Aortic Stiffness is Associated with Cardiac Function and Cerebral Blood Flow Pulsatility in Type2 Diabetes Mellitus

Shalini Sharma¹, Vikram Kala², Vivek Sharma³, Prerna Panjeta⁴

¹Associate Professor, Department of Physiology, ²Associate Professor, Department of General Medicine, BPS GMC (W), Distt. Sonepat, ³Professor, Department of Pharmacology, Pt. B.D. Sharma PGIMS, Rohtak, ⁴Assistant Professor, Department of Biochemistry, BPS GMC (W), Distt. Sonepat

Abstract

Introduction: Central hemodynamics has an important role in maintaining appropriate cerebral and other end-organ perfusion and is altered in type2DM. Arterial stiffening is an early phenomenon in patients with type2DM, affecting cardiac function by increasing the cardiac afterload and reducing diastolic coronary artery perfusion, also involving small vessel disease in the brain and subsequent hypoperfusion.

Aims and Objectives: The aim of present study was to determine whether aortic stiffness affects cardiac function and whether central elastic artery stiffness was associated with cerebral blood flow pulsatility and subsequent cerebral perfusion in type 2 DM patients.

Materials and Method: Fifty six patients with type2DM and 60 age-matched healthy volunteers were enrolled. Aortic PWV was measured using non-invasive cardiovascular risk analysis system (Periscope). Cerebral blood flow was measured by using Trans-Cranial Doppler.

Results: CFPWV of diabetic group showed significantly higher mean values (Group 1=931.00±215.98 cm/s, Group 2=1241±152.03 cm/s) than control subjects (758±151.82 cm/s). CFPWV was significantly (p value <0.01) increased between two diabetic groups. HbA1c was most significantly correlated to CFPWV (r=1.00, p<0.001) followed by weak correlation between central aortic stiffness quantified by PWV and PI (r=0.5, p>0.01).

Conclusion: In patients with type2DM, aortic stiffness is significantly associated with pulse pressure, aortic pulse pressure, aortic augmentation pressure as well as with cerebral blood flow pulsatility and subsequent cerebral perfusion, contributing to decreased cardiac function and cerebral hypoperfusion. Aortic PWV and TCD measurement might be useful prognostic marker of cardiac and cerebrovascular disease in type2DM.

Keywords: Pulse-wave velocity, type2DM, HbA1c, Pulsatility index, Arterial stiffning.

Introduction

Type2 diabetes mellitus (DM) is an important vascular risk factor for cerebral hypoperfusion and cognitive impairment. Central hemodynamics has an important role in maintaining appropriate cerebral and other end-organ perfusion and is altered in type2DM. Type2DM patients show functional and structural alterations of the arterial vessel wall, resulting in arterial stiffness. Arterial stiffening has been described as an early phenomenon in subjects with type2DM, already apparent before clinical onset of cardiovascular (CV) complications and also as an independent predictor of overt CV disease and mortality. Therefore, arterial stiffening may be related to the pathogenesis of CV complications in type2DM. This notion could be substantiated if an independent relationship be established between arterial stiffness and cardiac function in type2DM.
Furthermore, CV complications in type2DM also involve small vessel disease in the brain. Aortic stiffening can limit buffering capacity of the large central arteries such that small changes in cardiac stroke volume can result in excessive rises in local pulsatile pressure. These excess pressures may damage peripheral capillary networks, which is of relevance to the brain as a high flow organ with low resistance proximal large vessels and an extensive microcirculation. If a relationship between arterial stiffness and cerebral small vessel disease could be established as well, this would support the importance of arterial stiffness in CV complications and cerebral hypoperfusion in type2DM and timely intervention can be done to prevent complications. Stiffening of the aorta affects cardiac function by increasing the cardiac afterload and reducing diastolic coronary artery perfusion. Myocardial perfusion might fail to compensate for the increased metabolic energy demand, resulting in an impaired myocardial contractility function. Furthermore, stiffness of the central large arteries results in the deficient absorption of the pulse wave. This high pulsatile flow is transmitted from the aorta to the brain causing damage to the endothelial and smooth muscle cells, disrupting the cerebral small vessels. Also, aortic stiffness may represent coronary and cerebral endothelial dysfunction or wall thickening caused by shared underlying mechanisms. As aortic function plays a central role in maintaining adequate perfusion of both the heart and the brain, we hypothesized that aortic stiffness is associated with cardiac function as well as with cerebral small vessel disease in DM patients. To our knowledge, very few studies have evaluated the relationship between aortic pulse wave velocity, cardiac function and cerebral small vessel disease in one comprehensive protocol. Periscope is a non-invasive tool for the accurate assessment of aortic pulse wave velocity (PWV) as a marker of aortic stiffness. Accordingly, the aim of present study was to determine whether aortic stiffness affects cardiac function and whether central elastic artery stiffness was associated with cerebral blood flow pulsatility and subsequent, cerebral perfusion in type2DM patients. We hypothesized that individuals with type2DM have increased stiffening of central arteries, which may be one factor mediating cerebral hypoperfusion.

Materials and Method

The study population consisted of 56 patients with type2DM (mean±SD age 58±8 years; 23 men and 33 women); and 60 age-matched healthy volunteers (mean±SD age, 52±8 years; 27 men and 33 women). The control group was selected from subjects visiting our hospital for a health screening program, residents and working staff, who agreed to participate in this study. They were explained its purposes, risks, and potential benefits. All of the diabetic patients were selected from the Medicine OPD of associated hospital of BPSGMCW, Sonepat, where the diagnosis of type2DM had been made according to the established criteria. The subjects willing to participate were selected, based on certain inclusion and exclusion criteria.

Inclusion criteria included age 35-55 years, systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, no antihypertensive drug use, no ECG abnormality and renal disorder and willingness to participate in study.

Exclusion criteria included smoking, hypertension, DM, hyperlipidemia, pulmonary disease, renal disease, neurological disease or peripheral artery disease and use of medications of any kind.

Design

Participants provided written, informed consent to participate in this study. At visit 1, participants rested for 10 minutes in the supine position. This was followed by anthropometric measures, questionnaires relating to BP, medical history and all vascular and haemodynamic measures. Vascular testing was conducted at the same time of the day in a quite dimly lit, temperature-controlled laboratory. Participants were in post-absorptive state and were instructed to avoid vigorous exercises and caffeine/alcohol ≥12h before testing. Height and weight were assessed via wall-mounted ruler and electronic scale, respectively.

Instruments used

Arterial stiffness in terms of PWV was measured using non-invasive cardiovascular risks analysis system (PeriscopeTM). Cerebral blood flow was measured by using non-invasive Trans-Cranial Doppler TCD DWL MultidopX4 instrument with 2MHz hand-held pulsed wave Doppler probe. Instruments are available in central research lab of our institute. Middle cerebral artery (MCA) blood velocity was assessed using a 2-mHz TCD ultrasound probe (DWL Doppler Box-X, Compumedics, Germany) applied to the temporal window.
The study was approved by institutional ethical committee for research.

**Statistical Analysis**

All data is reported as mean±standard error of the mean. The data was analyzed by SPSS 17.0 program. Unpaired t-test was used to compare clinical characteristics of both groups. p value <0.05 was considered significant. An analysis of variance with repeated measures, was used to analyze main outcome variables. Pearson correlation analysis was used to analyze association between aortic PWV and pulsatility index (PI).

**Results**

The final number of patients recruited were 56 type2DM patients (23 men and 33 women, mean±SD age=58±8 years) and 60 age-matched healthy volunteers (mean±SD age=52±8 years; 27 men and 33 women) were included. Baseline characteristics of subjects are presented in Table 1.

**Table 1: Clinical characteristics of study participants**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control group (n=60)</th>
<th>T2 DM  (n=56)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52±8</td>
<td>58±8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.1±4.0</td>
<td>26.8±4.5</td>
<td>-</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>27/33</td>
<td>23/33</td>
<td>-</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>121±14</td>
<td>124±15</td>
<td>0.28</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78±9</td>
<td>79±9</td>
<td>0.494</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.1±0.4</td>
<td>8.5±0.4</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Data are represented as mean±SD, HbA1c glycosylated haemoglobin

The mean±SD values of age, BMI, systolic and diastolic blood pressure were higher among the subject groups (Table-1) but there was no significant difference (p value >0.05). The mean±SD values of HbA1c were 8.5±0.4 and 5.1±0.4 in diabetic and control group respectively. As compared to control group HbA1c was significantly higher (p value < 0.05) in diabetic group.

Table 2 shows the results of analysis of variance.

CFPWV and cerebral blood flow quantified by PI are displayed independently in Table 2.

**Table 2: Analysis of variance of CFPWV, PI and HbA1c**

<table>
<thead>
<tr>
<th>Parameter (Unit)</th>
<th>Control group (n=60)</th>
<th>Group I HbA1c (5.5-7.5%) (n=30)</th>
<th>Group II HbA1c (7.6-9.5%) (n=26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFPWV (cm/s)</td>
<td>758.72±151.82</td>
<td>931.00±215.98</td>
<td>1241.99±152.03</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pulsatility index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMCA</td>
<td>0.76±0.13</td>
<td>0.98±0.27</td>
<td>1.14±0.27</td>
<td>0.05</td>
</tr>
<tr>
<td>RMCA</td>
<td>0.81±0.15</td>
<td>0.99±0.31</td>
<td>1.10±0.25</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Associations between aortic PWV and cardiac function parameters are summarized in Table 3.

Aortic PWV was significantly correlated with pulse pressure, aortic pulse pressure, aortic augmentation pressure and HbA1c and weakly associated with ASI.

**Table 3: Aortic PWV and the association with central hemodynamic variables in patients with Type 2 DM**

<table>
<thead>
<tr>
<th>Cardiac function parameters</th>
<th>Mean±SD (n=50)</th>
<th>r</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>83.77±15.37</td>
<td>-0.38</td>
<td>0.30</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>59.59±18.69</td>
<td>0.33</td>
<td>0.13</td>
</tr>
<tr>
<td>RBracASI</td>
<td>28.84±12.14</td>
<td>0.35</td>
<td>0.10</td>
</tr>
<tr>
<td>LBracASI</td>
<td>1490.60±468.55</td>
<td>0.40</td>
<td>0.065</td>
</tr>
<tr>
<td>RAnK ASI</td>
<td>37.62±16.83</td>
<td>0.34</td>
<td>0.11</td>
</tr>
<tr>
<td>LAnK ASI</td>
<td>37.42±15.13</td>
<td>0.15</td>
<td>0.49</td>
</tr>
<tr>
<td>R-ABI</td>
<td>1.08±0.25</td>
<td>0.08</td>
<td>0.69</td>
</tr>
<tr>
<td>Ao Sys (mmHg)</td>
<td>121.40±24.55</td>
<td>0.51*</td>
<td>0.01</td>
</tr>
<tr>
<td>Ao PP (mmHg)</td>
<td>40.59±16.09</td>
<td>0.64**</td>
<td>0.01</td>
</tr>
<tr>
<td>Ao Dia (mmHg)</td>
<td>80.36±11.42</td>
<td>0.19</td>
<td>0.39</td>
</tr>
<tr>
<td>Ao Aug P (mmHg)</td>
<td>11.13±6.57</td>
<td>0.51**</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data represented as mean±standard deviation

Association between aortic PWV and PI as an index of cerebral blood flow and perfusion in type2DM is illustrated in Fig.1. Aortic PWV was weakly correlated with PI of MCA (r=0.05, p=0.23) and no association with PI of ACA and PCA in type 2DM patients.

This study is first to report an integrated approach to establish relationship among arterial stiffness, cardiac function and impaired cerebrovascular blood flow in the form of PI in diabetes, using non invasive TCD and digital periscope.

The present study shows possible association between arterial stiffness and reduced cardiac function in type2DM patients. In our relatively young type2DM patients group, aortic stiffness was significantly associated with aortic systolic pressure and aortic augmentation pressure. Diabetic patients are at increased risk of developing systolic left ventricular [LV] dysfunction, leading to progressive heart failure and subsequent death.14,15 In our study populations aortic diastolic pressure was in normal range and no association was found with PWV. Similar results were reported in previous studies.16 So aortic stiffness might have important role in cardiac function, already manifesting...
before occurrence of cardiac dysfunction or failure and compensatory remodelling. High blood pressure has an association with LV dysfunction and hypertrophy. However, in type2DM patients, LV dysfunction and hypertrophy is not well known. Our study on type2DM patients is in line with these findings. No relationship was found between aortic PWV and aortic diastolic pressure and LV dysfunction in relatively young diabetic group.

In this study, we found that aortic stiffness quantified by PWVs is weakly associated with blood flow velocity in cerebral MCA in type2DM patients. The results imply that arterial stiffness is an important determinant of cerebral blood flow velocity. The results supports the suggestion by Kreja et al that arterial stiffness could cause decreases in cerebral blood flow velocity. In humans, central elastic arteries in the cardiothoracic region (aorta and carotid artery) buffer the pulsatile pressure generated from the left ventricle, which fosters continuous peripheral blood flow and protects the microcirculation from end-organ damage. Stiffened central elastic artery in diabetes mellitus patients, increases left ventricular afterload and augment central and peripheral pulse pressure. Therefore, central artery stiffness in type2DM patients may be one factor mediating cerebral hypoperfusion. Despite these changes in carotid artery stiffness, there were mild change in MCA flow pulsatility and no changes in ACA and PCA flow pulsatility at these time points reinforcing our conclusion that increase in arterial stiffness may not have detrimental effect on cerebrovascular flow pulsatility in short duration type2DM patients as concluded by Wesley et al. Further studies are required to explore central hemodynamic and cerebrovascular changes in type2DM patients. Lippera et. al also demonstrated significantly increased pulsatility of MCA in diabetic patients.

Previous research, suggested association between arterial stiffness and PI in turn impaired cerebrovascular functions.

Limitations

The present study reveals that aortic stiffness reflects both cardiac function and cerebral small vessel disease, however small number of subject limits the generalization of the results. This study utilized middle aged type2DM patients with relatively short duration of DM. Despite this our data suggests that TCD and PWV assessment can be utilized in evaluation of interventions designed to prevent vascular complications of diabetes.

Conclusion

In conclusion, this study shows that in patients with type2DM, stiffness of aorta is significantly associated with pulse pressure, aortic pulse pressure, aortic augmentation pressure well as with cerebral blood flow pulsatility and subsequent cerebral perfusion, contributing to decreased cardiac function and cerebral hypoperfusion. By documenting that aortic stiffness reflects stages of both cardiac function and cerebral small vessel disease, our study results suggests that TCD and aortic PWV assessment might be a useful marker of cardiac and cerebrovascular disease in patients with type2DM. Future studies are needed to assess the prognostic implications of our observations.

Conflicts of Interest: There is no conflict of interest.

Source of Support : None

Abbreviations

CBF Cerebral Blood Flow
CFPWV Carotid Femoral Pulse Wave Velocity
DM Diabetes Mellitus
HbA1c Glycosylated haemoglobin
MCA Middle Cranial Artery
PI Pulsatility Index.
TCD Trans Cranial Doppler

References

Hypertens 2003;21:2035-44.


