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Original Article

Physiology Section

Arterial Parameters in Type-2 Diabetes and Healthy Subjects by using Impedance Plethysmography: A Case-control Study

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ABSTRACT

Introduction: A reduced blood supply to lower limb, due to arterial disease, is a common cause of foot ulceration in patients with Diabetes Mellitus (DM). Impedance Plethysmography (IPG) is based on the measurement of changes in the electrical resistance (impedance) caused by blood volume changes.

Aim: To compare parameters of type-2 diabetic subjects with those of healthy subjects along with different age group and to associate with Blood Flow Index (BFI), Fasting Blood Sugar (FBS), Post-Prandial Blood Sugar (PP_2BS) and Body Mass Index (BMI).

Materials and Methods: This case-control study was conducted at Government Medical College and in UHTC, Bhavnagar, Gujarat, India, from May 2012 to August 2013 on 100 healthy subjects and 100 type-2 diabetic subjects. IPG arterial parameters like BFI, Pulse Arrival Time (PAT), Pulse Termination Time (PTT), Differential Pulse Arrival Time (DPAT), Z_0 (Basal impedance) recorded. The data were analysed by unpaired t-test and ANOVA test.

Results: This study had 200 subjects of age more than 30 years. The diabetic subjects included 56 males and 44 females whereas the healthy subjects included 67 males and 33 females. There was bilateral significant reduction of BFI, PAT at knee, ankle and calf segment among diabetics group in males and females; and a bilateral significant reduction of PTT at ankle segment among diabetic males and females. DPAT value increased at knee, calf and ankle segment on both sides in male and female; except right ankle segment in diabetic group in females as compared to healthy subjects. Z_0 increased at knee, ankle and calf segment in diabetic group on both side in males and females. BFI decreased with an increase in the duration of diabetes. The effect of FBS, PP_2BS and BMI in diabetic subjects suggested a negative association with BFI.

Conclusion: There was decrease in BFI, PAT, PTT and increase in DPAT in the knee, calf and ankle region of diabetic subjects. BFI negatively correlated with FBS, PP_2BS and BMI among diabetics and decreased with increased duration of DM.

Keywords: Ankle, Blood flow index, Calf, Fasting blood sugar, Knee, Post-prandial blood sugar

INTRODUCTION

The DM is a significant risk factor for development of Peripheral Arterial Disease (PAD) [1]. India is already leading the world with the highest number of DM 31.7 million subjects and this number is expected to reach nearly 79.4 million by 2030 [2]. A reduced blood supply to lower limb, due to arterial disease, is a common cause of foot ulceration in patients with DM. All lower extremity amputations, 40-70% are related to diabetes, with majority occurring as a result of PAD [3,4]. Early detection of reduced blood supply in DM can help to prevent the diabetic foot prior to PAD [5].

Impedance plethysmography is based on the measurement of changes in the electrical resistance (impedance) caused by blood volume changes [6]. The sensitivity of IPG technique is 97.5% and specificity is 98.1% in diagnosing PAD [7]. IPG is superior to doppler sonography, laser doppler flowmetry, strain gauge plethysmography, pulse volume recorder, photo plethysmograph, angiography, ankle brachial pressure index [8-13].

IPG association has been widely used for the evaluation of patients at risk or suspected to have lower extremity Deep Vein Thrombosis (DVT) [14]. Electrical impedance methods are reliable, convenient non invasive, and cost effective to measure and analyse haemodynamics in clinical practice. One can detect blood flow disorders such as arterial occlusive diseases (and estimate severity), early stage arteriosclerosis, functional blood flow disturbances, deep venous thromboses, migraines, and general arterial blood flow disturbances [15].

Hence, the present study was conducted to find the importance of IPG in early detection of vasculopathy of type-2 DM. The IPG parameters of type 2 diabetics were compared with those of healthy subjects and a comparison different age groups was done. Association was sought for Blood Flow Index (BFI) with Fasting Blood Sugar (FBS), Post-Prandial Blood Sugar (PP_2BS) and Body Mass Index (BMI) of Bhavnagar district (Gujarat), India.

MATERIALS AND METHODS

This case-control study was conducted in the Cardiovascular Laboratory, Department of Physiology, Government Medical College, and in UHTC, Bhavnagar, Gujarat, India, from May 2012 to August 2013. Institutional Review Board approved the study vide letter no.284/2012. Informed consents were obtained from the study participants. The study tool was IPG instrument Nivomon Series Product computerised software by Larsen and Toubro (L&T) Company.

Sample size calculation: Calculation of sample size was done by formula $n=Z^2pq/e^2$ where,

Z: statistic for a level of confidence (For Z of 95%, which is conventional, Z-value is 1.96).

p: expected prevalence or proportion (p is 0.5), (q=1-p).

e^2: precision (e is considered 0.05 to produce good precision and smaller error of estimate).

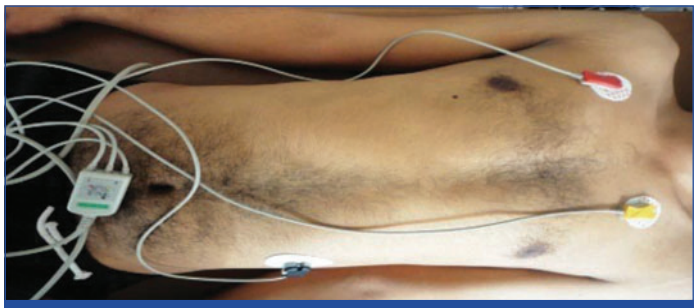
The calculated sample size was 73, each in the control and diabetic group. Total 100 subjects were taken each in the healthy and diabetic subjects considering 10% of lost to follow-up or confounder.

Inclusion criteria: Subjects with age more than 30 years in healthy subjects and type-2 diabetics subjects of either sex. Those who can give written informed consent were included in study.

Exclusion criteria: Subjects with history of significant illness of other system especially cardiovascular system, factors affecting blood flow like smoking, obesity, hypertension, other peripheral vascular disease like burger disease etc, subjects who did not consent to the study were excluded.

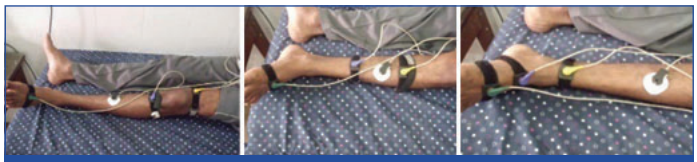
Study Procedure

Each subject was examined clinically to exclude any pathology affecting vascular function. The recording was done in supine position at room temperature and surface Electrocardiogram (ECG) electrodes were used on the chest of subject in three lead configurations as shown in [Table/Fig-1].



[Table/Fig-1]: ECG electrodes placement in three lead configurations on chest.

The accessory band electrodes (I_1, I_2-current electrodes and V_1, V_2-sensing electrodes) were strapped to body segment of interested area of the subject by choosing appropriately sized bands at desired location to capture IPG waveform as shown in [Table/Fig-2] and in following [Table/Fig-3].



[Table/Fig-2]: Placement of accessory band electrodes on lower limb segment.

No.	Segment	I_1	V_1	V_2	I_2
1.	Knee	Forehead	Above knee	Below knee	Feet
2.	Calf	Forehead	Below knee	Above ankle	Feet
3.	Ankle	Forehead	Above ankle	Below ankle	Feet

[Table/Fig-3]: Placement of accessory band electrodes on lower limb segment.

I_1, V_1, V_2 and I_2 of IPG cable were connected to the band electrodes at the extremities of measurement area to capture IPG waveform. Inter-electrode distance between V_1 and V_2 was tried to maintain <10 cm for each site. IPG waveform was recorded at least for 30 seconds and reduces noise interference in averaged waveform, long recording to a maximum of 150 seconds was taken. As soon as waveform acquisition was stopped, all results of arterial parameters BFI, PAT, PTT, DPAT, Basal impedance (Z_0) displayed on screen. Surface and band electrodes were carefully removed with minimal discomfort to subject after recording was over from all desired sites.

The diabetic subjects were divided on the basis of duration of diabetes into four groups as follows.

Group A: 0-5 years (39)

Group B: 6-10 years (33)

Group C: 11-15 years (15)

Group D: >15 years (13)

STATISTICAL ANALYSIS

Recorded data was presented as mean±SD (Standard Deviation) by Microsoft excel and analysed using unpaired t-test and Analysis of Variance (ANOVA) t-test by software GraphPad InStat (DATASET1. ISD). The p-value ≤0.05 was considered as statistically significant.

RESULTS

This study had 200 subjects of age more than 30 years. The diabetic subjects included 56 males and 44 females whereas the healthy subjects included 67 males and 33 females. The physical parameters of healthy and diabetic subjects were analysed as shown in [Table/Fig-4].

The BFI, PAT, PTT, DPAT and Z_0 were analysed in all the subjects of the study as shown in [Table/Fig-5-9]. Unpaired t-test in between healthy and diabetics subjects was significant with p-value <0.05 and highly significant with p-value<0.001.

Associating mean of BFI at knee, ankle and calf segment of diabetic subjects according to duration of diabetes through ANOVA t-test, it was evident that with increasing age groups, BFI was not increasing significantly except right ankle (group A v/s group D <0.05) and left ankle (group A vs. group C <0.05, group A vs. group D <0.05) [Table/Fig-10]. The association of FBS, PP_2BS and BMI with BFI in diabetics is represented in [Table/Fig-11].

Physical parameters	Male			Female		
	Healthy subjects	Diabetic subjects	p-value	Healthy subjects	Diabetic subjects	p-value
Age (years)	50.02±15.57	54.34±10.58	0.810	59.79±10.20	57.20±9.64	0.081
Height (cm)	168.02±6.20	164.21±7.16	0.354	150.93±3.40	156.99±7.05	0.354
Weight (kg)	66.70±11.22	66.38±10.80	0.603	64.52±13.84	65.86±14.54	0.873
BMI (kg/m^2)	23.55±3.26	24.64±3.89	0.092	24.25±4.70	26.85±5.54	0.092
Systolic BP (mmHg)	122.35±7.29	129.89±13.65	0.554	124.42±11.54	128.41±9.69	0.502
Diastolic BP (mmHg)	81.25±6.67	81.92±5.93	0.558	80.90±5.91	80.09±4.52	0.558
Heart rate (beats/min)	79.09±4.52	79.35±4.95	0.755	78.55±4.89	77.84±9.65	0.755
FBS mmol/L	87.94±6.28	143.86±40.92	<0.0001	88.94±6.16	164.09±53.7	<0.0001
PP_2BS mmol/L	123.10±8.85	217.77±58.75	<0.0001	125.76±10.35	240.1±77.86	<0.0001

[Table/Fig-4]: Physical parameters inhealthy and type-2 diabetics subjects (data is in Mean±SD. unpaired t-test applied).
p-value <0.05 was considered as significant and p-value <0.001 highly significant; FBS: Fasting blood sugar; PP_2BS: Post-prandial blood sugar; BP: Blood pressure

Segment	Side	BFI in males			BFI in females		
		Healthy Subjects	Diabetics subjects	p-value	Healthy subjects	Diabetics subjects	p-value
Knee	Right	0.76±0.12	0.59±0.23	<0.0001	0.76±0.12	0.56±0.25	0.007
	Left	0.78±0.15	0.58±0.20	<0.0001	0.76±0.18	0.60±0.25	0.0047
Calf	Right	0.78±0.13	0.61±0.15	<0.0001	0.74±0.13	0.59±0.16	<0.0001
	Left	0.76±0.15	0.62±0.20	<0.0001	0.75±0.12	0.59±0.16	<0.0001
Ankle	Right	0.80±0.17	0.65±0.15	<0.0001	0.79±0.17	0.67±0.22	0.0130
	Left	0.79±0.16	0.64±0.28	0.0003	0.80±0.15	0.67±0.28	0.0529

[Table/Fig-5]: Blood flow index in healthy subjects and type-2 diabetics subjects (data is in Mean±SD, unpaired t-test applied).
p-value <0.05 was considered as significant and p-value <0.001 highly significant

Segment	Side	PAT in males			PAT in females		
		Healthy subjects	Diabetic subjects	p-value	Healthy subjects	Diabetic subjects	p-value
Knee	Right	227.13±20.65	183.03±28.47	<0.0001	219.09±21.11	189.77±34.87	<0.0001
	Left	230.90±27.73	184.29±30.32	<0.0001	231.52±29.80	190.68±34.05	<0.0001
Calf	Right	231.19±23.77	203±29.76	<0.0001	228.79±25.95	198.18±26.87	<0.0001
	Left	234.17±30.11	203.35±27.55	<0.0001	240.30±30.87	197.05±26.46	<0.0001
Ankle	Right	239.70±39.04	205.32±40.83	<0.0001	239.09±36.52	197.27±31.50	<0.0001
	Left	253.28±35.05	204.04±37.68	<0.0001	251.82±42.52	204.32±38.42	<0.0001

[Table/Fig-6]: Pulse arrival time (ms) in healthy and type-2 diabetics subjects (data is in Mean±SD, unpaired t-test applied).
p-value <0.05 was considered as significant and p-value <0.001 highly significant

Segment	Side	PTT in males			PTT in females		
		Healthy subjects	Diabetics subjects	p-value	Healthy subjects	Diabetics subjects	p-value
Knee	Right	405.13±38.1	415.71±69.56	0.298	414.85±48.22	404.59±67.60	0.4609
	Left	405.52±42.26	402.68±59.31	0.76	413.93±41.15	404.09±61.24	0.4274
Calf	Right	411.19±7.30	401.07±58.08	0.288	406.66±42.11	396.14±51.81	0.3430
	Left	424.33±2.93	393±54.85	0.0005	431.82±50.95	397.72±50.52	0.0046
Ankle	Right	426.57±3.86	401.96±58.01	0.016	436.36±49.36	389.09±61.83	0.0005
	Left	440.90±53.25	397.5±64.59	<0.0001	433.03±46.27	396.36±71.14	<0.0001

[Table/Fig-7]: Pulse termination time (ms) in healthy and type-2 diabetics subjects (data is in Mean±SD, unpaired t-test applied).
p-value <0.05 was considered as significant and p-value <0.001 highly significant

Segment	Side	DPAT in male			DPAT in female		
		Healthy subjects	Diabetic subjects	p-value	Healthy subjects	Diabetic subjects	p-value
Knee	Right	188.24±20.65	232.68±68.77	<0.0001	195.75±48.68	214.82±73.92	0.203
	Left	174.62±45.24	218.40±58.99	<0.0001	182.42±41.15	213.40±74.65	0.038
Calf	Right	180±44.96	198.07±58.37	0.055	177.88±42.11	197.95±53.12	0.078
	Left	189.70±37.85	189.64±55.6	0.995	191.52±45.97	200.68±51.73	0.423
Ankle	Right	186.87±56.70	196.64±47.57	0.308	197.27±47.58	191.81±51.86	0.637
	Left	187.61±57.13	193.43±57.79	0.577	181.21±44.70	192.05±64.43	0.411

[Table/Fig-8]: Differential pulse arrival time (ms) in healthy and type-2 diabetics subjects (data is in Mean±SD. Unpaired t-test applied).

Segment	Side	z_0 in Males			z_0 in Females		
		Healthy subjects	Diabetic subjects	p-value	Healthy subjects	Diabetic subjects	p-value
Knee	Right	33.56±11.70	41.98±17.25	0.002	33.54±12.53	44.90±17.66	0.025
	Left	34.34±9.19	42.47±18.23	0.002	34.70±11.34	45.27±17.34	0.003
Calf	Right	38.10±13.92	39.29±17.03	0.669	35.64±13.11	46.64±16.22	0.002
	Left	37.37±15.32	39.06±18.99	0.586	38.41±14.52	46.06±16.22	0.035
Ankle	Right	60.06±14.33	62.25±8.41	0.316	61.63±13.55	62.05±8.80	0.870
	Left	62.87±13.08	63.22±10.34	0.871	64.68±12.56	62.15±10.80	0.310

[Table/Fig-9]: Basal impedance (Z (Ω)) in healthy and type-2 diabetics subjects. (data is in Mean±SD, unpaired t-test applied).
p-value <0.05 was considered as significant and p-value <0.001 highly significant

Segment	Group A	Group B	Group C	Group D	p-value
Right knee	0.57±0.13	0.56±0.37	0.50±0.10	0.47±0.17	0.423
Left knee	0.59±0.16	0.59±0.12	0.51±0.12	0.50±0.11	0.508
Right calf	0.64±0.15	0.60±0.16	0.58±0.13	0.60±0.15	0.399
Left calf	0.66±0.19	0.62±0.20	0.63±0.17	0.54±0.11	0.245
Right ankle	0.68±0.17	0.65±0.23	0.63±0.18	0.52±0.15	0.858 A v/s D <0.05
Left ankle	0.61±0.21	0.59±0.19	0.65±0.15	0.46±0.13	0.229 A vs. C <0.05 A vs.D <0.05

[Table/Fig-10]: Comparison of blood flow index of IPG waveforms at knee, ankle and calf segment of diabetics subjects according to duration of diabetes. (data is in Mean±SD. ANOVA applied).
Group A: 0-5 years (39), Group B: 6-10 years (33), Group C: 11-15 years (15), Group D: >15 years (13); p-value <0.05 was considered as significant and p-value <0.001 highly significant

Blood flow index									
Variables	Segment	Right	Left	Segment	Right	Left	Segment	Right	Left
FBS	Knee	-0.0550	-0.0039	Calf	- 0.1491	- 0.0585	Ankle	+0.1238	- 0.0873
PP_2BS		-0.0255	-0.0848		- 0.1417	- 0.1269		+0.1711	+0.0508
BMI		-0.3151	-0.1853		- 0.0277	- 0.1573		- 0.0722	-0.0255

[Table/Fig-11]: Effect of FBS, PP_2BS and BMI on BFI of study group (Correlation coefficient r).
'+' sign indicates positive correlation '-' sign indicates negative correlation; FBS: Fasting blood sugar; PP_2BS: Post-prandial blood sugar; BMI: Body mass index

DISCUSSION

With increasing the duration of diabetes has an even worse effect on blood flow to the lower extremities. In this study, a significant reduction in BFI at the knee, calf and ankle was observed in diabetic subjects compared to healthy subjects on both sides in men and women. Diabetes affects the vasodilation capacity of the vascular endothelium by blocking the nitric oxide pathway [16]. This gradually decreasing BFI in diabetic subjects due to microvascular disease include polyol pathway (aldose reductase and sorbitol dehydrogenase, which catalyse reactions that can lead to sorbitol accumulation-associated osmotic and oxidative stress damage to endothelium), protein kinase C, inflammation and growth factors imbalances [17].

This study revealed BFI was found to decrease with the increase in the duration of diabetes. Suzuki E et al., showed that blood flow at popliteal artery (evaluated by using gated two-dimensional cine-mode phase-contrast magnetic resonance imaging) in lower limb in diabetic population (having long term hyperglycaemia) had lower blood flow volume than those of non diabetic subjects [18]. These may be due to various factors affecting the blood flow through the tissue such as the circumference of the limb, temperature, occupation, haematocrit, vessel size and organisation, etc., [19]. This may also be a result of age-related changes in blood vessels [18].

The effect of FBS, PP_2BS and BMI in diabetic subjects suggested a negative association with BFI. Poor diabetes control indicates a decrease in blood circulation at all sites (knee, calf, ankle) in the lower limb. As a result, diabetics are more prone to PAD than healthy subjects.

Pulse arrival time decreased at all three sites (knee, calf, and ankle) on both sides of diabetic subjects compared with healthy subjects. Below knee arterial calcification is associated with peripheral arterial occlusive disease in diabetes and that the severity of peripheral neuropathy independently correlates with calcification severity [20]. Calcification of the arterial walls is common in diabetes, with approximately one third of diabetic patients developing calcified arteries (medial arterial calcification) [21]. This leads to loss of elasticity and stiffness in the vessels. Atherosclerosis and calcification of the peripheral arterial walls in DM resulted in false normal ankle brachial index levels [13]. The blood vessels exhibit a progressive reduction in the number of elastic fibers and an increase in the number of collagen fibrils. Calcium salt deposition occurs in the elastic and muscular arteries at more advanced ages. All these factors lead to a decrease in distensibility and windkessel effect of the blood vessels, as well as an arteriosclerosis that affects PAT [18].

In this study, the mean value of PTTs in males decreased at all three sites (knee, calf, and ankle) on both sides of diabetic subjects relative to healthy subjects, except right knee segment. The mean PTT value in females decreased at all three sites (knee, calf and ankle) on the right and left side of diabetic subjects relative to the control group. However, the majority of subjects with diabetes (72%) had lower value than healthy subjects. This may be due to age related changes occurring in blood vessels [18].

The mean value of DPAT in males increased at all three sites (knee, calf and ankle) on both sides of diabetic subjects relative to healthy subjects. The mean value of DPAT in females increased at all three sites (knee, calf and ankle) on both sides of diabetic subjects relative to the control group, except for the right ankle segment. However, the majority of subjects with diabetes (44%) had higher value the healthy subjects. A slight decrease in DPAT at the left calf segment in males and right ankle in females of diabetics.

Basal impedance from a variety of biological tissues such as blood, muscles, bones, fat, etc show a marked variation and from this, fat shows a higher resistance than blood, muscle [22]. Z_0 also depends on vessel size (diameter, length), vessel arrangement (serial or parallel) and blood viscosity. Z_0 basal impedance was greater among diabetic subjects than healthy subjects at all sites. This greater Z_0 may be due to greater fat content in diabetic subjects than healthy subjects and fat shows greater resistance [23].

Limitation(s)

The exact anatomical location of the block by the technique could not be found. Follow-up period was required to evaluate the long-term effects of blood flow in diabetic patients for at least five years. Further study in large sample size will needed to validate values obtained in this study to determine vascular status clinically.

CONCLUSION(S)

There was significant reduction in BFI, PAT as well as significant increased DPAT value in at knee, calf and ankle region in diabetic group in males and females except DPAT value in female at right ankle segment. PTT in male decreased at all sites knee, calf and ankle segment on right and left side in diabetic group as compare to control group except right knee segment and in female decreased at all sites on both side in diabetic group. BFI had a negative association with FBS, PP_2BS and BMI in diabetic group and decreased with increased duration of DM. IPG technique is assess vascular status along with routine follow-up examination may reveal early prediction of reducing arterial blood flow to the lower extremities which may be useful for early implementation of treatment to avoid PAD. So, IPG is a valuable non invasive test in making diagnosis, prognosis and therapeutic decision in diabetic patients.

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