CAROTID ARTERY INTIMA MEDIA THICKNESS – A CORRELATIVE STUDY OF DIABETICS WITH POSTPRANDIAL HYPERGLYCEMIA VERSUS CONTROLS WITH EUGLYCEMIA

INTRODUCTION

Diabetes mellitus is the leading cause of mortality and morbidity worldwide. The severe metabolic dysregulation associated with diabetes mellitus (DM) is known to be preceded by dysfunctional changes in the endothelium. There is enough evidence to show that postprandial hyperglycemia is pathophysiologically relevant. Risso1 showed that hyperglycemia induces apoptosis. Postprandial hyperglycemia causes oxidative stress, impairs endothelial function, facilitates monocyte adhesion to endothelial cells and thickens intima media contributing to development of atherosclerosis independent of HbA1c level.2 These findings suggest that variability in glycemic control could be more deleterious to endothelial cells than a constant high concentration of glucose.

Carotid artery intima media thickness measurements are being widely applied as a measure of atherosclerosis in studies on determinants of presence and progression of atherosclerosis.3–6 The intima media thickness of carotid arteries provides an index of atherosclerosis in other vascular regions7–9 and has been shown to be associated with most risk factors for atherosclerosis.10 Therefore measurement of carotid intima media thickness may be used as a screening test to identify high risk subjects. A close histological relation between carotid and coronary atherosclerosis has been noted in autopsy studies. Further more carotid artery intima media thickness has been good indicator of the presence and extent of coronary artery disease in observational studies.11–13

Acute glucose fluctuations seem to show a more specific triggering effect on oxidative stress than does chronic sustained hyperglycemia.14 Also proptosis was enhanced in endothelial cells exposed to intermittent, rather than constant high glucose concentration. These findings suggest that variability in glycemic control could be more deleterious to endothelial cells than a constant high concentration of glucose. Several reports have shown that the exposure of endothelial cells to hyperglycemia stimulates reactive oxygen species over production. Postprandial hyperglycemia (PPHG) is now identified as an independent risk factor for CVD suggesting that PPHG is a better predictor of risk than is FBS or HbA1c alone (Table 1).15,16,17

B made ultrasonography along with resolution imaging and Doppler has proved to be popular non-invasive, accurate, cost effective means of detecting and assessing carotid artery disease. Doppler study is done for assessing the systolic and diastolic velocities, lumen size along with plaque occurrence site.18 We therefore assessed the carotid intima media thickness by high resolution ultrasonography and compared the intima media thickness of diabetics with postprandial hyperglycemia with that of non-diabetics.

CAROTID ARTERY INTIMA-MEDIA THICKNESS (CA-IMT)

An early sign of atherosclerosis is hypertrophy of the arterial wall. Increased intima-media wall alteration, is easily assessed in the carotid arteries by high resolution B-mode ultrasound. In healthy adults, CA-IMT ranges from 0.25 to 1.0 mm and values >1.0 mm are often regarded as abnormal. Age is one of the powerful determinants of IMT, with increase from 0.01 to 0.02 mm per year. For younger age groups (20–30 years) mean IMT values of 0.0 mm have been reported while IMT values of 0.9 mm have been reported in elderly subjects (60–70 years).19,20
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Table 1: Morbidity and mortality related to post challenge and postprandial hyperglycemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECODE study</td>
<td>10 prospective studies among 35,388 men and 7126 women not previously diagnosed with diabetes</td>
<td>2-hour blood glucose levels following 75-g OGTT better predictor of all-cause and cardiovascular deaths than FFB levels</td>
</tr>
<tr>
<td>Chicago Heart Association</td>
<td>12,220 men with diabetes or asymptomatic hyperglycemia</td>
<td>Increased risk of CVD mortality with higher postload glucose level (after 50-g OGTT)</td>
</tr>
<tr>
<td>Temelkova-Kurtschiew et al</td>
<td>582 men and women at risk for type 2 diabetes</td>
<td>2-hour blood glucose levels and spikes more strongly associated with CIMT than FPG or HbA1c</td>
</tr>
<tr>
<td>Diabetes Intervention study</td>
<td>1139 men and women with newly diagnosed type 2 diabetes</td>
<td>PPHG, but not FPG, significant risk factor for MI and mortality</td>
</tr>
<tr>
<td>Campanian Postprandial Hyperglycemia Study</td>
<td>93 men and 82 women with type 2 diabetes not previously drug-treated</td>
<td>Reduction of PPHG, but not FPG, associated with reductions in CIMT</td>
</tr>
</tbody>
</table>

CA-IMT correlates with other risk factors like hypertension, hyperlipidemia, smoking, presence and severity of CAD. Regression or slowing of progression of increased CA-IMT by anti hypertensive and lipid lowering drugs as well as by controlling postprandial hyperglycemia have been reported. Ethnic differences in IMT were reported in insulin resistance atherosclerosis (IRA) study, where blacks were found to have increased IMT. The predictive power of IMT for risk of MI or stroke is well established. Mohan et al in their CUPs study showed that age was independent risk factor for IMT and diabetics had higher mean IMT values than non-diabetics.

AIMS AND OBJECTIVES

1. To compare carotid artery intima media thickness of diabetic patients with postprandial hyperglycemia with that of non-diabetics
2. To determine the effect of duration of the disease on carotid artery intima media thickness.

MATERIAL AND METHODS

This prospective study was conducted at Jaslok Hospital and research centre, Mumbai over a period of 1 year. During this period 60 subjects were selected for the study.

GROUP 1

Uncontrolled or newly detected non insulin dependent diabetes mellitus patients who were detected to have 2 hours post prandial hyperglycemia were included (30 patients).

GROUP 2

Control group with normal blood glucose levels, normal blood pressure and normal lipid profile. (30 controls)

As regards postprandial hyperglycemia, we followed the guidelines of American diabetic association (ADA) 2007 i.e. in diabetics two hours post prandial blood sugar >200 mgm% and for controls two hours postprandial blood sugar <140 mgm%.

Patients with hypertension, dyslipidemia, coronary artery disease, prior coronary angioplasty or CABG and patients admitted with acute illness were excluded from the study. All subjects underwent following tests CBC, FBS, PPBS, HbA1c, Lipid profile, renal profile, liver profile, ECG, x-ray Chest.

MEASUREMENT OF CAROTID ARTERY INTIMA MEDIA THICKNESS (CA-IMT)

Position of the patient: The patient in supine position with pillow kept between the shoulder blades to achieve extension of the neck. Neck exposure was enhanced by tilting and rotating the head away from the side being examined.

Site: The common carotid artery (CCA) was defined as the 1.5 cm segment proximal to the dilatation of the carotid bulb (the flow divider). Origin of the carotid bulb was defined as the point at which arterial wall diverges to form the bulb.

METHOD

To measure carotid artery IMT, ultrasonographic scanning of the CCA was performed in the supine position with neck extended. This was performed using high frequency 7.5 MHz linear vascular imaging probe with a GE – LOGIQ 500 PRO Series scanner, at a depth of 2 cms; the carotid vessels being relatively superficial. The carotid vessels were followed from the clavicular head, cephalad to its bifurcation. On a longitudinal, 2-dimensional ultrasound (B-mode ultrasound) image of the carotid artery, the anterior (near) and posterior (far) walls of the carotid artery, are displayed as 2 bright white lines separated by a hyperechogenic space. The distance between the leading edge of the first bright line of the far wall and the leading edge of the second bright line indicates IMT.

For the near wall, the distance between the trailing edge of the first bright line and the trailing edge of the second bright line at the near wall provides the best estimate of the near wall IMT. In accordance with the Rotterdam study ultrasound protocol, a careful search was done to obtain the optimal representation of both the near and far walls of the CCA. When an optimal longitudinal image was obtained, the IMT was measured at the end diastole at three different sites in the far wall and near wall of the carotids on both sides; and readings were obtained at the anterior, lateral and postero-lateral projections.

B-MODE ULTRASOUND TECHNIQUE

This technique involves the use of high resolution B-mode
ultrasound imaging and Doppler ultrasound to obtain images of vessels (arteries & veins). It allows direct visualization of the arteries & veins and provides functional, as well as anatomical information. This technique is highly reliable in the investigations of arteries and veins. It is the most appropriate investigation to use when detailed analysis of the anatomy and physiology of the vascular system is required. With this technique, two parallel echogenic lines separated by an anechoic space can be visualized at the levels of the artery wall. It was shown that these lines were generated by the blood-intima and media-adventitia interfaces. The distance between two lines gives a reliable index of thickness of the intima-media complex.

**Statistical Analysis**

All statistical analyses were performed using SPSS version 13 for windows. Descriptive statistics (n, minimum, maximum, mean, median, mode, standard deviation) outlined the variables used within the study. Every analysis was performed on observed data. A single categorical variable is described by frequency distribution.

A cross tabulation with Pearson (chi) Test was used to measure differences in two categorical variables between two groups for example case and control groups.

If expected frequency in at least one cell of cross tabulation would be less than 5, the Fisher’s Exact Test is used instead of Pearson (chi) Test to assess similarity between two groups. Similarly, t-test is used to measure differences between continuous variables.

**Comments**

Patients and controls were divided into 2 groups according to age, <50 years and >50 years

Analysis of variance is used to test the quality of means for continuous variables between more than two groups. A P value of <0.05 was considered significant.

**OBSERVATIONS**

The observations of our study are given below in Tables 2-6

In the cases group there were 57% (n=17) patients below 50 years of age with mean IMT 0.82 and 43% (n=13) patients above 50 years with mean IMT 0.94. Similarly in the control group there were 77% (n=23) subjects below 50 years with mean IMT 0.55 and 23% (n=7) subjects above 50 years with mean IMT 0.59.

Cases had more IMT values than controls in both age groups and the result was statistically significant.

**DISCUSSION**

Intima-media thickness of the common carotid artery is considered to be an excellent non invasive measure of generalized atherosclerosis and also a surrogate marker of coronary artery disease.^{19,24} The international atherosclerotic project has suggested that the carotid and cerebral arteries and the aorta undergo the atherosclerotic process approximately at the same age as the coronary arteries. With increasing age there is increase in the intima media thickness. Pujia et al^{26} reported a close co-relation between age and IMT in patients with diabetes mellitus. Mohan et al^{23} in Chennai urban population study (CUPS) studied IMT of carotid arteries in...
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South India diabetic and non diabetic subjects and observed higher IMT values with increasing age.

In our study, cases had more IMT (0.94) values than controls (0.59) and it reached statistical significance above age >50yrs (p<0.000). Kawamori et al27(1992) in their study on prevalence of carotid atherosclerosis in diabetic patients concluded that IMT is directly related with age in diabetic subjects. In our study male patients with PPH had significantly higher IMT values (0.92) than controls (0.59) and similar observations were found in females where cases and controls had IMT-0.80 and 0.49 respectively. There is no significant gender bias in IMT. Both males and females having PPH had high IMT values.

It has been proved several times that PPH is the earliest glycemic abnormality seen in patients with type II DM. Impaired Glucose Tolerance (IGT) is characterized by PPH with fasting plasma glucose in the normal range. Several studies have shown that the risk of worsening retinopathy, neuropathy and nephropathy increases with increasing post prandial levels.28,29 In the Honolulu heart study, the rate of sudden death doubled with a PPBS> 151mg% and a two fold increase in CAD related mortality was seen.

The Whitehall study, Paris prospective study and Helsinki police men study30 all reported that 2 hours post challenge glucose predicts all cause and CHD mortality. Thickness of the intima-media complex in large vessels is a first evidence of atherosclerosis. Thus measurement of IMT is a useful method to establish the atherosclerostes at subclinical stage.

In our study we compared the IMT of 30 subjects with PPHG with same number of subjects with normal PPBS. We found a statistically significant difference in the IMT between the two groups, the mean IMT of the cases group was (0.87) and the control group was (0.56)

Table 4: FBS and PPBS of cases and controls

<table>
<thead>
<tr>
<th>Blood Sugar</th>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>Std Deviation</th>
<th>Std. Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>Controls</td>
<td>30</td>
<td>84.63</td>
<td>10.653</td>
<td>1.945</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>30</td>
<td>122.33</td>
<td>27.942</td>
<td>5.102</td>
</tr>
<tr>
<td>Post Prandial</td>
<td>Controls</td>
<td>30</td>
<td>121.00</td>
<td>10.722</td>
<td>1.958</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>30</td>
<td>261.77</td>
<td>53.924</td>
<td>9.845</td>
</tr>
</tbody>
</table>

Comments

The mean FBS in the cases group was 122 mg%/dl and mean FBS in the control group was 84.6 mg/dl

The mean PPBS in the cases group was 261.8 mg/dl while mean PPBS in the control group was 121mg/dl

Table 5: PPBS of patients and IMT

<table>
<thead>
<tr>
<th>Post – Prandial</th>
<th>Mean Carotid Artery intima Media Thickness (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Sugar</td>
<td>N</td>
</tr>
<tr>
<td>&lt; 200</td>
<td>4</td>
</tr>
<tr>
<td>200-300</td>
<td>15</td>
</tr>
<tr>
<td>&gt;300</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
</tr>
</tbody>
</table>

Comments

We divided 30 patients on the basis of their Post Prandial blood sugar into 4 groups

PPBS <200 (n=4, 13%) mean IMT 0.80
200-300 (n=15, 50%) mean IMT 0.85
>300 (n=11, 37%) mean IMT 0.91

Our study also showed similar findings. Out of the 30 subjects who had PPHG, 60% patients had normal FBS and 40% patients had high FBS. However there was no significant difference in their IMT values. Both the subgroups i.e. normal
Given the strong body of evidence for its use, carotid Doppler and CIMT should become routine screening tools for atherosclerosis in India. We have a population with high incidence of diabetes, a high prevalence of dyslipidemia and, with increasing urbanization, an ever-increasing population with detrimental lifestyle changes. Detection and appropriate management of sub clinical atherosclerosis will go a long way in preventing life-threatening complications related to atherosclerosis, thus prolonging survival and improving quality of life.

CONCLUSIONS

1. Post prandial hyperglycemia is directly responsible for increase in C-IMT and as the level of post prandial blood sugar increases there is proportionate increase in the IMT

2. With increasing age there is proportionate increase in IMT in patients with post prandial hyperglycemia as compared to those without post prandial hyperglycemia

3. There is increase in IMT with increase in the duration of diabetes mellitus

4. There is no gender bias in IMT among patients with post prandial hyperglycemia

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