36). Furthermore, there has been no relationship between fatty liver and cardiovascular diseases in Vanjiappan *et al.* study (37).

Diabetic nephropathy is one of the causes of chronic kidney disease (CRF) in the world. In contrast to diabetes type I, the relationship between diabetic nephropathy and diabetic retinopathy has been unknown in patients with diabetes type II. In our study no relationship was observed between abnormal ABI and diabetic nephropathy but this relationship has been reported in some studies (24).

In Wu *et al.* study that was conducted on 7068 people and 1156 people of them were diabetic, there was no relationship between micro-albuminuria and abnormal ABI but the relationship was existed in non-diabetic people (38) and more investigation in order to determine this relationship is required.

Bosevski *et al.* in Australia in 2015 tried to track patients for 31 months to find the factors affecting the progression of atherosclerotic diseases in people with diabetes type 2 (39). Intima-media thickness increase was 0.07mm in one year. In this study, over 87% of patients had carotid intima-media increase and vascular plaque was observed in 41.8% of them. Furthermore, instead of body mass, blood pressure was associated with intima-media thickness increase. In the mentioned study, in spite of the results of the present study, lipid profiles were known effective in creating plaque. However, the effectiveness of serum lipids in increasing the intima-media thickness in the normal population has been studied (40).

Many studies have investigated the predicting factors of vascular atherosclerotic diseases. For example, Hayashi et al. investigated ABI and CIMT as atherosclerosis markers in patients with diabetes type II in Japan (29). The findings of our study showed that ABI alone is less associated with atherosclerosis and simultaneous measurement of carotid ABI and IMT has the power of offering a good prognosis and both should be evaluated during screening in diabetic patients, although both criteria appear to be powerful tools for predicting diabetes complications (25). In the study of Erzen *et al.*, the comparison of ABI, CIMT, pulse pressure and endothelial dysfunction indicators (ED) in young patients with myocardial infarction with classic risk factors showed that ED and CIMT are better than classic risk factors in evaluating the risk of coronary arteries disease (41). In spite of these results, evidences of possible risk factors for vascular diseases incidence in diabetic patients are still varied and sometimes contradictory. Therefore, conducting researches widely and in more extensive dimensions is required.

The strengths of our study were investigating patients in terms of fatty liver and CIMT thickness and their relationship with abnormal ABI, in addition to micro-vascular complications of diabetes, and its weaknesses were the cross-sectional study and non-inclusion of drugs abusers, especially statins, which might have effect on serum lipids levels, since the obtained results related to lipids must be judged with caution.

Conclusion

In the present study, female gender, diabetes duration, systolic blood pressure and retinopathy incidence were found to be effective factors in the incidence of abnormal ABI amounts and ABI had a direct and reverse relationship with developing vascular diseases in patients with diabetes type II. Patients with abnormal ABI were more likely to have retinopathy.

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