Research Article

Assessment of Peripheral Arterial Disease in Diabetes Mellitus Type 2 Patients by Doppler Ultrasonography and Correlation with Risk Factors

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Abstract

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia due to defects in insulin secretion, action or both. Several different types of DM exist and are caused by a complex interaction of genetics, environmental factors and life style choices.

Aims and Objectives: To study the prevalence and morphological pattern of peripheral arterial lesions in patients with DM by duplex color doppler ultrasonography and to correlate the findings with the various risk factors and variables.

Materials and Methods: A complete history and physical examination including examination of the lower limbs with respect to peripheral arterial disease, basic routine blood and urine laboratory investigation, assessment of peripheral arterial disease by doppler ultrasonography of lower limb arteries and assessment of diabetic complications were carried out on 50 cases of type 2 DM of more than 5 years duration and 25 controls of non-diabetic population. Type 1 DM and type 2 DM patients with duration of diabetes less than 5 years were excluded from the study as were the patients of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).

Keywords: Peripheral arterial disease, Diabetes mellitus, Doppler ultrasound, Ankle-brachial index

Introduction

Diabetes is growing in an epidemic proportion and is a public health problem worldwide and it is of extreme significance in India as it has the highest number of people suffering from diabetes.[1] Long-term complications are of serious concerns to any person with DM and it almost always results from the macro and microvascular complications. The overall prevalence of peripheral arterial disease (PAD) in patients with DM in India is 3.2% in a study from south India[2] compared to 15.9% in the western world.[3] Duration of diabetes and other co-morbidities significantly influence development of these complications. The most important initial test after the routine physical examination is the ankle-brachial index (ABI) as this test is simple and reproducible and can be done in the office itself. It is also seen that by using more sophisticated screening techniques like the duplex color doppler or the high-resolution ultrasound, about 30% with normal ABI would have plaques/stenosis and hence PAD is not that uncommon as hitherto believed.

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Aims and Objectives

- To study the prevalence of peripheral arterial disease of lower extremities in patients with type 2 DM by non-invasive method (Duplex doppler ultrasound)
- To study the morphological patterns of arterial lesions in cases of peripheral arterial disease
- To correlate the findings of Duplex doppler ultrasound of lower limbs with various risk factors and variables

Materials and Methods

The study duration was of one year and was conducted in diabetes clinic, medical wards and radiology department of Dr. Ram Manohar Lohia Hospital, New Delhi. Fifty cases (28 males and 22 females) of type 2 DM with duration of DM of more than 5 years were taken as cases. Patients who were recently diagnosed with type 2 diabetes mellitus (i.e. DM of less than 5 years duration) were excluded from the study as were the patients with type 1 DM, impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Twenty-five controls (14 males and 11 females) were also recruited from medical outpatient department and wards admitted for other reasons and in them diabetes was excluded by estimation of fasting and 2-hour postprandial blood sugar samples.

Definitions Used to Define Diabetic Complications

Myocardial ischemia: History of exertional angina and/or unequivocal ECG changes of ischemia but no evidence of infarction was defined as having myocardial ischemia. *Myocardial infarction* was documented if there was either a history of myocardial infarction and/or unequivocal changes on ECG suggestive of recent or past myocardial infarction.

- *Nephropathy* was taken as proteinuria more than 300 mg/day in presence of retinopathy and in the absence of urinary tract infection, hypertension or cardiac failure.
- *Renal insufficiency* was considered if the serum creatinine was raised to more than 1.8 mg/dL in males and 1.6 mg/dL in females.
- *Background diabetic retinopathy (BDR)* was labeled if microaneurysms, exudates or dot hemorrhages were present in the retina.
- *Proliferative diabetic retinopathy (PDR)* was considered if there was presence of new vessels on the disc or elsewhere or advanced diabetic eye disease with vitreous hemorrhages and/or presence of retinal detachment.
- *Peripheral arterial disease (PAD)* was defined if an ankle-brachial index was less than or equal to 0.9 in either foot. Clinically PAD was diagnosed when either dorsalis pedis or posterior tibial arterial pulsations were absent.

History and Examination

Both cases and controls were evaluated by detailed history which included age, sex, duration of diabetes, presence of hypertension and family history of DM. History of smoking and alcohol abuse was also taken. Enquiry was particularly made of the number of bidi/cigarette smoked in a day and for how long. Patients who had smoked cigarettes for more than a year in the past and were still smoking were denoted as a “smoker”. A specific enquiry regarding intermittent claudication, night and rest pain in either leg was recorded.

All patients underwent a thorough clinical examination. Indirect auscultatory arterial *blood pressure* was measured by a standard cuff size, calibrated sphygmomanometer and stethoscope after at least 10 minutes’ rest. Precautions were taken for creating standard conditions of blood pressure recording as per WHO recommendations. Standing *height* was measured to the nearest 0.1 cm, without shoes, the heel, buttocks, shoulders and occiput against the wall, eyes looking straight ahead, visual axis being horizontal with the top of the external auditory meatus level with the inferior margin of the bony orbit, with a set square resting on the scalp and against the wall. *Weight* was measured in normal indoor clothing and without shoes. *Waist circumference* was taken at the midpoint between the lowest point of the thoracic cage and the iliac crest and hip circumference at the intertrochanteric level using a measuring tape. Body mass index and waist/hip ratios were calculated for each patient. A resting 12-lead *electrocardiogram* (ECG) was recorded in the supine position for all patients. *Indirect ophthalmoscopy* was performed in all patients after use of a mydriatic by a trained ophthalmologist. A thorough examination of lower limbs was carried out which included palpation of all the peripheral pulses, blanching of the limbs on elevation, dependent rubor, loss of hair in legs, gross appearance of skin, presence or absence of atrophy of subcutaneous tissue, infection or gangrene and examination of nails. All the findings were recorded on a preformed proforma.

Biochemical Investigations

Both the cases and controls underwent the following blood tests: fasting and postprandial blood glucose, serum cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL), blood urea and serum creatinine,

glycosylated hemoglobin (HbA1C), urinary estimation for sugar, albumin and 24-hour urinary proteins.

After an 8-hour fasting, venous samples were collected, with patients lying supine. Blood glucose was determined by the enzymatic glucose oxidase/ peroxidase method using the reagent kit (Autopak, Ames Miles India Ltd.). Post-prandial venous samples were taken 2 hours after a 75 gm oral glucose load. The laboratory reference value of fasting blood glucose was taken as 70–100 mg/dL and post-prandial (2 hour) as up to 140 mg/dL. Blood urea was determined using the Enzokit (Ranbaxy Diagnostics). The reagent kit utilizes the Berthelot (urease) method for the estimation of urea. This is the method of choice because of its precision, specificity due to enzyme urease and high sensitivity due to high molar absorption of the final color. Serum creatinine was determined using the Autopak Reagent kit. This kit utilizes the picrate method. The laboratory reference value for serum creatinine is 0.9–1.8 mg/dL in males and 0.8–1.6 mg/dL in females. The quantitative determination of HbA1c was done using the glycated hemoglobin kit (Sigma Diagnostics, St. Louis, USA) in whole blood at 415 nm. Gross albuminuria was tested using the Ames multiple reagent strips (Bayer Diagnostics India Ltd). Immunochemical, semi-quantitative determination of micro-albuminuria was estimated using the micral test strips (Boehringer Manheim, Germany).

Assessment for Peripheral Arterial Disease

Clinically PAD was diagnosed when either dorsalis pedis or posterior tibial arterial pulsations were absent. The neck and lower extremities were studied by Duplex doppler ultrasound (ATL (PHILIPS) HDI 3500) machine. The study was performed on common carotid, superficial femoral, popliteal, profunda femoris, posterior tibial artery and dorsalis pedis artery. With patient lying supine the common femoral arteries were traced till the superficial femoral artery enters the hunter's canal in the lower part of thigh. The patient was turned prone for evaluation of popliteal artery. Tibial artery was best examined in the supine position with the inversion of the foot. The foot was everted to examine the posterior tibial arteries. On gray-scale Duplex sonography the features evaluated were the vessels size, vessel wall intimal thickening, atheromatous plaques, calcification and presence of intraluminal thrombus. After gray-scale examination, color flow imaging was done and pulsed doppler spectral waveforms were obtained from any area in which flow disturbance or turbulence was noted. The features noted were peak systolic velocities (PSV), end diastolic velocities (EDV), resistance index (RI), pulsatility index (PI), presence of stenosis, grade of stenosis, and post-stenotic turbulence. The degree of stenosis was graded according to the criteria laid down by Jager et al.[4] A normal doppler scan is regarded if there is triphasic waveform with thin spectral band. A 1–19% stenosis is when there is normal triphasic flow with normal peak systolic velocity with spectral broadening. A 22 to 49% stenosis is regarded if there is normal triphasic flow with PSV increased by more than 30% with respect to proximal recording site. A 50 to 99% stenosis is when there is triphasic waveform with PSV increased by more than 100% with marked spectral broadening. Distal waveform is abnormal. A 100% occlusion is said to be present if there is no forward flow detected with altered flow patterns both proximal and distal to occlusion. Data from vessels requiring doppler angles greater than 70 degrees were considered unreliable and such vessels were classified as non-visualized.

The findings of doppler ultrasound of lower limbs were then correlated with parameters like age and sex, duration of diabetes, family history of DM, smoking, lipid profile, hypertension and carotid intimal thickness. T-tests were used for comparison of means while the chi-square test was used for comparison of frequencies. Multiple logistic regression analysis was done using PAD as the dependent variable and variables tested included age/sex, body mass index, waist hip ratio, smoking, duration of diabetes, fasting and postprandial plasma glucose, glycosylated hemoglobin, serum cholesterol, serum triglycerides, HDL, LDL, VLDL, serum creatinine, ECG evidence of myocardial ischemia, urine sugar, albumin, 24-hour urinary protein, microalbuminuria, retinopathy, carotid artery intima media thickness (CAIT -right and left).

Assessment of Carotid Artery Intima-Media Thickness (IMT)

The common carotid artery was used for determination of intima-media thickness using high-resolution B-mode ultrasonography.

Assessment of Ankle-Brachial Index (ABI)

The ankle-brachial index was calculated on every patient. Systolic blood pressure was taken using brachial arterial in the upper limb and dorsalis pedis or posterior tibial artery in the lower limbs, using doppler ultrasound, and the mean of two readings was taken as the ankle-branchial pressure. An ankle-brachial index less than 0.9 in either foot was defined as PAD for the purpose in this study. The test was performed with patient lying supine on the bed. The normal sphygmomanometer pressure cuff with its lower border at 2–3 cm above antecubital fossa is placed on the right arm and the systolic blood pressure is taken using doppler sonography. The same procedure is repeated on left arm also. Then the pressure cuff are tied in the lower limb 2–3 inches above the medial malleolus and systolic BP is taken in the same way as above, using either the posterior tibial artery or the dorsalis pedis artery. Then the ankle systolic pressure

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is divided by highest arm pressure to establish ABI measurement for each leg.

Results and Discussion

The mean age of the cases in our study was 57.98±7.73 years and mean duration of diabetes was 10.83±4.89 years. The mean waist-hip (W/H) ratio was 0.9564 and the mean calculated Body Mass Index was 25.215±3.045 kg/m^2. The mean fasting glucose level was 131.63±24.55 mg/dL and the mean post prandial glucose level was 102.8±36.28 mg/dL. The mean glycated hemoglobin (HbA1C) was found to be 7.594±1.484%. the mean urinary albumin excretion was found to be 70.63 mcg/mg creatinine ±127.38 in cases, and 10.24±5.12 in control population. The age of the patients in PAD group had a mean of 65.20±3.27 years while that in the non-PAD group it was 57.22±7.45 years. The duration of diabetes mellitus had mean of 15.60±4.34 in PAD, while the mean was 10.30±4.69 in non-PAD group. The mean of fasting blood sugar in PAD group was 152.00±27.82 mg/dL and in the non – PAD group it was 129.37±23.42 mg/dL. The mean of post prandial blood sugar in the PAD group was 220.60±22.67 mg/dL while that in the non-PAD group it was 186.91±36.10 mg/dL.

Prevalence of PAD

The present study comprised 50 patients of type 2 DM and 25 healthy non-diabetic controls. Using the color doppler sonography, the prevalence of PAD was found to be 10% which was also statistically significant (p value <0.05). This is less than those found by Kumar et al.[5] (about 22.5%) and Agrawal et al.[6] (28%). However, a study from south India had a prevalence of PAD (8.3%) which was similar to our study.[7] A similar study from Egypt, using ABI, found the prevalence of PAD to be 11% which is also similar to our case.[8] The prevalence of PAD in Taiwan diabetics was lower (7%), maybe due to lower cut-off of ABI used in the study of 0.8.

It is of interest that unlike most western studies, there was a small but significantly higher prevalence rate of PAD in women in our study. The reason for this is not clear but this underscores the fact that like ischemic heart disease, PAD also occurs commonly in diabetic women as in diabetic men. Similarly, Vitalis et al. from the United Kingdom also found a higher prevalence of PAD in females.[9] They also reported a lower prevalence of PAD among Asians as compared to Whites.

PAD and Duration of Diabetes Mellitus

It was seen that the duration of diabetes was more in patients with peripheral arterial disease and less in patients without PAD. This difference was statistically significant (p<0.05). This correlation has been found in many Indian as well as western population studies, such as that reported by Weragoda et al. from Sri Lanka.[10] They reported a history of diabetes mellitus, hypertension and dyslipidemia of more than 10 years duration to be a significant risk factor of PAD.[10] A cross-sectional study done by Codjo et al., and using ABI <0.9 as a marker of PAD, showed an increasing age, the absence of activity with high income, absence of physical activity, the duration of diabetes, the presence of peripheral neuropathy and glycosylated hemoglobin ≥7% to be significant risk factors for PAD.[11]

BMI of the Study Population

The mean BMI of diabetic patients in our study was found to fall between normal weight and overweight range (22.17 to 28.26 kg/m^2). This may be due to the study population being type 2 diabetic which are generally over weight.

PAD and HTN

The prevalence of hypertension in patients with DM was found to be 28% while only 20% in those with PAD. Hypertension was not found to be associated with PAD. This may be due to the small number of study population. This is in contrast to other studies like that reported from Sri Lanka by Weragoda et al.[10] Another study found that the atherosclerotic disease progression in femoropopliteal arteries was associated with increased age, a diagnosis of ischemic heart disease (IHD) and hypertension (all p<0.05).[12]

PAD and Smoking

It is of interest that smoking did not appear to be a predictor of PAD in this study. The reason for this is not clear but it may be related to small sample size of the study. Admittedly, the validity of a smoking history is also debatable, as many smokers would deny it. Earlier studies have shown an association between smoking and PAD while many studies reveal that smoking is an important risk factor for PAD.[10]

Correlation of PAD with Other Parameters

In the present study, the univariate regression analysis showed that total cholesterol and LDL cholesterol was statistically associated with PAD in population with DM. The multiple logistic regression analysis showed that there was statistical correlation between PAD and age of the patient, duration of diabetes, fasting and post-prandial (2 hour) blood sugar and carotid intima-media thickness (IMT) of both sides. These factors have been implicated in some of the Indian as well as European studies. A study from Spain, done by Garcia et al., found an association of carotid IMT with age, hypertension, microalbuminuria, and mean waist perimeter. They concluded that IMT should be regarded as a risk factor for general vascular disease.[13] Balta et al. concluded that

carotid IMT gives the clinicians an idea about presence of systemic inflammation and should be evaluated in patients with CAD.[14] Han et al. also supported Balta et al. by saying that the risk factors for both CIMT and CAD are similar and CIMT rises in elderly and patients with CAD. In these patients there is also an increase in various inflammatory markers.[15] Paraskevas suggested the use of statins to reduce inflammation.[16]

PAD and Plaque in Carotid Artery and Lower Limb Arteries

The prevalence of presence of plaques in common carotid artery was found to be 46% out of which the right CCA, left CCA and both CCA had a distribution of 14%, 16% and 16% respectively. None of the plaques caused any significant stenosis to the flow of blood. The maximum area reduction of the lumen was 36.84%. Most of the plaque was found to have a smooth surface, homogenous and non-calcified. The most common site was the bulb of common carotid artery. The prevalence of plaque in the lower limbs was 20% while the prevalence of significant stenosis or obstruction was 6%.

Conclusions

In this case-control study, the following conclusions can be drawn. The doppler sonography detects more cases of peripheral arterial disease than by simple clinical examination. However, simple inspection of feet along with clinical examination will detect more than 50% of cases of PAD. The duration of diabetes, age of patient, fasting and post-prandial (2 hour) blood sugar and carotid artery intimal thickness of both sides is related to presence of peripheral arterial disease. A complete doppler sonographic evaluation of lower limb arteries will detect plaques more often than by simple determination of ankle-brachial index.

Conflict of Interest: None

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