

# Evaluating glycemic control and its correlation with peripheral artery disease in ambulatory type 2 diabetic patients of an urban area of Gujarat, India

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## Abstract

**Background and Aim:** Persistent hyperglycemia and insulin resistance in type 2 diabetes mellitus (T2DM) increases the risk for peripheral artery diseases (PAD), which can be measured by ankle brachial pressure index (ABPI), a simple yet validated tool. In the present study, we attempted to correlate the glycemic control with PAD and to find its significance, if any.

**Methods:** We recruited 147 ambulatory T2DM patients under treatment with minimum 1 year of disease duration representing the various socioeconomic strata. Fasting blood sugar (FBS), postprandial blood sugar (PP2BS) and glycosylated hemoglobin (HbA1c) were measured at an accredited laboratory, and the glycemic control was defined as per American Diabetes Association 2012 criteria. PAD was tested by ABPI, using vascular doppler following standard protocol, defined as  $ABPI \leq 0.9$  and compared within them in groups based on glycemic control.

**Results:** We found glycemic control in just one-third of the subjects who correlated negatively with ABPI values for all three parameters (OR: HbA1c - 3.00, FBS - 2.88, PP2BS - 2.13). Odds risk for PAD in poorly controlled glycemics proved to be the highest for HbA1c and statistically significant for FBS ( $P$  value 0.016).

**Conclusion:** Poor glycemic control and under-use of ABPI assessment for PAD need to be rectified. All means of glycemic control were correlated with PAD, of which FBS is a better predictor than HbA1c.

**Key words:** Ankle brachial pressure index, hyperglycemia, peripheral artery disease, type 2 diabetes mellitus

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## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is in a rising trend, and it is projected that more than 75% of total T2DM patients will be living in India and China by 2025.<sup>[1]</sup> Insulin resistance is associated with development of peripheral artery diseases (PAD) that is evident clinically as low ankle brachial pressure index (ABPI)<sup>[2]</sup>, a tool that

is cost-effective, validated, subjective, reproducible, simple, non-invasive, fairly sensitive and specific.<sup>[3]</sup> PAD progresses silently due to associated neuropathy<sup>[4]</sup>, and early detection of PAD is of prime importance. Hyperglycemia imposes risk of lower extremity diseases like foot infection, foot ulcer and the most dreadful, lower limb amputation.<sup>[5]</sup> It is also evident that aggressive glycemic control decreases these lower extremity diseases significantly.<sup>[6]</sup> Fasting blood sugar (FBS), postprandial blood sugar (PP2BS) and HbA1c are glycemic triad with proven efficacy of diseases control, however preferred in different magnitude by different types of health care providers. Though many studies have attempted to correlate them individually with PAD, most of them are western studies, and they have not included all the three parameters. Further, these studies were done mainly in hospitalized patients with/without

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complications. In the present study, we attempted to correlate these three means of glycemic control with PAD as evidenced by ABPI.

## MATERIALS AND METHODS

### Study population

This cross-sectional field study was carried out by Department of Physiology, Government Medical College, Bhavnagar, from September 2012 to September 2013 on known ambulatory T2DM patients of either sex, taking oral hypoglycemic agents as regular treatment (but not insulin) for a minimum of 1 year with recent reports of glycemic control done. After taking approval for the study from the institute ethics committee, sample size was calculated by software, RaoSoft (Database web survey software for gathering information of Raosoft, Inc. Seattle, Washington, USA) for the entire population of the city of 6 lakhs with 9.7% national prevalence of diabetes. Total 147 (65 males, 82 females) subjects were sufficient to yield 95% confidence level and 5% margin of error. Subjects were chosen randomly from (i) medicine OPD of Sir Takhtsinhji General Hospital (a tertiary care teaching government hospital) (ii) diabetic OPD of Sir Jaswantsinhji Hospital (urban health and training center affiliated to Sir T Hospital and Preventive Medicine department) (iii) diabetic camp at Shree Bajarangdas Bapa Arogyadhaam (a trust multispecialty hospital) and (iv) private OPD patients. By choosing patients from different set-ups belonging to different socioeconomic strata, we tried to have a blend of heterogeneous subjects, which formed a fairly representative sample whose result can be applied to generalized population. Subjects taking irregular treatment, newly diagnosed, having previous vascular intervention, having amputated limb, ABPI more than 1.4 (that is due to atherosclerosis of the arteries seen with ageing), taking vasodilators and smokers were excluded from the study.

### General assessment

All recruited subjects underwent personal interview in the form of pre-designed, pre-validated questionnaires<sup>[7]</sup> that included general features, demographic characteristics, symptom of PAD, investigations and treatment taken. Specific emphasis was given to get the reports of glycemic control.

### Glycemic control

To evaluate glycemic control of the T2DM, subjects underwent (1) measurement of FBS and PP2BS done by GOD POD method and (2) HbA1c done by immune turbidimetry method. These tests were carried out using a fully automated analyzer I LAB-650/MIURA, A-1004 of Iris Healthcare Maharashtra, India, at NAAC-certified

Biochemistry laboratory of our college using standard operating procedures. We defined glycemic control as per criteria laid by American Diabetes Association 2012<sup>[8]</sup> and good glycemic control was defined as (1) HbA1c < 7 g%, (2) FBS < 130 mg% and (3) PP2BS < 180 mg%. Subjects were divided into two groups based on these criteria into those with good or poor glycemic control.

### ABPI assessment

ABPI 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 frequency, Diabetik Foot Care India Limited, Chennai, India) having 12 cm occluding cuff. ABPI was derived by dividing the higher reading of the ankle pressure at dorsalis pedis artery by brachial pressure of same side.<sup>[9]</sup> ABPI > 0.9 was considered as normal and ABPI ≤ 0.9 was defined as PAD.<sup>[10]</sup>

### Statistical analysis of data

The data was transferred on excel spreadsheet and descriptive analysis was expressed as mean ± SD. All calculations were accomplished by using Graph Pad InStat 3 software. Observed difference in mean distribution of ABPI values in groups with or without threshold glycemic control for all three variables was calculated by student *t* test. We evaluated the strength of association of each of the glycemic control parameter for PAD by finding the odds risk keeping confidence interval 95% considering ABPI ≤ 0.9 as positive outcome and ABPI > 0.9 as negative outcome. We excluded subjects with ABPI > 1.4. Difference was considered statistically significant with *P* value < 0.05.

## RESULTS

Table 1 depicts demographic and clinical characteristics of study population of ambulatory T2DM showing more females than males, average age of onset of disease in mid-50s, average duration of disease as 7 years and expectedly high average BMI. On evaluating the glycemic control triad, HbA1c was  $7.87 \pm 2.10$  g/dL, FBS was  $166.16 \pm 62.82$  mg/dL and PP2BS was  $223.79 \pm 89.64$  mg/dL. Ankle pressure on average was lower than brachial pressure with ABPI being  $0.96 \pm 0.20$ . It shows prevalence of good glycemic control as per American Diabetes Association guidelines of 2012 to be present in 34 out of 70 (49%) for HbA1c; 46 out of 130 (35%) for FBS and 66 out of 128 for PP2BS (52%). On defining PAD by low ABPI, it seemed to be present in 64 out of 147 (44%).

Table 2 depicts the correlation between ABPI values of groups based on glycemic control for HbA1c, FBS and PP2BS, reflecting that subjects with poor glycemic control showed lower ABPI as compared to those having

**Table 1:** Demographic and clinical characteristics of the known under treatment ambulatory type 2 diabetics under study (n=147)

General features	Mean±SD
Age (years)	55.39±10.69
Gender	
Male	65
Female	82
Total	147
Duration of diabetes (years)	6.83±6.49
Age of onset of diabetes (years)	48.57±9.78
BMI (kilogram/meter <sup>2</sup> )	26.09±5.13
Glycemic control-values	Mean±SD
Hb1Ac (g/dL)	7.87±2.10
Fasting blood sugar (mg/dL)	166.16±62.82
Postprandial blood sugar (mg/dL)	223.79±89.64
Glycemic control-prevalence	Number (%)
Hb1Ac (g/dL)	34/70 (49)
Fasting blood sugar (mg/dL)	46/130 (35)
Postprandial blood sugar (mg/dL)	76/128 (52)
Ankle brachial pressure index-values	Mean±SD
Ankle pressure (mm of Hg)	115.71±89.64
Brachial pressure (mm of Hg)	121.14±19.40
ABPI	0.96±0.20
PAD defined by low ABPI-prevalence	Number (%)
PAD present - ABPI≤0.9	64/147 (44)
PAD absent - ABPI>0.9	83/147 (56)

BMI: Body mass index; PAD: Peripheral artery disease; ABPI: Ankle brachial pressure index; SD: Standard deviation

**Table 2:** Ankle brachial pressure index in the patients with type 2 diabetes mellitus (n=147), stratified by glycemic control (American Diabetes Association Guidelines 2012)

Parameter of glycemic control	Ankle brachial pressure index		P value
	Good control	Poor control	
Hb1Ac (n=70)	0.99±0.17	0.94±0.24	0.139
FBS (n=130)	1.00±0.21	0.94±0.18	0.050*
PP2BS (n=128)	0.98±0.22	0.94±0.17	0.181

\* indicates statistical significance of the observed difference, FBS: Fasting blood sugar; PP2BS: Postprandial blood sugar

good glycemic control. However, this difference was statistically significant only for FBS and not for the other two.

Actual result for PAD correlation is seen after defining ABPI ≤ 0.9 as PAD and ABPI > 0.9 as normal. Based on this, we calculated strength of association between glycemic control (HbA1c, FBS, PP2BS) and PAD (ABPI ≤ 0.9 being defined as positive outcome) to get odds risk [Table 3]. The odds risk was significant for all, being highest for HbA1c (OR: 3.00, 95%CI 1.09 – 8.24, P = 0.033), followed by FBS (OR: 2.88, 95%CI 1.22 – 6.81, P = 0.016) and PP2BS (OR: 2.13, 95% CI 1.03 – 4.41, P = 0.042). Though HbA1c demonstrated the highest odds risk; the P value was most significant for FBS.

## DISCUSSION

Presently, greatest public health challenge for developing countries like India is the control T2DM and its complication like PAD, which is causing mortality at a rate double than those for communicable diseases.<sup>[11]</sup> South Asians are more susceptible to the detrimental effects of oxidative stress induced by hyperglycemia even at lower glucose thresholds than white Europeans.<sup>[12]</sup> Chronic hyperglycemia as seen in T2DM is related to increased risk for PAD.<sup>[13]</sup> Level of glucose fluctuation plays a significant role in vascular endothelial dysfunction in T2DM.<sup>[14]</sup> In the present study, in a sample population from an urban area of west India, we tried to assess the pattern of glycemic control in under-treatment T2DM subjects and to correlate the presence or absence of threshold glycemic control with PAD status as reflected by ABPI. FBS, PP2BS and HbA1c are three parameters to assess the glycemic control of T2DM patients for diagnosis as well as prognosis.<sup>[8]</sup> In our study, we found good glycemic control in just one-third cases for FBS and in only half for PP2BS and HbA1c, a pattern that indicates need for better glycemic control. Similarly to assess PAD, ABPI is a cost-effective and validated tool<sup>[3]</sup> and looking at the burden of the disease for countries like ours, it is a boon but it's still under-rated and under-used by the health care personnel. ABPI was abnormally low in nearly 44% subjects, which is alarmingly high and this could be due to the silent progression of the disease and negligence of patients. We found that only one-third of the T2DM subjects of our study group were having threshold glycemic control as per standard norms. Poor glycemic control is one of the features of T2DM subjects in Indian population, especially in Gujaratis as reported in a previous study.<sup>[15]</sup> Therefore, PAD is highly prevalent in Gujarat.<sup>[16]</sup> We also found a high prevalence of risk factors for PAD in T2DM subjects in this region of the country, most of which were modifiable, and glycemic control being one of them.<sup>[17]</sup> This along with the fact that Indian patients with diabetes have poor foot care practice,<sup>[18]</sup> warrants further studies to assess the use of ABPI as screening tool on a wide scale and intensification of the concept of a strict glycemic control for better prognosis of PAD and other complications of the disease. Hyperglycemia and insulin resistance are key features of T2DM that causes vascular disease by: (i) critical role of endothelium in obesity-induced insulin resistance; (ii) hyperglycemia-dependent microRNAs deregulation and impairment of vascular repair capacities; (iii) alterations of coagulation, platelet reactivity, and micro particle release; (iv) epigenetic-driven transcription of ROS-generating and proinflammatory genes.<sup>[19]</sup>

On comparing the absolute ABPI values based on three glycemic control parameters, we found statistically significant difference only for FBS control and not for

**Table 3:** Correlation between risk (odds risk) of peripheral artery disease (ABPI $\leq$ 0.9) and poor glycemic control (ADA Guidelines 2012) in type 2 diabetics under study ( $n=147$ )

Parameter of glycemic control	Poor glycemics		Good glycemics		Odds risk	95% CI	P value
	ABPI $\leq$ 0.9	ABPI $>$ 0.9	ABPI $\leq$ 0.9	ABPI $>$ 0.9			
Hb1Ac ( $n=70$ )	27	9	17	17	3.00	1.09,8.24	0.033*
FBS ( $n=130$ )	27	16	17	29	2.88	1.22,6.81	0.016*
PP2BS ( $n=128$ )	46	18	36	30	2.13	1.03,4.41	0.042*

\*' indicates statistical significance, CI: Confidence interval; FBS: Fasting blood sugar; PP2BS: Postprandial blood sugar

HbA1c or PP2BS. However, defining PAD as positive outcome (ABPI  $\leq$  0.9) we found risk for the same in poor glycemics to be most for the HbA1c, followed by FBS and PP2BS. Still based on the *P* value for this odds ratios for the three variables, we found highest correlation with FBS than HbA1c. Few recent studies have shown PAD to correlate more with FBS, as for the findings of the present study<sup>[13,20,21]</sup> and few others found the relation with HbA1c as weak and non-significant.<sup>[20,22,23]</sup> This can be attributed to the fact that the HbA1c is linked more significantly with microvascular complications of T2DM like neuropathy, nephropathy and retinopathy than macrovascular complications like PAD.<sup>[24]</sup>

HbA1c has been reported to be a better index of overall glycemic exposure than glucose (FBS or PP2BS), as it is less subjected to biological variability, pre-analytic instability, prandial status and acute stress.<sup>[25]</sup> There are concerns of cost-effectiveness of HbA1c in a large scale assessment in this part of the globe. Despite these concerns, HbA1c has got promising prognostic significance and should be used as a benchmark evaluation test wherever feasible.<sup>[26]</sup> There is one study<sup>[27]</sup> indicating that in natural progression of T2DM, hyperglycemia is a late manifestation than vasculopathy. Therefore, it may be advised to practice ABPI assessment to reduce the burden of secondary and tertiary care in tertiary care hospitals, and probably it should also be practiced in primary health care services to rectify this problem.<sup>[28]</sup> As we found better ABPI in all patients with good glycemic control, it appears to be fundamental to have hyperglycemia under control and the predictive importance of all the three of glycemic control triad.

#### Limitations of the study

Though sample size was comparatively small, we included subjects from all socioeconomic strata because heterogeneous representation provides a better applicability of the findings to the wider population. However, to further confirm our observation, a study in a larger sample size is required. The present study highlights the importance of having strict glycemic control, usefulness of FBS and HbA1c, and PAD assessment by measures like ABPI for further work in this field of research.

## CONCLUSION

T2DM subjects of Gujarati population showed high prevalence of poor glycemic control, that is one out of three and high prevalence of low ABPI, both of which correlate with each other for all the three glycemic control parameters. By comparing PAD status by ABPI values among T2DM subjects grouped by glycemic control triads, we found significant correlation for all the three measures of glycemia with advantage of FBS as compared to HbA1c.

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