Research Paper

Is the peripheral arterial disease in low risk type 2 diabetic patients influenced by body mass index, lipidemic control, and statins?

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ABSTRACT

Objective: To correlate BMI, lipidemic control, and statin therapy with PAD measured by ABI in low risk type 2 diabetics. **Materials and Methods:** A sample of 101 nonsmoking, asymptomatic type 2 diabetics (50 males, 51 females) with known glycemic (fasting blood sugar, postprandial blood sugar, glycosylated hemoglobin) and lipidemic (total cholesterol, lipoproteins, and triglycerides [TGAs]) control was taken. Vascular Doppler was used to derive ABI and PAD was defined as ABI <0.9. ABI values were compared amongst groups and $P < 0.05$ was considered statistically significant. **Results:** We found fairly good lipid but poor glycemic control and prevalence of PAD 30%. There was insignificantly low ABI profile in patient having BMI ≥25, hyperlipidemia and absent statin therapy with odds ratio being highest for TGAs ≥150 (3.23) followed by BMI ≥25 (2.61), high-density lipoprotein ≤50 (1.61), low-density lipoprotein ≥100 (1.20), and disuse of statin (1.14) with significance only for BMI. **Conclusion:** We observed small, insignificant PAD risk by dyslipidemia or non-use of statins in low-risk ambulatory T2DM patients, not so by BMI. This suggests importance of good glycemic control, maintenance of optimum weight, and lifestyle modifications as primary prevention rather than opting for costly and inefficient secondary prevention.

Key words: Ankle-brachial index, lipidemic control, peripheral artery disease, statin, type 2 diabetes mellitus

INTRODUCTION

Asian Indian phenotype is more vulnerable to diabetes[1] and cardiovascular diseases (CVD).[2] type 2 diabetes mellitus (T2DM) increases the risk of developing peripheral artery disease (PAD) as published in our previous studies.[3] PAD, the silent killer in T2DM denies classical claudication[4] and in countries like ours can culminate into diabetic foot threatening limbs. This requires assessment in preclinical stage by simple yet under-used tool like ankle-brachial index (ABI)[5] which was utilized in our study. In previous articles, we have published high prevalence of PAD,[6] effect of risk factors,[3] importance of good glycemic control,[7] and benefit from angiotensin II converting enzyme inhibitors[8] in our T2DM subjects. ABI is a simple,

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validated tool to quantify PAD[4] and a resting ABI of <0.90 indicates a hemodynamically significant arterial stenosis.[9] Use of lipid lowering statin and controlled diabetic dyslipidemia are known to benefit coronary artery disease (CAD) and lipidemic control, body mass index (BMI) and non-use of statin are proven risk factors for diabetic vasculopathy[4,10] in high-risk patients. We tried to correlate effects of these three factors on PAD in under treatment ambulatory low-risk T2DM patients looking for significance if any.

MATERIALS AND METHODS

Study population

This observational cross-sectional study was carried out from September 2012 to September 2013 on known diabetic patients taking regular treatment (not insulin) for minimum of 6 months. After taking approval from institution review board of our college for study, sample size was calculated by software RaoSoft (Raosoft, Inc. free online software, Seattle, WA, USA). With 35% prevalence of ABI <0.9 in type 2 diabetics from our population,[3] a sample size of 101 type 2 diabetics provided 90% power to detect a twofold difference in ABI <0.9 at the alpha = 5% significance level. Subjects were chosen randomly from (i) medicine outdoor patient department (OPD) of a tertiary care government hospital attached to our medical college, (ii) diabetic OPD of urban health and training center affiliated to our hospital and community medicine department of our college, (iii) diabetic camp at a trust multispecialty hospital, (iv) private OPDs.

Inclusion criteria

A total of 101 type 2 diabetics (50 males and 51 females) were selected by random allocation in age group 30–80 years, not taking insulin, taking regular medicines, and having recent investigations for glycemic and lipidemic control.

Exclusion criteria

We excluded the subjects with following risk factors so as to have a low risk group for the study, presence of leg symptoms suggestive of claudication, smoking, subjects taking irregular treatment, newly diagnosed (duration <6 months), having previous vascular intervention, having amputated limb, ABI more than 1.4 (due to atherosclerosis), taking vasodilators. Exclusion of first two of this list defines low CVD risk in study group.[5]

Peripheral artery disease risk factor assessment

All recruited subjects underwent personal interview in the form of predesigned questionnaires that included general features, demographic characteristics, symptom of PAD, investigations, and treatment taken.

Tests for lipidemic and glycemic control

All the study subjects were tested for fasting lipid profiles and reports done within 1 week were considered. Total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very LDL, and triglycerides (TGAs) were measured using standard procedure. Similarly, recent reports of glycemic controls including fasting blood sugar (FBS), postprandial blood sugar (PP2BS), and glycosylated hemoglobin (HbA1c) were taken.

Definition of lipidaemic and glycemic control

The following defines the lipidaemic and glycemic control[11]

- Glycemic control - HbA1c <7%, FBS <130 mg/dL, and PP2BS <180 mg/dL
- Lipidemic control - LDL <100 mg/dL, HDL >50 mg/dL, and TGAs <150 mg/dL.

Ankle-brachial index assessment

ABI was measured in supine position by investigators themselves after taking consent, using principle of Doppler effect by portable instrument Versadop (table top vascular Doppler with 8 MHz of Diabetik Foot Care India Limited, Chennai, India) having 12 cm occluding cuff. ABI was derived by dividing the higher reading of the ankle pressure at dorsalis pedis artery by brachial pressure of the same side.[12] ABI ≥0.9 was considered as normal and ABI <0.9 was defined as PAD.[13]

Statistical analysis

The data were transferred on Excel spreadsheet and descriptive analysis was expressed as mean ± standard deviation. All calculations were accomplished using InStat 3 Software (GraphPad, USA). Difference in mean distribution was calculated by Student's *t*-test. We evaluated strength of association of individual risk factor for PAD by finding the odds ratio keeping confidence interval (CI) 95% with ABI <0.9 as positive outcome and ABI ≥0.9 as negative outcome. Difference was considered statistically significant with $P < 0.05$.

RESULTS

Table 1 shows general characteristics of the study group that has representation of both sexes, mean age 55.59 ± 10.68 years, duration of diabetes 7.91 ± 6.91 (range 1–25) years, mean BMI 26.27 ± 4.95, poor glycemic control, comparatively fair lipidemic control and lipid profile showing low HDL, high LDL, and high TGAs, copybook picture of diabetic dyslipidemia.

Table 2 shows comparison of ABI in the patients with T2DM ($n = 101$), stratified by use of statins, BMI control, lipidemic control (American Diabetes Association guidelines 2013) reflecting that none of these correlates with crude ABI values and though good control shows better ABI, it lacks statistical significance.

Table 1: Baseline characteristics of participants (*n*=101)

General features	Mean±SD
Age (years)	55.69±10.68
Gender	
Male	50
Female	51
Total	101
Duration of diabetes (years)	7.91±6.91
BMI (kg/m^2)	26.27±4.95
Glycemic control-values (mg/dL)	
HbA1c	8.16±1.91
FBS	160.73±62.70
Postprandial blood sugar	219.79±82.40
Glycemic control-prevalence (mg/dL), *n* (%)	
HbA1c	34/101 (34)
FBS	38/101 (38)
Postprandial blood sugar	35/101 (35)
Lipidemic control-values (mg/dL)	
Total cholesterol	157.08±44.51
HDL-C	50.64±13.84
LDL-C	92.93±31.24
VLDL-C	23.71±15.60
TGAs	129.30±75.31
Lipidemic control-prevalence (mg/dL), *n* (%)	
LDL <100	57/101 (57)
HDL >50	48/101 (48)
TGAs >150	70/101 (70)
ABI-values (mm of Hg)	
Ankle pressure	117.03±23.30
Brachial pressure	120.56±16.45
ABI	0.97±0.20
PAD defined by low ABI - prevalence, *n* (%)	
PAD present - ABI <0.9	36/101 (30)
PAD absent - ABI ≥0.9	65/101 (70)

BMI=Body mass index, ABI=Ankle-brachial index, PAD=Peripheral artery disease, HDL=High density lipoprotein, LDL=Low density lipoprotein, VLDL=Very low density lipoprotein, HbA1c=Glycosylated hemoglobin, FBS=Fasting blood sugar, SD=Standard deviation, TGAs=Triglycerides

Table 2: Ankle-brachial index in the patients with type 2 diabetes mellitus (*n*=101), stratified by use of statins, body mass index control, lipidemic control (American Diabetes Association guidelines 2013)

Parameter	Statins taken (*n*=47)	Not taken (*n*=54)	*P*
Age (mean±SD)	56.91±9.31	54.67±11.69	0.38
Male/female (*n*)	24/23	26/28	0.84
Duration (mean±SD)	9.45±7.01	6.61±6.60	0.03*
ABI (mean±SD)	0.94±0.22	0.99±0.17	0.19
	BMI <25 (*n*=44)	**BMI ≥25 (*n*=57)**	
Age (mean±SD)	59.89±9.35	52.46±10.58	0.0005*
Male/female (*n*)	31/13	19/38	0.0003*
Duration (mean±SD)	8.41±7.08	7.52±6.80	0.32
ABI (mean±SD)	0.94±0.21	0.98±0.20	0.34
	LDL <100 (*n*=45)	**LDL ≥100 (*n*=56)**	
Age (mean±SD)	55.36±11.64	56.11±9.46	0.96
Male/female (*n*)	20/25	30/26	0.43
Duration (mean±SD)	8.10±7.34	7.67±6.40	0.91
ABI (mean±SD)	0.98±0.20	0.95±0.21	0.46
	HDL >50 (*n*=48)	**HDL ≤50 (*n*=53)**	
Age (mean±SD)	54.96±9.10	56.26±11.80	0.25
Male/female (*n*)	28/20	22/31	0.11
Duration (mean±SD)	7.65±6.58	8.10±7.20	0.98
ABI (mean±SD)	0.99±0.23	0.95±0.18	0.37
	TGA <150 (*n*=72)	**TGA ≥150 (*n*=29)**	
Age (mean±SD)	55.47±10.56	53.83±10.89	0.28
Male/female (*n*)	37/35	13/16	0.66
Duration (mean±SD)	8.48±7.17	6.55±6.15	0.21
ABI (mean±SD)	0.95±0.21	1.00±0.19	0.33

*Indicates statistical significance. ABI=Ankle-brachial index, BMI=Body mass index, HDL=High density lipoprotein, LDL=Low density lipoprotein, TGA=Triglyceride

Picture of PAD correlation becomes clear by qualitative comparison, after defining ABI <0.9 as PAD and ABI ≥0.9 as normal. Based on this, we calculated strength of association between PAD and use of statins, BMI control, lipidemic control (ABI <0.9 defined as positive outcome) to get odds ratio as shown in Table 3. The odds ratio was more than 1 for all, being highest for TGAs (OR: 3.24, 95% CI 0.82–12.77, $P = 0.09$), followed by BMI <25 (OR: 2.61, 95% CI 1.09–6.28, $P = 0.03$), HDL > 50 (OR: 1.61, 95% CI 0.71–3.66, $P = 0.26$), LDL < 100 (OR: 1.20, 95% CI 0.30–2.73, $P = 0.66$), and statins (OR: 1.14, 95% CI 0.50–2.58, $P = 0.75$). Although all risk factors except for BMI showed odds risk, all lacked statistical significance.

DISCUSSION

Our previous study has revealed low ABI prevailing in 35% of subjects having T2DM in our region.[3] The present study group was excluded for smoking, claudication, and all subjects were ambulatory. This gave us a chance to explore dyslipidemia and its correction by statins on diabetic vasculopathy. BMI is a simple anthropometric measure of optimum body composition and BMI ≥25 is a risk factor for PAD in T2DM[4] that proved to be the only significant risk factor of the three under study. A recent work revealed an independent, positive, and graded association of increasing obesity to both prevalent and incident high-ABI, and to mean increases in ABI values over time.[14] Weight and BMI seemed to be at least as strongly, if not more strongly, associated with a high ABI than were measures of abdominal obesity.[14] In another study, we found that the quantitative variable BMI correlates significantly with qualitative body fat distribution parameters derived by bio-electrical impedance analysis in our population regardless of gender or presence of type 2 diabetes.[15] It further consolidates the significance of BMI as a factor affecting PAD and supports the weight control strategy as cost-effective one to reduce the same and other complications. BMI is strongly and independently associated with the risk of being diagnosed with type 2 diabetes.[16] BMI under control is of prime importance for overall prognosis in T2DM and a good primary prevention

Table 3: Comparison of risk (odds ratio) for peripheral artery disease (ankle-brachial index <0.9) in the patients with type 2 diabetes mellitus (*n*=101), stratified by use of statins, body mass index control, lipidemic control (American Diabetes Association guidelines 2013)

Variable	Uncontrolled		Controlled		OR	95% CI	*P*
	ABI <0.9	ABI ≥0.9	ABI <0.9	ABI ≥0.9			
Statins	20	34	16	31	1.14	0.50-2.58	0.75
BMI <25	23	21	13	31	2.61	1.09-6.28	0.03*
LDL <100	21	35	15	30	1.20	0.3-2.73	0.66
HDL >50	20	28	16	36	1.61	0.71-3.66	0.26
TGA <150	16	28	3	17	3.24	0.82-12.77	0.09

*Indicates statistical significance. ABI=Ankle-brachial index, BMI=Body mass index, HDL=High density lipoprotein, LDL=Low density lipoprotein, TGA=Triglyceride, OR=Odds ratio, CI=Confidence interval

for many complications. In our previous study, we found hyperlipidemia to increase risk for PAD by 1.76 times in T2DM patients and poor glycemic control imposes odds ratio of 1.14 (FBS >130 mg/dL) for PAD.[3] Another study revealed odds ratio of 3.0 for HbA1c, 2.88 for FBS, and 2.13 for PP2BS[8] for PAD, unless controlled. Lipidemic control is more important and for CAD it has strict guidelines to be followed[11] and for PAD dyslipidemia has proven molecular mechanism.[17] We found small insignificant risk for abnormal ABI with high LDL, low HDL and high TGAs with the highest risk for the last parameter. Hypertriglyceridemia is an individual risk factor as recently indicated[18] and the same was underscored in our study. However, we could not find odds ratio for these three to be statistically significant and that can be attributed to low-risk profile and may indicate less importance of blood lipid control in PAD development in T2DM with low-risk profile. It also suggests greater importance of glycemic control which was seen in just one of three and not managed very optimally in our type 2 diabetics as we pointed previously.

Optimum body fat distribution indicates the overall metabolic well-being in T2DM which is more of an abnormal lipid metabolism than merely abnormal glucose homeostasis.[19] The first 3 out of 5 are simple measures yet ignored and just 20 out of 101 subjects were practicing it when inquired in our study group. In a study, we found that type 2 diabetics have more ectopic fat on the expense of skeletal muscle that persists even after matching by weight or BMI, both quantitatively and qualitatively.[20] Hence, correlation of BMI and PAD should be seen even seriously as real correlation between qualitative body fat and PAD can be even stronger. Excess BMI and ectopic distribution is seen as a fore-runner of insulin resistance which can lead to type 2 diabetes.[21] It can be maintained by diet control, weight reduction, exercise, glycemic control and at the most lipidemic control with statins.[22] Hence, maintaining optimum body weight by lifestyle modification can serve as cheap and effective preventive measure.

Statins remain a cornerstone treatment for correcting diabetic dyslipidemia with proven efficacy to reduce cardiovascular events[9,17,18,22] but the focus is mainly on its preventive role for CAD and not much on PAD. Most of the studies are done in indoor patients or with symptomatic high-risk patients who would definitely be benefited by such preventive pharmacotherapy. We did not find any significant correlation of statin therapy with better ABI that is contradictory to few studies[23,24] which found it to be important. However, these studies have focused mainly cardiac outcome, and it is stated that residual CVD risk still remains after statin therapy.[25] In India, as reviewed previously there is a question about cost-effectiveness of statin as primary preventive measure.[26] As published previously, overall compliance to statin therapy remains suboptimal with patient-, physician-, and economic-related factors all playing a role.[27] The same observation can be explained by highlighted importance of good glycemic control which was not seen in more than two-third of the cases. Only limited evidence showed that primary prevention with statins may be cost-effective and improve patient quality of life and caution should be taken while prescribing statins for primary prevention among people at low cardiovascular risk like our case group.[28] In our type, 2 diabetics use of Angiotensin II converting enzyme inhibitors have proven significant added advantage[7] that was completely denied to this study group and controlled FBS having proved impact on better PAD profile was sub-optimum in majority. These two also highlights why despite being at low risk, use of statin, and better lipid profile was not significantly affecting PAD profile of type 2 diabetics.

Dyslipidemia is one of the major risk factor for CVD.[29] In T2DM patients, dyslipidemia is characterized by raised serum TGAs, decreased HDL cholesterol (HDL-C), and raised LDL cholesterol (LDL-C).[30] We found the same profile in majority of our subjects. Our study, however, suggested lesser significance of uncontrolled HDL, LDL, and TGAs as risk factors for PAD in low risk T2DM patients, which is in line with a study done by Ramos *et al*.[31] A recent study has shown that diabetic dyslipidemia is not sufficient to initiate the atherosclerotic lesion, because the progression of atherosclerosis process could be normalized after intensive glycemic control with insulin in mice.[32] As recently pointed out that routine care produces as good a result as intensive management for PAD prevention[33] and life style modification is still left with scope[25] added by the fact that routine blood lipid check-up or feasibility of hypolipidemic agents is beyond reach for many patients, and rather more emphasis should be given to improve glycemic control, and motivation for weight reduction and exercise holds the key.

To conclude with, we found significant effect of controlled BMI, but not of controlled lipidemia or use of statins on PAD prevalence in low-risk ambulatory T2DM patients. BMI, being

a modifiable and a cost-effective option, should be targeted to optimum along with optimum glycemic control that can serve as primary prevention and further studies are required to support this.

Limitation of study

There were certain limitations of this study. We had moderate sample size, and further consolidation requires larger size and vertical follow-up to establish cause-effect relationship. We excluded indoor patients who might have some significant difference, but majority is still with ambulatory and asymptomatic patients who may be offered the screening. There is the presence of confounding variables which might affect the result but cannot be negated.

CONCLUSION

In low-risk type 2 diabetics free of PAD symptoms, BMI definitely but lipidemic control and statin therapy are not suggested to have clinically significant impact on PAD screened by ABI. It emphasizes the importance of strict glycemic control, weight reduction, lifestyle modifications, and necessity of screening for PAD by ABI. All, being primary preventive measures against PAD in T2DM, are needed to combat this silent killer aftermath.

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Conflicts of interest

There are no conflicts of interest.

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