Original Article

Impact of diabetic retinopathy on pulse wave analysis-derived arterial stiffness and hemodynamic parameters: A cross-sectional study from Gujarat, India

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Purpose: Type 2 diabetes mellitus (T2DM) is known to produce diabetic retinopathy (DR). Pulse wave analysis (PWA) provides arterial stiffness (AS) and central hemodynamic (CH) parameters. We studied the effect of DR on AS and CH parameters in type 2 diabetics (T2D). **Methods:** We performed a cross-sectional study on 47 T2Ds attending a private ophthalmology clinic screened for DR by optical coherence tomography angiography and divided into NDR (non-DR), NPDR (non-proliferative DR), and PDR (proliferative DR). Mobil-o-graph (IEM, Germany) based oscillometric PWA yielded AS and CH parameters. They were further compared between groups stratified by DR with *P* value set at 0.05. **Results:** Participants had a mean age 62, mean diabetes duration 9 years, high mean BMI, and high prevalence of physical inactivity, hypertension, and poor diseases control. Significant differences were lacking in NPDR, NDR, and PDR in rate pressure product (mean 112.71 vs 116.06 vs 119.57), central pulse pressure (mean 46.50 vs 43.09 vs 42.72), stroke work (mean 153.36 vs 132.36 vs 146.08), augmentation index (mean 29.43 vs 33.14 vs 31.64), and aortic pulse wave velocity (mean 10.06 vs 9.08 vs 9.06). There was no clear pattern of distribution of most parameters among the three subgroups. **Conclusion:** We found a lack of association between DR and cardiovascular ageing studied by AS and hemodynamic parameters. It suggests a possible difference in risk factors for both of these aftermaths of T2DM and calls for further prospective studies with a large sample size.

Key words: Arterial stiffness, diabetic retinopathy, hemodynamic, pulse wave analysis, type 2 diabetes

Type 2 diabetes mellitus (T2DM), the lifelong companion, is causative of various microvascular and macrovascular complications.[1] Pulse wave analysis (PWA) provides discrete cardiovascular parameters noninvasively and objectively like arterial stiffness (AS) and central hemodynamics (CH).[2,3] Cardiovascular ageing is accelerated with T2DM as previously documented by our PWA-based study.[4] In type 2 diabetics (T2Ds), these parameters have shown to be superior to simple brachial blood pressure[4] inferring to changes in heart and aorta rather than of peripheral artery. AS and CH have found to be useful to determine cardiovascular progeria. However, the association of these parameters with microvascular complication is not studied in our T2Ds. We set out to study the effect of the presence and severity of diabetic retinopathy (DR), a microvascular complication on PWA-derived macrovascular parameters—AS and CH, in a sample of T2Ds by a cross-sectional study.

Methods

Our research protocol got approval from the Institutional Review Board of our medical college [IRB (HEC) no. 678/2017 dated 31/03/2017]. We performed a cross-sectional study on

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patients with T2Ds attending a private ophthalmology clinic with a facility of a retinal specialist at Bhavnagar, Gujarat, India. The information is already present under Materials and methods section in first sentence itself. Our research protocol got approval from the Institutional Review Board of our medical college [IRB (HEC) no. 678/2017 dated 31/03/2017].

We included the patients of ambulatory, non-athletic, T2Ds taking regular anti-diabetics, with or without hypertension (HTN), with current known glycemic control, nonalcoholic, nonsmoking, not having any known acute or chronic systemic disease, and willing for written informed consent. Apart from these criteria, individuals with abnormal pulse recording, using insulin, persons using any alternative system of medicines, and pregnant women were excluded.

The sample size was calculated using Raosoft software (Raosoft Inc., free online software, Seattle, WA, USA). To get a 95% confidence level and 10% margin of error, considering diabetes prevalence at 7.4%, a sample size of 47 was adequate for the study population. We excluded two patients due to

arm circumference beyond the available cuff size, one patient due to poor quality of PWA record, and two patients due to irregular pulse wave rhythm.

Demographic characteristics, risk factors, self-reported moderate physical activity, relevant disease history, and detailed history of pharmacotherapy were noted. Systolic BP (SBP) ≥140 mmHg and diastolic BP (DBP) ≥90 mmHg or use of antihypertensive medication was defined as HTN. SBP <140 mmHg and DBP <90 mmHg were taken as factors indicating BP control. Glycemic control was considered as per the American Diabetes Association guidelines 2018[5] using fasting plasma glucose (<130 mg/dl) and 2-h plasma glucose (<180 mg/dl).

Ocular examination recorded were Snellen's presenting, best-corrected visual acuity, slit-lamp examination of eye. Fundus photography was performed by instrument Topcon 3D OCT Maestro 2 (Topcon medical system Inc., Tokyo, Japan). It was further analyzed by software for the retinal diagnosis and the optic disc evaluation separately for each eye. DR grading[6] was performed as per the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria: nondiabetic retinopathy (NDR), nonproliferative diabetic retinopathy (NPDR), and proliferative diabetic retinopathy (PDR) and each eye was assigned its retinopathy level. For each participant, the final diagnosis was determined from the DR level of the worse eye using ETDRS criteria.

We used a portable, personal computer-attached, validated, calibrated instrument Mobil-o-Graph (IEM GMBH, Stolberg, Germany) owned by physiology department. It works on the principle of oscillometric pressure PWA whose protocol is designed by the European Society of Hypertension. Pressure oscillations generated by brachial arterial pulsation are transmitted to the brachial BP cuff and measured by a transducer that is fed into a microprocessor. Computerized PWA software records brachial pulse wave and by a validated generalized transfer factor, derives aortic (central) pulse wave as shown in Fig. 1. It further undergoes point-based and area-based PWA by computer software to derive various cardiovascular parameters as shown in Fig. 2.

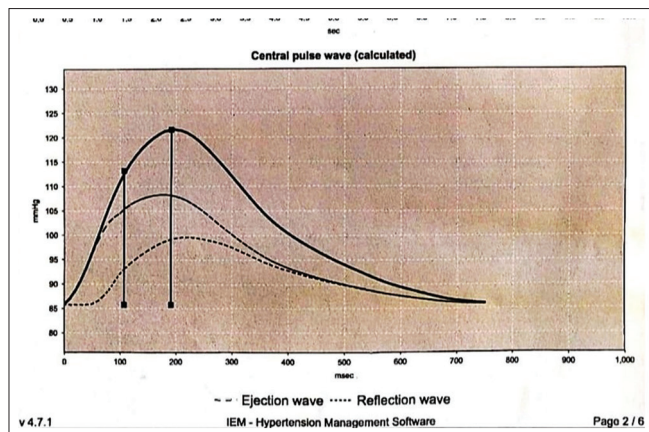Measurement protocol[7] is the same as used by our previous study and mentioned here: Based on the measured mid-arm

circumference, a BP cuff is chosen and applied to the left arm using a standard protocol. All readings were taken after 10 min rest in post-absorptive phase in a calm room without external influences and avoiding arm movement.

These are the same as used by a previous study in T2Ds,[4] listed here and shown in Fig. 2:

Heart rate (HR), body mass index (BMI), body surface area (BSA),

Brachial blood pressure (bBP)—systolic (bSBP), diastolic (bDBP), pulse (bPP), and mean (bMBP),

Central blood pressure (cBP)—systolic (cSBP), diastolic (cDBP), and pulse (cPP),

Measured central hemodynamics—cardiac output, cardiac index, and peripheral resistance,

Derived central hemodynamics:

Stroke volume—cardiac output/heart rate

Stroke volume index—stroke volume/body surface area

Stroke work = (pulse pressure) × (stroke volume) × 0.0144

Figure 1: Pulse wave analysis report showing measured aortic pulse wave

Figure 2: Pulse wave analysis reports showing calculated parameters

Table 1: Baseline and blood pressure parameters in diabetics stratified by presence and grade of diabetic retinopathy (*n*=47)

Parameter, unit	NDR (*n*=14)	NPDR (*n*=22)	PDR (*n*=11)	P	Whole group (*n*=47)
Age, years	63.93±10.16	59.05±10.79	62.00±9.09	0.16	61.19±10.24
Male/female, no	7/7	13/9	8/3	0.52	28/19
Height, cm	163.29±7.27	165.05±9.45	164.00±13.39	0.63	164.28±9.76
Weight, kg	77.29±12.76	72.05±12.58	71.73±8.78	0.38	73.53±11.88
BMI, kg/m^2	28.34±4.96	26.60±5.32	26.93±3.95	0.52	27.20±4.88
BSA, m^2	1.86±0.16	1.80±0.18	1.81±0.18	0.57	1.82±0.17
Duration, years	7.08±7.04	10.27±0.48	9.9±5.57	0.38	8.83±6.52
P A, +/-	2/12	3/19	6/5	0.02*	11/36
HTN, +/-	9/5	8/14	7/4	0.17	24/23
HL, +/-	1/13	8/14	2/9	0.12	11/36
BPC, +/-	5/9	8/14	3/8	0.86	16/31
GC, +/-	9/5	5/17	5/6	0.04*	19/28
bBP (mmHg)					
SBP	148.64±27.02	141.91±22.43	146.36±12.74	0.66	144.96±21.92
DBP	88.07±12.60	82.41±12.95	89.27±9.53	0.17	85.70±12.29
MBP	115.93±16.72	109.64±15.79	115.45±10.11	0.39	112.87±14.98
PP	60.57±24.30	59.50±17.09	57.09±9.18	0.89	59.26±17.89
HR, bpm	75.15±7.87	81.86±12.70	81.73±9.49	0.16	79.83±10.97
RPP, mm Hg.bpm	112.71±27.54	116.05±24.60	119.57±16.67	0.78	115.80±23.60

BMI=body mass index, BSA=body surface area, PA=physical activity, HTN=hypertension, HL=hyperlipidemia, BPC=blood pressure control, GC=glycaemic control, bBP=brachial blood pressure, SBP=systolic blood pressure, DBP=diastolic blood pressure, MBP=mean blood pressure, PP=pulse pressure, HR=heart rate, RPP=rate pressure product, '*' indicates statistical significance

Table 2: Central hemodynamics and arterial stiffness parameters in diabetics stratified by presence and grade of diabetic retinopathy (*n*=47)

Parameter, unit	NDR (*n*=14)	NPDR (*n*=22)	PDR (*n*=11)	P	Whole group (*n*=47)
c BP (mmHg)					
cSBP	136.21±25.57	127.00±19.54	133.82±14.68	0.39	131.34±20.58
cDBP	89.71±12.63	89.91±12.75	91.09±9.64	0.16	87.32±12.26
cPP	46.50±21.68	43.09±12.82	42.72±9.86	0.77	44.02±15.22
Central Hemodynamics					
CO, L/min	5.31±0.76	5.15±0.84	5.57±0.43	0.32	5.30±0.75
PR, mm Hg/mL	1.32±0.17	1.29±0.18	1.24±0.09	0.48	1.29±0.16
CI, L/min/m^2	2.87±0.47	2.85±0.40	3.11±0.30	0.20	2.91±0.41
SV, ml/beat	71.07±10.22	63.82±11.07	69.03±9.58	0.11	67.16±10.83
SVI, ml/m2/beat	38.31±5.94	35.47±5.95	38.37±5.52	0.39	36.99±5.91
SW, g m/beat	153.36±40.43	132.36±40.05	146.08±27.49	0.25	142.00±38.1
Arterial stiffness					
AP, mm Hg	16.07±12.43	13.64±7.09	12.72±5.60	0.95	14.15±8.67
Ref (%)	67.21±9.29	65.41±6.60	69.27±4.27	0.39	66.85±7.12
AIx@ 75 (%)	29.43±15.63	33.14±11.03	31.64±10.79	0.69	31.68±12.35
PWV, m/s	10.06±1.26	9.08±1.95	9.06±1.09	0.17	9.37±1.63
TAS, ml/mmHg	0.86±0.33	0.94±0.23	0.83±0.13	0.44	0.89±0.24
PPA	1.34±0.17	1.40±0.14	1.36±0.14	0.31	1.37±0.15
cPP					
<40	7	11	6	0.97	24
≥40	7	11	5		23
aPWV					
<10	7	5	8	0.19	20
≥10	7	17	3		27

cSBP=central systolic blood pressure, cDBP=central diastolic blood pressure, cPP=central pulse pressure, CO=cardiac output, PR=peripheral resistance, CI=cardiac index, SV=stroke volume, SVI=stroke volume index, SW=stroke work, AP=augmentation pressure, Ref=reflection percentage, AIx@75=augmentation index at heart rate 75 beats per minute, PWV=pulse wave velocity, TAS=total arterial stiffness, PPA=pulse pressure amplification

Measured AS parameters: augmentation pressure, augmentation index at HR 75/min (AIx@75), reflection magnitude %, aortic pulse wave velocity (aPWV)

Derived AS parameters:

Total arterial stiffness (TAS) = pulse pressure/stroke volume

Pulse pressure amplification (PPA) = brachial to aortic pulse pressure

All data were entered into and further sorted by excel spreadsheet. Numerical data were expressed as mean ± standard deviation, while qualitative data were expressed as number (percentage). Epi Info software version 7.2 (free software from Division of Health Informatics and Surveillance, Center for Surveillance, Epidemiology and Laboratory Services) was used for statistical calculations. Comparison of quantitative data was done by simple ANOVA test, depending on the parametric or nonparametric distribution. We compared the difference in the distribution of qualitative data by the Chi-square test. Logistic regressions were used to find an association between DR and quantitative PWA parameters. Statistical significance level was kept at $P < 0.05$.

Results

We included 14 patients (30%) with NDR, 22 patients (47%) with NPDR, and 11 patients (23%) with PDR in this study.

Table 1 shows the baseline and PWA parameters of the study group as a whole and that of three subgroups—NDR, NPDR, and PDR. The study group overall had a mean age of 61.19 ± 10.24 years, mean duration of diabetes of 8.83 ± 6.52 years, representation of both sexes, high mean BMI 27.20 ± 4.88, low physical activity, co-existence of HTN in half participants, poor disease control, and most PWA parameters were on higher side overall. Table 2 shows that NDR, NPDR, and PDR groups had comparable age, gender distribution, anthropometric measures, and disease duration. Prevalence of risk factor distribution was comparable except for the significantly higher prevalence of both physical inactivity and glycemic control in NDR group. PWA parameters of AS, brachial hemodynamics (BH), and CH were not significantly different between groups and they revealed no uniform pattern of worsening across the three groups. Prevalence of cPP >40 and aPWV >10 was higher in PDR group but both lacked statistical significance.

Discussion

Having proved beyond brachial blood pressure utility of PWA parameters— AS and CH in T2DM,[4] we studied their association with a microvascular complication—DR, in T2D from the private setup.

The proportion of DR was high (70%; 33 out of 47) but it cannot be commented upon further due to the small sample. The study group had overall AS and CH raised and higher than our previously published articles on newly normotensive T2D,[4] diagnosed hypertensives[8] and euglycemic hypertensives.[9] This relatively worse profile may be due to the study set up of the current study, which was private set up as against government setup in other studies[4,8,10] and raised brachial hemodynamics which predicts AS and BH. The mean duration being 9 years explains the high prevalence of DR and raised

hemodynamics and AS. Other factors can be low physical activity, coincidental HTN, poor disease control, high BMI, and poor health literacy of the study population.[9]

We found no association between DR and PWA parameters: AS, BH, and CH. This is in contrast to others studies,[11-13] which reported a significant impact on AS, BH, and CH of DR as well as retinal microvascular changes.[14-16] There can be few reasons. First, it can be due to the methodology used: objective, detailed OCTA used by us versus subjective ophthalmoscopy for DR detection; and use of direct, aortic parameters (aPWV) by us than regional (ankle brachial or carotid femoral) PWV. Second, raised AS, BH, CH, and DR in the study population may have obscured the association. Third, abnormal AS and CH are seen even before incident diabetes or HTN as we previously reported by PWA studies in young first-degree relatives of diabetic[17] and hypertensive[18] parents. Fourth, as recently published,[1] there is a bidirectional relationship between the macrovasculature and microvasculature at the crossroads between T2DM and HTN. Hence, the microvascular dysfunction can be a contributor to T2DM and vice and versa so that the association maybe not as simple leading to negative results like in the present study. Fifth, we found a similar lack of association between another microvascular complication diabetic nephropathy with reference to most PWA parameters[19,20] in our population, in line with the result of the current study.

No significant impact of DR severity was seen on AS, BH, and CH parameters. This is in contrast to most studies[11-13] and can be due to few reasons. First, the AS-DR relationship is strongest with PDR type,[11,13] which was prevalent lesser than NPDR in the study. Second, we did not have baseline data as reported recently[21] that baseline PWV is not associated with microvascular dysfunction. The same could have happened in our participants as diagnosis of type 2 diabetes is late. Third, half of T2Ds were hypertensives taking anti-hypertensives known to modify AS, BH, and CH without class difference[22] and half were not taking antihypertensive though their blood pressure was on the higher side. These two can confound the relationship between DR stage and PWA parameters. Fourth, Indian ethnicity is more vulnerable among Asians for microvascular complications of T2DM[23] that may lack association with macrovascular changes of AS and CH.

With the aforementioned lack of association between cardiovascular progeria and DR in our sample population with T2DM further work is suggested. For further reinforcement, a cohort study with baseline data and vertical follow-up over a period is needed to see how these two run over the progression of disease. Similarly, with baseline data in normotensive T2D, DR can be studied prospectively in relation to PWA parameters.

The use of the latest techniques for DR and PWA with a broad spectrum of study parameters was a strength of the study. The small study sample, lack of baseline data, presence of HTN as a confounder, and lack of vertical follow up were limitations that can be ameliorated by further studies.

Conclusion

We found a lack of association between DR and cardiovascular ageing as studied by PWA-derived AS and hemodynamic parameters. With a limited small sample size, our study suggests a possible difference in risk factors for microvascular

complications like retinopathy and macrovascular proceedings like cardiovascular ageing as aftermaths of type 2 diabetes. It also calls for further prospective studies with a large sample size to ascertain the cause-effect relationship.

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Conflicts of interest

There are no conflicts of interest.

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