Effect of glycemic status on carotid artery stiffness and cerebral blood flow

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Abstract

Background and Objectives: Increase in arterial stiffness with age and/or disease increases risk for cardiovascular events such as myocardial infarction and stroke. The brain is a high flow organ, particularly susceptible to hemodynamic pulsatility. Diabetes is a group of chronic diseases characterized by hyperglycemia. The injurious effects of hyperglycemia are classified into macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy). It is important for physicians to understand the relationship between diabetes and vascular disease.

Thus, this study was undertaken to test the hypothesis that elevated blood glucose levels in diabetes mellitus increases arterial stiffness, which further leads to increase in carotid pressure/flow pulsatility and CBFv pulsatility.

Methods: Fifty six (56) patients with type 2 DM and 60 age-matched healthy volunteers were prospectively enrolled. Arterial stiffness was measured using non-invasive PC based cardiovascular risk analysis system (Periscope TM). The TCD examination was performed by using Trans-Cranial Doppler.

Results: CFPWV of diabetic group showed significantly higher mean values (Group 1=931.00±215.98cm\s, Group 2=1241±152.03 cm\s) than control subjects (758±151.82 cm\s). CFPWV was significantly ($p<0.05$) increased among two diabetic groups. Glycosylated Hemoglobin was most significantly correlated to CFPWV ($r=1.00$, $p<0.05$) followed by weak correlation between CFPWV and PI ($r=0.2$, $p>0.05$).

Conclusion: Type 2 Diabetes Mellitus (T2DM) increases carotid artery stiffness and pressure pulsatility index, without affecting cerebral blood flow pulsatility. This study depicts TCD findings of diabetes related cerebral hemodynamic changes and suggest that the PI reflects microangiopathic changes of cerebral vessels.

Keywords: Carotid-femoral pulse-wave velocity, Diabetes mellitus, Glycosylated Hemoglobin, Pulsatility index, Trans Cranial Doppler.

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Introduction

Increase in arterial stiffness with age and\ or disease increases risk for cardiovascular events such as myocardial infarction and stroke.[1,2] Increased arterial stiffness also contributes to target organ damage such as renal dysfunction and retinal damage.[3,4] The elastic properties of the large central arteries (i.e. aorta and carotid) functions to dampen the amplitude of fluctuations in pressure and flow, thereby preventing transmission of excess energy into target organs.[5] Similar to the kidney and eye, the brain is a high flow organ particularly susceptible to hemodynamic pulsatility.[6] Repeated exposure of the cerebral vasculature to pulsatile pressure/flow may precipitate microvascular hypoperfusion and subsequent ischemia contributing to rarefaction, white matter hyper-intensities and ultimately cerebrovascular impairment.[7] Recent studies have found a strong association between arterial stiffness, pressure/flow pulsatility and cerebral perfusion.[8,9]

Diabetes mellitus (DM) is a group of chronic diseases characterized by hyperglycemia. Modern medical care uses a vast array of lifestyle and pharmaceutical interventions aimed at preventing and controlling hyperglycemia. In addition to ensuring the adequate delivery of glucose to the tissues of the body, treatment of diabetes attempts to decrease the likelihood that the tissues of the body are harmed by hyperglycemia.

The major vascular changes related to DM are macroangiopathy and microangiopathy occurring in the cerebral as well as systemic blood vessels.[10] Compared with healthy people, patients with DM show more extensive atherosclerosis of extracranial and intracranial vessels,[11] a higher prevalence of carotid artery stenosis[12] and increased carotid artery intima-media wall thickness.[13]

In addition, microvascular damage is also one of the major complications of DM.[10] In diabetic humans as well as experimental animals, morphological abnormalities, including arterial endothelial cell necrosis and thickened

capillary basement membranes, have been observed in small cerebral vessels[14] and these vascular changes may alter cerebral blood flow (CBF) which may eventually result in a cerebrovascular accident/ stroke.

The main purpose of DM control is to prevent its complications. Thus regular and systematic screening for diabetic complications, including blood glucose concentrations, glycosylated hemoglobin level (HbA1c), renal function, blood pressure, retinopathy and signs of diabetic foot has been recommended.[15]

Previously, clinical attempts to detect subclinical CBF changes related to DM had been performed, but they failed to provide consistent results. Trans-cranial Doppler ultrasonography (TCD), because it is noninvasive and easily applicable, appears to be more suiTable as a screening tool than previous methods. However, only a few studies have been performed in patients with DM. By using TCD, Lippera et al[16] demonstrated increased pulsatility and reduced cerebrovascular reactivity (CVR) of the middle cerebral artery (MCA) in diabetic patients with retinopathy, but the effect of hypertension, a major factor also influencing cerebral hemodynamics, was not excluded. In another study,[17] reduced cerebrovascular reactivity of the MCA has been found in normotensive patients of long term type 1 DM.[18] Thus, we performed TCD measurements of the MCA in stroke-free, normotensive patients with type 2 DM.

The current study was undertaken to test the hypothesis that elevated blood glucose levels in diabetes mellitus increases arterial stiffness, which further leads to increase in carotid pressure/flow pulsatility and CBFv (cerebral blood flow velocity) pulsatility. The aim of study was to evaluate arterial stiffness and cerebral blood flow in healthy population in correlation with diabetic patients with good and poor regulated serum glucose levels.

Materials and Methods

The current study was conducted in department of physiology and medicine of BPSGMC for women, Khanpur Kalan, Sonepat. The study was approved by institutional ethical committee for research.

Fifty six (56) patients with type 2 DM (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) were recruited for the study. The control group was selected from subjects visiting Medical Centre for a health screening program who agreed to participate in this study and residents of medical campus, after a full explanation of its purposes, risks, and potential benefits. All of the diabetic patients were selected from the Medicine OPD of associated hospital of BPSGMC for women, Khanpur Kalan, Sonepat, where the diagnosis of type 2 DM had been made according to the established criteria[19] and they were followed up at regular intervals. The volunteers willing to participate were selected based on certain inclusion and exclusion criteria.

Inclusion criteria included, age 45-65 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 self-reported smoking, hypertension, hyperlipidemia, pulmonary disease, renal disease, neurological disease, peripheral artery disease and use of any antihypertensive drugs.

Design

Participants provided written, informed consent to participate in this study. Participants were in a post-absorptive state and anthropometric measures, questionnaires relating to BP, medical history and hemodynamic data were recorded.

Participants rested for 10 min in the supine position. This was followed by all vascular and hemodynamic measures. Vascular testing was conducted at the same time of day, in morning hours (8 am to 10 am) in a quiet, dimly lit, temperature-controlled laboratory. Participants were instructed to fast for ≥3 h and avoid vigorous exercise and consuming caffeine or alcohol ≥12 h before testing.

Instruments used

Height and weight were assessed via wall-mounted ruler and electronic scale, respectively. Arterial stiffness was measured using non-invasive digital cardiovascular risk analysis system (Periscope TM). The TCD examination was performed by using non-invasive Trans-Cranial Doppler. Instruments are available in central research lab of our institute. MCA blood velocity was assessed using a 2-mHz TCD ultrasound probe (DWL Doppler Box-X, Compumedics, Germany) applied to the temporal window. Mean CBF velocity and pulsatility index (PI) were measured at a depth of 50–65 mm.[20]

Statistical analysis

All data is reported as mean ± standard error of the mean and statistical significance was established $p<0.05$. The data was analyzed using the Statistical Package for Social Sciences (SPSS) 17.0 program. Unpaired t-test was used to compare clinical characteristics of control group and experimental group. Experimental group was further subdivided into two groups 1 and 2 on the basis of good and poorly controlled levels of HbA1c. An analysis of variance with repeated measures (2 conditions × 4 time points) was used to analyze main outcome variables. Bonferroni analysis post-hoc test was used to investigate significant interactions.

Results

The final number of patients recruited were 56 type 2 DM 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: Showing Clinical characteristics of study participants

Characteristics	Control group (n=56)	T2 DM group (n=60)	P value
Age (years)	52±8	58±8	>0.05
BMI (kg/m^2)	24.1±4.0	26.8±4.5	>0.05
Gender (M/F)	23/33	27/33	>0.05
Systolic blood pressure (mmHg)	121±15	124±14	0.494
Diastolic blood pressure (mmHg)	78±9	79±9	0.28
HbA1c (%)	5.1±0.4	8.5±0.4	<0.05

Data are represented as mean ± SD, HbA1c: glycosylated hemoglobin

The mean ± S.D. values of age, body mass index, systolic and diastolic blood pressure were higher among the patient group as compared to control group (Table-1) but there was no significant difference (p value >0.05). The mean ± S.D values of HbA1c were 8.5±0.4 and 5.1±0.4 in diabetics and control group respectively. As compared to control group mean value of 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 shown in Table 2(A).

CFPWV among diabetic group showed significantly higher mean values (Group1 = 931.00±215.98cm\s, Group2 = 1241±152.03cm\s) than control subjects (758±151.82cm\s). The mean ± S.D. values of PI in LMCA and RMCA are higher in diabetic group as compared to control group but the difference was not statistically significant (p value >0.05).

Table 2(A): Showing Effect of increasing level of HbA1c on CFPWV & PI variables (ANOVA)

Parameter (Unit)	Control group HbA1c (<5.5%) (n=56)	Group I HbA1c (5.5-7.5%) (n=34)	Group II HbA1c (7.6 - 9.5)% (n=26)	P value
CFPWV(cm/s)	758.72±151.82	931.00±215.98	1241.99±152.03	<0.05
Pulsatility Index (PI) LMCA	0.76±0.13	0.98±0.27	1.14±0.27	0.7
RMCA	0.81±0.15	0.99±0.31	1.10±0.25	0.3

CFPWV - Carotid Femoral Pulse Wave Velocity, HbA1c- Glycosylated hemoglobin,
LMCA - Left Middle Cranial Artery, RMCA- Right Middle Cranial Artery
Group1=good regulation of HbA1c, Group2=poor regulation of HbA1c

Table 2(B): Showing Post hoc Bonferroni test

	Control vs. Group I	Control vs. Group II
CFPWV (cm/s)	P=0.09	P <0.05

Post hoc analysis (Table 2(B)) revealed that CFPWV was significantly (p value <0.05) increased among two diabetic groups.

Correlation analysis (Table 3) of the data obtained from the patients revealed that glycosylated hemoglobin was most significantly correlated to CFPWV (r=1.00, p<0.05) followed by weak correlation between CFPWV and PI (r=0.2, p>0.05). No significant association was found between average pulsatility index and CFPWV.

Table 3: Showing Pearson Correlations Analysis of Mean CFPWV in relation to HbAlc

	CFPWV	LMCA	RMCA
HbAlc%	R=1.00* P<0.05	R=0.18 P=0.42	R=0.2 P=0.200
CFPWV(cm/s)		R=0.18 P=0.43	R=0.2 P=0.21

Correlation significant at 0.01level (2 tailed)
CFPWV - Carotid Femoral Pulse Wave Velocity, HbA1c- Glycosylated hemoglobin,

LMCA - Left Middle Cranial Artery, RMCA- Right Middle Cranial Artery

Discussion

The purpose of the current study was to assess the possible association between cerebral perfusion and aortic stiffness in type 2 DM patients without hypertension, by using noninvasive TCD and periscope. The current study was designed to investigate changes in pulsatile hemodynamics (not the steady component or mean flow) during previously established times of elevated arterial stiffness following type 2 DM. The main findings of our study were that aortic stiffness in patients with type 2 DM is strongly associated with HbA1c and is weakly associated with cerebral PI.

In the present study, we demonstrated for the first time an association between arterial stiffness and impaired cerebrovascular blood flow in the form of PI in diabetic patients, using noninvasive TCD and digital periscope. This relationship was at least in part independent of other confounding variables including age, BMI etc.

In the present study despite, substantial increase in CFPWV in diabetic patients, cerebrovascular blood flow though decreases, but does not show significant difference. Arterial stiffness increases with age and is known to be promoted by several factors including hypertension, diabetes and chronic renal disease.[21] Arterial stiffness has also been associated with PI[8] and in turn impaired cerebrovascular functions.[9]

In the present study, despite substantial increase in carotid stiffness in Type 2 DM patients as compared to control group, there were minimal changes in CBFv pulsatility. Carotid artery stiffness increased reinforcing previous observations regarding the central artery stiffness.[22] Increased arterial stiffness has previously been linked to pulsatile flow in the cerebrovascular bed.[23] Despite the changes in CCA stiffness, there was no significant change in MCA flow pulsatility at these time points reinforcing our conclusion that increase in arterial stiffness may not detrimentally impact cerebrovascular flow pulsatility in short duration type 2 DM patient.[24] Future research is needed to explore central hemodynamic and cerebrovascular changes during earlier type 2 DM patients.

Cerebrovascular flow is regulated by a complex of metabolic, myogenic and neurogenic mechanisms as well as by the passive properties of blood vessels including arterial stiffness. Increased rigidity of the arterial wall limits its capacity for vasodilatation in response to physiological stimulus.[24]

Various pathophysiological mechanisms during life time leads to vessel wall aging. Increased arterial stiffness and increased pulsatility index are normal in increase age. In our case we have shown that glucose control is of great importance in diabetic patients in order to prevent vascular aging.[25] According to literature, two studies have investigated the relationship between arterial stiffening and cerebrovascular reactivity, one was performed in a healthy population and the second one in diabetic patients. The first study found a very good inverse correlation between Breath Holding Index (BHI) and arterial stiffness[26] and concluded that in a healthy population the relationship was a function of aging. The second study was performed in diabetic patients and similar trends were shown. The BHI was decreasing with increasing arterial stiffness in diabetics, more so in patients with poor glycemic control. However, the exact correlation coefficient was not provided.[27]

We have shown that diabetic patients are at increased risk for cardiovascular and cerebrovascular diseases but further studies are required in order to evaluate impact of changes in blood glucose levels on cerebrovascular vessels and other clinical manifestations (cognitive decline, everyday activity etc.) in type 2 DM. Secondly, our findings may have prognostic implications. Of note, assessment of aortic PWV is currently not part of the clinical routine assessment in DM patients. Our study results suggest that aortic PWV could be useful in the cardiovascular risk screening of patients with type 2 DM.

Limitations

This study has some limitations, including a possible bias related to patient selection and a relatively small number of subjects. This study utilized type 2 DM patients who are middle aged and most of them have short duration of DM. Results may not be directly applicable to other clinical populations. TCD cannot measure blood flow per second since diameter is not measured. In spite of this, TCD may have utility in the evaluation of interventions designated to prevent vascular complications of diabetes.

Conclusion

Type2DM increases carotid artery stiffness and pressure pulsatility index without affecting cerebral blood flow pulsatility. Increase in carotid pressure pulsatility in Type2 DM, is due to an increases in forward wave pressure and not pressure from wave reflections. This study defines TCD findings of diabetes-related cerebral hemodynamic changes and suggests that the PI reflects micro-angiopathic changes of cerebral vessels.

Conflicts of Interest: None

Source of Support: None

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