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Assessment of endothelial function in prediabetes using Flow Mediated Dilatation (FMD) by applying sphygmomanometer cuff in a limited resources rural setup: A case control study

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ABSTRACT

Background: Diabetes mellitus is a life-threatening disease that affects both developing and industrialised countries. Prediabetes is a state where identification of the risk factors can help in preventing the complications of diabetes. Coronary artery disease and cardiovascular disease result from atherosclerosis seen in hyperglycemic states which is manifested early on as endothelial dysfunction. In this study, we used flow mediated dilatation (FMD) of brachial artery with ultrasound which gives knowledge about endothelial function in disease as well as health. *Aims:* To assess endothelial function in individuals diagnosed with prediabetes using FMD of brachial artery and compare it with healthy non-diabetic subjects. We also assessed if FMD was affected by anthropometric parameters or lipid profile. *Methods:* This case control research comprised of 50 patients who met the American Diabetes Association prediabetes criteria (ADA) and 50 controls. Clinical history was taken and data related to brachial artery diameter at baseline and post hyperemia was taken and FMD% was calculated. *Results:* Out of 50 patients, 4 patients had FMD (<4.5%) and were classified as having endothelial dysfunction. It was found that patients classified as Obese as per BMI (kg/m^2) were significantly higher in cases that had FMD<4.5% (27.08 ± 0.97 vs. 23.51 ± 2.54, p value=0.008). *Conclusion:* Individuals with prediabetes did not have significantly lower brachial artery diameter at baseline, post-hyperemia brachial artery diameter and FMD. But we found that diameters of the brachial artery at rest and post stress and FMD% were significantly affected by parameters like LDL, waist circumference and BMI.

Keywords: Prediabetes, Endothelial function, Flow-mediated dilatation (FMD)

DISCOVERY SCIENTIFIC SOCIETY

1. INTRODUCTION

Diabetes mellitus is a collection of metabolic illnesses marked by persistent hyperglycemia caused by insulin production, insulin action, or both (American Diabetes Association, 2014). Unnoticed and unchecked hyperglycemia in DM can cause a range of consequences over time, including serious damage to blood vessels, the eye, kidneys, and nerves (Papatheodorou et al., 2017). These complications have been bunched under microvascular (retinopathy, nephropathy and neuropathy), macrovascular (myocardial infarction and cerebrovascular disease) and account for significant mortality and morbidity (Rydén et al., 2013).

Prediabetes is defined by glycaemic variables more than normal levels, but less than that of diabetes thresholds. It is estimated that 5% to 10% of individuals every year with prediabetes will progress to DM and a similar number return to normoglycemia (Tabák et al., 2012). Pre-diabetes is becoming more common over the world; scientists predict that by 2030, more than 470 million people will have the disease (Tabák et al., 2012). Prediabetes is defined as per the "American Diabetes Association (ADA)" as a metabolic clinical condition able to predispose affected individual to a future development of diabetes. Three conditions are included in prediabetes: (1) Impaired fasting glucose (IFG) defined as fasting plasma glucose levels ranging from 100 mg/dl to 125 mg/dl, (2) Impaired glucose tolerance defined as 2-hour plasma glucose levels, which range between 140 mg/dl and 199 mg/dl after an oral glucose tolerance test (OGTT) and 3) Glycated haemoglobin (HbA1C) - a value 5.7% and 6.4% is considered as a prediabetic condition (American Diabetes Association, 2011).

Prediabetes is related to the concurrent presence of dysfunction of β-cells and insulin resistance, which are the abnormalities that initiate prior to detection of glucose changes. Evidence from observational studies demonstrates that prediabetes is associated with "early forms of nephropathy, chronic kidney disease, small fibre neuropathy, diabetic retinopathy, and enhanced risk of macrovascular disease" (Tabák et al., 2012). Assessment of diabetes risk can be improved by multifactorial risk scores by utilization of non-invasive measures as well as blood-based traits, in addition to glycaemic values. It has been observed that diabetes-associated atherosclerosis is a common cause of cardiovascular disease among the patients (Cersosimo & De Fronzo, 2006). This is because the metabolic changes in diabetes are capable of impairing morphological as well as functional characteristics related to vascular walls and this condition acts as a precursor to the formation of atherosclerotic plaques (Cersosimo & DeFronzo, 2006).

Prediabetes begins the process of impairment of endothelium-dependent vasodilation, vascular smooth muscle dysfunction and increased arterial stiffness, thereby resulting in advanced atherosclerotic vascular changes (Bonora et al., 2003; Rijkelijkhuizen et al., 2007; Papa et al., 2013). Flow mediated dilatation is a non-invasive technique which represents endothelium-dependent vasodilatation (Corretti et al., 2002).

Several researches done over the last decade have used this approach to show a relationship between endothelial dysfunction, decreased glucose tolerance, and type 2 diabetes mellitus (Manzella et al., 2005; Caballero et al., 2003). However the research is sparse specifically in prediabetes. Thus, the present study was undertaken to evaluate the endothelial function by FMD in asymptomatic, apparently healthy individuals who have prediabetes, so that appropriate preventive measures can be taken in the specific population for a better outcome.

2. METHODS

The case control research was carried out at Acharya Vinoba Bhave Rural Hospital in central India from September 2019 to October 2021. The study included 50 cases diagnosed with prediabetes as per ADA criteria and 50 age and sex matched healthy non-diabetic controls. Patients with diabetes mellitus, patients with history of systemic hypertension or taking treatment for the same, patients with congestive cardiac failure or coronary artery disease, patients with chronic kidney disease or chronic liver disease were excluded from the study

Study protocol

A written informed consent was taken from the patients. The enrolled patients were explained about the study. The detailed demographic information regarding age and sex, complete clinical history including smoking history was taken. A current smoker is someone who has smoked at least 100 cigarettes in their lifetime and continues to do so (Center for Disease Control and Prevention, 1994). Blood pressure, anthropometric measurement, height, weight, body mass index (BMI), Waist circumference, and Waist-hip ratio were all recorded. A typical mercury manometer was used to measure blood pressure in the sitting posture after 5 minutes of rest. For all patients, weight was measured using a calibrated spring balance without heavy clothing and barefooted with the same standardised weighing machine.

A stadiometer was used to measure height barefooted to the closest centimetre.BMI (weight in Kg)/ (height in meters)^2 was calculated and WHO categories of Body Mass Index (BMI) for Asia-Pacific Region were used to classify patients. National

Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A, Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report (Pan & Yeh, 2008).

The waist circumference was measured midway between the top of the iliac crest and the border of the last palpable rib, according to the WHO stepwise methodology (WHO, 2008). The circumference of the hips was measured around the broadest part of the buttocks. The waist circumference was divided by the hip circumference to get the measurement (WHO, 2008). Measure of biochemical parameters like blood sugar readings and lipid profile was done using VITROS 5600 integrated system.

Brachial artery Doppler and FMD

Ultrasound Doppler of the brachial artery was done using Ultrasound Colour Doppler Arietta 70 (B-mode ultrasonography). The ultrasonography was performed at room temperature in a supine posture. The arterial diameter of the brachial artery was measured using a high-resolution Echo-Doppler using a 7.5 MHz high frequency linear vascular probe with an axial resolution of 0.1 mm. This was done in the right arm at a fixed position, which was taken as a point 2 cm proximal to the bifurcation of the brachial artery as viewed on Doppler. Before the first scan, the individuals were permitted to rest for at least 10 minutes; measures were taken at rest and during responding hyperaemia. The diameter of the proximal and distal walls, i.e., the interface between the tunica media and adventitia; which was easier to recognise than the surface of the endothelium layer; was measured on a two-dimensional ultrasonic calliper, and the least diameter was taken.

The first scan was performed after 10 minutes of rest, and then ischemia was produced for 5 minutes by inflating a pneumatic tourniquet (sphygmomanometer cuff) at the ipsilateral forearm to a pressure of 200 mmHg. The tourniquet was then deflated suddenly to enhance blood flow in the brachial artery closest to the tourniquet. The diameter of the lumen was measured 90 seconds after the cuff was deflated. Flow mediated dilatation (FMD percent) is a measure of endothelium dependent dilation defined as a percentage increase in lumen diameter during post ischemia hyperaemia relative to basal lumen diameter (Flammer et al., 2012).

Statistical Analysis

The final analysis was done with application of chi-square test, Mann-Whitney test, Fischer exact test, Kolmogorov-Smirnov test, Spearman rank correlation coefficient and with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 21.0".For statistical significance, "p value of less than 0.05 was considered statistically significant".

3. RESULTS

100 patients were enrolled with 50 cases and 50 age and sex matched controls. Cases had mean age of 50.08 ± 6.75 years. No significant difference was found between distribution of age and gender between cases and controls. Among anthropometric parameters, waist circumference (cm) (87.98 ± 6.99 vs. 81.68 ± 7.36, P<0.0001) was significantly more in cases than controls. Blood pressure was more in cases than in controls. All other baseline characteristics are shown in table 1.

Table 1 Baseline characteristics between cases and controls.

Variable	Cases(n=50)	Controls(n=50)	Total	P value
Age(years)				
Mean ± SD	50.08 ± 6.75	51.68 ± 3.4	50.88 ± 5.38	0.139*
Gender				
Female	21 (42%)	16 (32%)	37 (37%)	0.3§
Male	29 (58%)	34 (68%)	63 (63%)	
Height(cm)				
Mean ± SD	171.88 ± 9.27	168.94 ± 5.9	170.41 ± 7.87	0.062*
Weight(kg)				
Mean ± SD	70.46 ± 10.54	66.66 ± 12.75	68.56 ± 11.79	0.108*
Body mass index(kg/m²)				
Mean ± SD	23.79 ± 2.64	23.21 ± 3.42	23.5 ± 3.06	0.388*
Waist circumference(cm)				
Mean ± SD	87.98 ± 6.99	81.68 ± 7.36	84.83 ± 7.81	<0.0001†

Hip circumference(cm)				
Mean ± SD	104.12 ± 10.47	100.47 ± 12.32	102.29 ± 11.53	0.114*
Waist/hip ratio				
Mean ± SD	0.85 ± 0.09	0.82 ± 0.08	0.84 ± 0.09	0.211†
Smoking history				
Present	14 (28%)	12 (24%)	26 (26%)	0.648§
Systolic blood pressure(mmHg)				
Mean ± SD	123.04 ± 8.66	117.48 ± 5.65	120.26 ± 7.79	0.0003†
Diastolic blood pressure(mmHg)				
Mean ± SD	81.4 ± 8.49	76.52 ± 4.02	78.96 ± 7.05	<.0001†
Fasting blood sugar(mg/dL)				
Mean ± SD	96.6 ± 11.36	88.64 ± 7.5	92.62 ± 10.38	0.0004†
HbA1C (%)				
Mean ± SD	5.92 ± 0.28	4.8 ± 0.58	5.36 ± 0.72	<.0001†
LDL (mg/dL)				
Mean ± SD	117.5 ± 16.53	107.18 ± 7.48	112.34 ± 13.78	0.0008†
HDL (mg/dL)				
Mean ± SD	39.32 ± 8.25	38.3 ± 9.41	38.81 ± 8.82	0.327†
Triglyceride(mg/dL)				
Mean ± SD	171.56 ± 37.62	132.06 ± 16.8	151.81 ±35.13	<.0001†
Total cholesterol(mg/dL)				
Mean ± SD	199.64 ± 48.55	151.9 ± 27.03	175.77 ± 45.87	<.0001†
Baseline diameter of brachial artery(mm)				
Mean ± SD	3.6 ± 0.45	3.71 ± 0.44	3.65 ± 0.44	0.261†
Post hyperemia diameter of brachial artery(mm)				
Mean ± SD	4.11 ± 0.48	4.27 ± 0.42	4.19 ± 0.45	0.102†
Change in diameter(mm)				
Mean ± SD	0.51 ± 0.15	0.56 ± 0.09	0.54 ± 0.13	0.097†
FMD (%)				
Mean ± SD	14.27 ± 4.72	15.5 ± 3.29	14.88 ± 4.1	0.369†

* Independent t test, § Chi square test, † Mann Whitney test, ‡ Fisher's exact test

It was found that patients classified as Obese as per BMI (kg/m²) were significantly higher in cases that had FMD<4.5% (27.08 ± 0.97 vs. 23.51 ± 2.54, p value=0.008). Proportion of patients with smoking history was significantly higher in FMD<4.5% as compared to FMD>4.5% (100% vs 21.74% respectively). (p value=0.004). Significant association was seen in waist circumference (cm), hip circumference (cm), LDL (mg/dL), HDL (mg/dL). Mean ± SD of hip circumference(cm) and median (25^{th}-75^{th} percentile) of waist circumference(cm), LDL (mg/dL) in FMD<4.5% was 117.5 ± 3.32, 97(94.5-98.5), 145.5(139.5-152.25) respectively which was significantly higher as compared to FMD>4.5% (102.96 ± 10.07(p value=0.006), 86(82.5-89.75) (p value=0.019), 116.5(100-124.75) (p value=0.002)) respectively. Median (25^{th}-75^{th} percentile) of HDL (mg/dL) in FMD>4.5% was 39(34.25-47.5) which was significantly higher as compared to FMD<4.5% (30.5(28.75-32.25) (p value=0.023)), as shown in table 2.

Table 2 Association of parameters with FMD% in cases with FMD<4.5% being kept as cut-off for endothelial dysfunction

Parameters	FMD<4.5% (n=4)	FMD>4.5% (n=46)	Total	P value
Gender				
Female	0 (0%)	21 (45.65%)	21 (42%)	0.129‡
Male	4 (100%)	25 (54.35%)	29 (58%)	
Body mass index(kg/m²)				
>25{Obese}	4 (100%)	14 (30.43%)	18 (36%)	0.058‡
Mean ± SD (overall)	27.08 ± 0.97	23.51 ± 2.54	23.79 ± 2.64	0.008*

Smoking history				
Present	4 (100%)	10 (21.74%)	14 (28%)	0.004‡
Age(years)				
Mean ± SD	48.25 ± 6.29	50.24 ± 6.84	50.08 ± 6.75	0.577*
Height(cm)				
Mean ± SD	169.75 ± 7.76	172.07 ± 9.44	171.88 ± 9.27	0.637*
Weight(kg)				
Mean ± SD	78 ± 5.16	69.8 ± 10.66	70.46 ± 10.54	0.137*
Waist circumference(cm)				
Mean ± SD	96 ± 4.32	87.28 ± 6.76	87.98 ± 6.99	0.019†
Median (25th-75th percentile)	97(94.5-98.5)	86(82.5-89.75)	86(84-95)	
Hip circumference(cm)				
Mean ± SD	117.5 ± 3.32	102.96 ± 10.07	104.12 ± 10.47	0.006*
Waist /hip ratio{male}				
Mean ± SD	0.82 ± 0.01	0.84 ± 0.08	0.84 ± 0.08	0.41†
Systolic blood pressure(mmHg)				
Mean ± SD	124 ± 8	122.96 ± 8.79	123.04 ± 8.66	0.914†
Diastolic blood pressure(mmHg)				
Mean ± SD	82.5 ± 5	81.3 ± 8.76	81.4 ± 8.49	0.985†
Fasting blood sugar(mg/dL)				
Mean ± SD	99 ± 16.69	96.39 ± 11.02	96.6 ± 11.36	0.774†
HbA1C (%)				
Mean ± SD	5.92 ± 0.05	5.92 ± 0.29	5.92 ± 0.28	0.884†
LDL (mg/dL)				
Mean ± SD	146.25 ± 8.66	115 ± 14.58	117.5 ± 16.53	0.002†
Median (25th-75th percentile)	145.5(139.5-152.25)	116.5(100-124.75)	119(102.5-130)	
HDL (mg/dL)				
Mean ± SD	30.5 ± 4.51	40.09 ± 8.07	39.32 ± 8.25	0.023†
Median (25th-75th percentile)	30.5(28.75-32.25)	39(34.25-47.5)	38.5(33.25-46)	
Triglyceride(mg/dL)				
Mean ± SD	190.25 ± 19.94	169.93 ± 38.48	171.56 ± 37.62	0.179†
Total cholesterol(mg/dL)				
Mean ± SD	235 ± 25.5	196.57 ± 49.02	199.64 ± 48.55	0.103†

* Independent t test, † Mann Whitney test, ‡ Fisher's exact test

Significant negative correlation was seen between FMD (%) with waist circumference (cm) with correlation coefficient of -0.292. Non-significant mild negative correlation was seen between FMD (%) with age (years), weight (kg), diastolic blood pressure (mmHg), fasting blood sugar (mg/dL), Triglyceride (mg/dL). Non-significant moderate negative correlation was seen between FMD (%) with body mass index (kg/m²), waist/hip ratio, LDL (mg/dL), total cholesterol (mg/dL). It is shown in Table 3, figure-1.

Table 3 Correlation of various parameters with FMD (%) in cases

Variables	FMD (%)	
	Correlation coefficient	P value
Age(years)	-0.162	0.2614
Height(cm)	-0.003	0.9844
Weight(kg)	-0.142	0.323

Body mass index(kg/m²)	-0.24	0.0932
Waist circumference(cm)	-0.292	0.0403
Hip circumference(cm)	-0.02	0.8892
Waist/hip ratio	-0.222	0.1212
Systolic blood pressure(mmHg)	-0.057	0.6925
Diastolic blood pressure(mmHg)	-0.081	0.5768
Fasting blood sugar(mg/dL)	-0.089	0.5366
HbA1C (%)	0.055	0.7057
HDL (mg/dL)	-0.201	0.1622
Triglyceride(mg/dL)	0.021	0.8844
Total cholesterol(mg/dL)	-0.083	0.5639

Spearman rank correlation coefficient

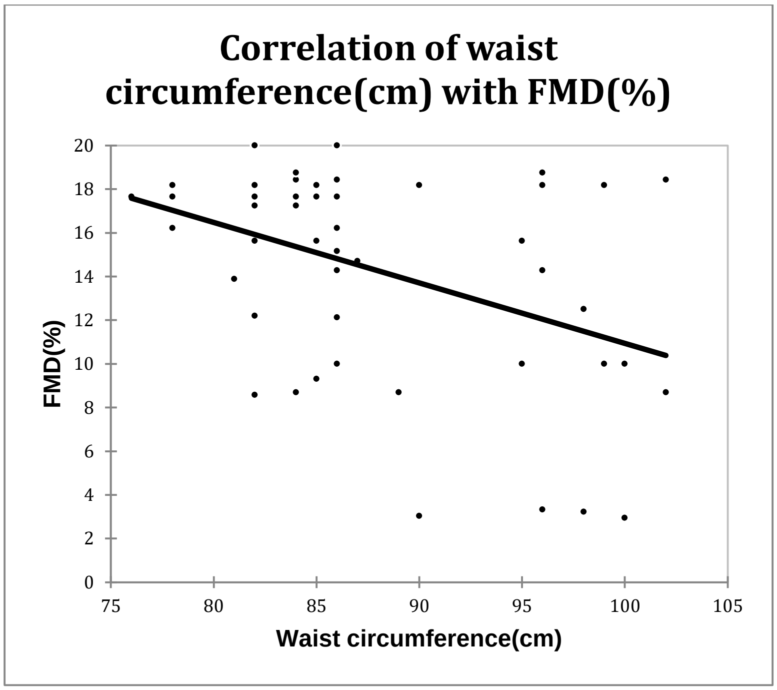

Figure 1 Correlation of waist circumference (cm) with FMD (%).

On performing univariate linear regression, waist circumference, LDL and body mass index: - >25{Obese} were the significant factors affecting FMD (%) in cases. With the increase in waist circumference by 1 cm, LDL by 1 mg/dL, FMD (%) significantly decreased by 0.277 and 0.108% respectively. It is shown in table 5. On performing multivariate linear regression, waist circumference and LDL were the significant factors affecting FMD (%) in cases. With the increase in waist circumference by 1 cm, LDL by 1 mg/dL, FMD (%) significantly decreased by 0.185 and 0.079% respectively. It is shown in table 6.

Table 5 Univariate linear regression to find out factors affecting FMD (%) in cases

FMD (%)	Beta coefficient	Standard error	P value	Lower bound (95%)	Upper bound (95%)
Age(years)	-0.045	0.101	0.659	-0.247	0.158
Height(cm)	0.010	0.073	0.889	-0.137	0.158
Weight(kg)	-0.060	0.064	0.355	-0.189	0.069
Waist circumference(cm)	-0.277	0.089	0.003	-0.456	-0.098
Hip circumference(cm)	-0.063	0.064	0.330	-0.193	0.066

Waist/hip ratio	-9.328	7.394	0.213	-24.194	5.539
Systolic blood pressure(mmHg)	0.015	0.079	0.846	-0.143	0.174
Diastolic blood pressure(mmHg)	-0.063	0.080	0.436	-0.223	0.098
Fasting blood sugar(mg/dL)	-0.050	0.060	0.409	-0.169	0.070
HbA1C (%)	-0.722	2.458	0.770	-5.665	4.220
LDL (mg/dL)	-0.108	0.038	0.007	-0.184	-0.031
HDL (mg/dL)	0.097	0.081	0.241	-0.067	0.261
Triglyceride(mg/dL)	-0.012	0.018	0.505	-0.048	0.024
Total cholesterol(mg/dL)	-0.022	0.014	0.110	-0.050	0.005
Gender					
Female					
Male	-0.857	1.361	0.532	-3.595	1.880
Body mass index(kg/m²)					
18.5-22.99{Normal BMI}					
<18.5{Underweight}	-6.636	3.390	0.056	-13.460	0.188
23-24.99{Overweight}	-0.886	1.654	0.595	-4.215	2.444
>25{Obese}	-3.342	1.553	0.037	-6.468	-0.216

Table 6 Multivariate linear regression to find out factors affecting FMD (%) in cases

FMD (%)	Beta coefficient	Standard error	P value	Lower bound (95%)	Upper bound (95%)
Waist circumference(cm)	-0.185	0.089	0.045	-0.365	-0.005
LDL (mg/dL)	-0.079	0.038	0.045	-0.155	-0.002
Body mass index(kg/m²)					
18.5-22.99{Normal BMI}					
<18.5{Underweight}	-5.891	3.133	0.067	-12.207	0.424
23-24.99{Overweight}	-0.497	1.509	0.743	-3.538	2.543
>25{Obese}	-2.085	1.461	0.161	-5.030	0.860

4. DISCUSSION

Several researches done over the last decade have used this approach to show a relationship between endothelial dysfunction however the research is sparse specifically in prediabetes. In this study prediabetic individuals did not have significantly lower brachial artery diameter at baseline and post-hyperemia brachial artery diameter and FMD. In this study that we conducted on 100 patients out of which 50 subjects were included with prediabetes with 50 controls, there was no significant difference in FMD% noted between tests and control subjects. An internal comparison done in the cases who had FMD<4.5% and FMD>4.5% it was observed that parameters like waist circumference, hip circumference, LDL, HDL and prevalence of smoking were found to have significant association to causing endothelial dysfunction.

Renuka et al., (2020) found that prediabetic patients have endothelial dysfunction due to hyperglycemia and insulin resistance. This study was under taken in pre diabetics to know the occurrence of endothelial dysfunction. They found endothelial dysfunction with FMD <4.5% which was found to have significant association with smoking, obesity, high LDL and low HDL. Similarly, in our study when we kept a similar cut-off, significant association was found between smoking, waist circumference, LDL and HDL. Su et al., (2008) also found that IFG and IGT patients had comparable baseline diameter of brachial but they had significantly impaired FMD.

Gupta et al., (2012) in a case control cross-sectional study on asymptomatic patients conducted by finger peripheral arterial tone had showed that endothelial dysfunction, which reflects cardiometabolic changes among obese adults, may act as an early risk marker in case of catastrophic cardiovascular events. Gateva et al., (2019) showed patients with prediabetes had significantly lower mean IMT than those with T2D. They showed that patients having newly diagnosed T2DM had increased IMT as well as tendency of increased ABI than normoglycemics and prediabetics. It was also found that prediabetics had lower HDL and higher triglycerides which was similar to our study.

Huemer et al., (2020) evaluated the association of parameters of peripheral arterial tonometry assessing endothelial function [reactive hyperemia index (RHI) and mean baseline amplitude (MBA)] with prediabetes. They showed microvascular endothelial dysfunction appears to have a role in the development of early derangements in glucose metabolism as well as insulin resistance, according to the findings. With the cut-off for FMD% kept at 4.5% we also found that patients with endothelial dysfunction (FMD<4.5%) showed association with BMI, waist circumference, hip circumference and LDL which were significantly higher and HDL was lower compared to those with normal endothelial function.

Literature though sparse suggests an association of endothelial dysfunction in prediabetes. It needs to be further explored so that this can be used practically for screening the population and initiating the preventive measures to curtail the associated complications. There is a dearth of studies in India that evaluated the endothelial function in prediabetes by brachial artery FMD. As a result, this research can serve as a springboard for bigger investigations to determine the utility of FMD in Indians with prediabetes.

Limitations

The study was done on a small sample size due to lack of paying capacity of subjects and thus the statistical association needs further validation with larger sample size. Second limitation was that participants were studied with single measurement of fasting glucose and HbA1c. Many possible confounding variables known as risk factors of prediabetes such as socioeconomic status, plasma insulin, habitual dietary intakes, alcohol and salt (sodium) intake, and sleeping disorder were not adjusted as confounders.

5. CONCLUSION

Though FMD is not a gold standard method for assessment of endothelial function when compared to another test like Coronary epicardial vasoreactivity but considering a rural setup with limited resources and financial constraints of patient, we found FMD to be a low-cost, easily accessible and effective method and the results obtained by our study were comparable to other similar studies conducted using FMD. The results of this study would be helpful in assisting healthcare providers for recognizing individuals at increased risk of prediabetes and subsequently decrease their chance of developing T2DM and CVD.

Ethical Clearance

Clearance was obtained from Institutional Ethics Committee (DMIMS(DU)/IEC/Aug-2019/8209)

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Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study.

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Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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