Carotid Intima Medial Thickness as A Surrogate Marker for Systemic Atherosclerosis in Type 2 Diabetes Mellitus

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ABSTRACT

Background: The objective was to measure the correlation between carotid intima medial thickness (CIMT) with duration of type 2 diabetes mellitus (DM) and its correlation with biochemical markers and body mass index (BMI).

Methods: The study was conducted in a tertiary care hospital in Kolkata. Total 100 patients were selected randomly who met the inclusion criteria. Among total patients, 20 cases were newly detected type 2 DM patients and 80 were cases of established diabetes, with different duration of DM. CIMT was measured by carotid artery ultrasonography using an echo tomography system having midfrequency of 7.5MHz and detection limit of 0.1mm. Duration of diabetes was measured as present age minus age of detection of DM. BMI was measured by the guideline of WHO. The parameters were estimated such as microalbuminuria by radioimmunoassay, fasting blood sugar (FBS) level and HbA1C by HPLC method, uric acid by uricase method. Data was collected using a predetermined proforma and statistical analyses were done.

Results: Duration of DM was positively correlated with CIMT and association was statistically significant (P<0.02). There was increase in CCA-IMT and ICA-IMT across increasing level of FBS and HbA1C (P<0.01). Microalbuminuria is considered a novel atherosclerotic risk factor, was found significantly associated with mean CIMT (P<0.001). CIMT was also significantly associated with HbA1C (F=0.001). The significantly (P<0.01) increased level of uric acid indicated higher carotid plaque.

Conclusion: CIMT is an objective measure of subclinical atherosclerosis, which is a non-invasive, less expensive, duration and reproducible way of demonstrating subclinical atherosclerosis. Thus, it can serve as a window for atherosclerosis status in other major arteries like coronary artery and cerebral arteries. The CIMT is closely associated with several markers viz. uric acid, blood sugar, HbA1c, albumin and BMI during the progression of type 2 DM.

Keywords: Carotid intima medial thickness, Duration of diabetes mellitus, Albuminuria, Blood sugar level, BMI, Uric acid

INTRODUCTION

Type 2 diabetes mellitus patients showed 2- to 6-fold higher risk for cardiovascular disease compared to healthy control (without diabetes).1,2 According to Haffner et al.3, atherosclerosis has been occurred from pre-diabetic stage, which led to several cardiac diseases. The patients suffering from sequel of atherosclerosis such as coronary artery disease, myocardial infarction, cerebro-vascular disease meet the clinician at a time when the only treatment option is to minimize the debility already incurred. Moreover, atherosclerosis is responsible for several clinical syndromes that collectively account for large number of morbidity and
The carotid intima medial thickness was studied by Pignoli et al. [8] in which it is measured as the distance from leading edge of first echogenic line to leading edge of second echogenic line in carotid ultrasonography. The first line represents the lumen intimal interface the collagen containing upper layer of tunica adventitia forms the second line. Extra cranial carotid arteries are superficial, easily accessible and any early change in tunica intima-media of carotid arteries can be easily detected by ultrasonography scanning. It is relatively less expensive, on invasive, less time consuming and reproducible. CIMT has been used as a subclinical index of atherosclerosis [8]. Several studies have shown an association between type 2 DM and myocardial infarction or stroke in elderly or middle-aged subjects [6]. However, there have been few studies that have evaluated the progression of CIMT in subjects with type 2 diabetes mellitus [7-12] and the study is lacking in West Bengal, India. From past to recent research, the study of CIMT in diabetic subjects is of a research interest because the prevalence and incidence of atherosclerotic vascular disease in Indian population is much higher than western population [13]. Moreover, it was reported that an independent association between uric acid, blood sugar, HbA1c, albumen, obesity and carotid atherosclerosis [13-18]. Moreover, the measurement of CIMT is serving as a predictor of coronary heart disease, and its association with duration of type 2 diabetes mellitus. ACC-AHA consensus conference does not recommend screening of general population [19].

The objective was to measure the progression of carotid intima medial thickness (CIMT) with long-term duration of type 2 diabetes mellitus is confirming with assessment of biomarkers such as uric acid, blood sugar, HbA1c, albumen and obesity through BMI.

METHODS

Study area and sample size
The study was conducted in Calcutta National Medical College and Hospital, Kolkata. Total hundred patients were studied, both newly detected type 2 DM patients and established cases of diabetes were selected. Total one hundred patients were studied, both newly type 2 DM patients and established diabetes patients were selected. Determination of type 2 DM was based on World Health Organization Criteria [15].

Inclusion Criteria
1. Diabetes diagnosis after 30 years of age as per important criteria.
2. No episode of ketoacidosis and absence of ketonuria.
3. Insulin therapy if any started after at least 5 years after diagnosis.

Exclusion Criteria
1. Patients receiving antiplatelet agents.
2. Those receiving lipid lowering drugs.

Measurement of CIMT
Three determinations of IMT were conducted on the site of greatest thickness in common carotid, carotid bulb and internal carotid bilaterally, and these six values were averaged and was used as the representative value for each case. Fig 1 is exhibited CMIT scan image.

Assessment of carotid atherosclerosis
Ultrasoundographic scanning of carotid arteries were performed using an echotomographic system, Agilent point HX with an electronic linear transducer (Midfrequency of 7.5 MHZ). Scanning of extra cranial common carotid arteries, carotid bulbs, and internal carotid arteries in the neck was performed bilaterally from three different longitudinal projections (i.e. anterior oblique, lateral, posterior oblique) as well as transverse projections as reported in earlier study by Pignoli [8]. All the images were photographed. The scanning session was completed an average of 30 min as per Pignoli [8]. The detection limit of the echosystem was 0.1mm. At each longitudinal projection the site of maximum thickness including plaque was sought along the arterial wall from the common carotid to internal carotid artery. All scans were conducted by radio diagnosis consultant who was unaware of the clinical characteristic of the subjects.

Assessment of the duration of DM
The duration of DM was calculated for established diabetes as current age minus reported age at the time of diagnosis [15].

Assessment of Body Mass Index (BMI)
Three key anthropometric measurements are important to evaluate the degree of obesity – weight, height, and waist circumference. Weight was measured in Kg and height was measured in meter. Body mass index was calculated using the equation weight (kg) / height (m2). Classification of weight status was done using clinical guideline on the identification, evaluation, and treatment of overweight and obesity [20].

Assessment of biochemical markers
Fasting Blood sugar (FBS) blood samples were collected. Plasma glucose was measured by glucose oxidase technique on an auto analyzer as per WHO criteria, 24hr urinary albumin was measured by radioimmunooassay, HbA1c was estimated by HPLC method and uric acid was estimated by uricase method.

Statistical analyses
All the data were collected in a prescribed proforma and subsequently analyzed by using statistical software (SPSS, version 20).

RESULTS
Among 100 subjects, 20 were newly detected and 80 patients had established type 2 diabetes mellitus. Mean age of the study population was 60.39±8.364 years. Among 100 patients, 48 were males and 52 were females.

Study of duration of diabetes and CIMT
Among total 100 subjects 20 subjects were newly diagnosed, i.e. they were diagnosed to be diabetic during the present
In the study, among them 6 were male and 14 were female, and mean CIMT was 0.794±0.26 mm. 80 subjects were of established diabetes, and they were subdivided in four groups. In the second group duration of the disease was from 0.1 to 3 years. In this group there were total 12 subjects of them 6 were male and 6 were female, and mean CIMT was 1.083±0.13 mm. In the third group the duration of diabetes was from 3.1 to 7.5 years. In this group there were total 20 subjects among them 8 were male and 12 were female. Mean CIMT in this group was 1.574±0.19 mm. In the fourth group the duration of diabetes was from 7.6 to 15.5 years. There were total 28 subjects in this group. 16 of them were male and 12 were female and mean CIMT in this group was 1.778±0.36 mm. In the fifth group the duration of diabetes was from 15.6 to 31 years. There were total 20 subjects, 12 among them were male and 8 were female. Mean CIMT in this group was 2.123±0.46 mm. It was observed that as the duration of diabetes increases the mean CIMT is also increasing. This association is statistically significant at a level of P<0.02 (Table 1).

Study of Fasting Blood sugar (FBS) and CIMT
Mean FBS in study population was 290.16±91.282 mg/dl. In the study population FBS was divided in five groups. In the first group, (FBS<134 but>100 mg/dl), Common Carotid artery Intima medial thickness (CCA - IMT) and Internal Carotid artery Intima Medial Thickness (ICA-IMT) was 0.633 mm and 0.607 mm respectively. There was gradual step wise increase in CCA-IMT and ICA-IMT with increasing blood sugar level. In the fifth group (FBS>401) mean CCAIMT and ICAIMT was 2.069 mm and 2.169 mm respectively. Table 2 showed the association between CIMT and FBS was statistically significant (P<0.01).

Study of Albuminuria and CIMT
24 hr urinary albumin was measured among studied patients. Those having urinary albumin <30 mg/24 hours were considered normal, those between 30-300 mg/24 hour were considered as having micro albuminuria and those having >300 mg/24 hour were considered as having proteinuria. In Table 3, albuminuria was significantly associated with CIMT (P<0.001).

Study of HbA1c and CIMT
There is statistically significant association between HbA1c and CIMT. Mean HbA1c level was 8.91±1.119 at a significance level of P<0.01 (Table 4).

Study of uric acid and CIMT
With increasing uric acid level incidence of carotid plaque also increases (Fig 2). This was found to be statistically significant both in male and female.

Study of obesity and CIMT
The participants in the study were divided in three groups depending on BMI calculated based on anthropometric measurements. Those having BMI <18.5 were considered underweight and those between 18.5 and 24.99 were considered normal. Those between 25.0 and 29.99 were over-weight and those over 30.0 were considered obese. In Table 5, there were total 13 subjects with normal BMI. Among them 6 were male and 7 were female. Mean CIMT in this group was 0.768 mm. 22 subjects were over-weight, among them 10 were male and 12 were female. Mean CIMT in this group was 1.005 mm, which is 0.237 mm thicker than the normal subjects. There were 65 obese individuals among them 32 were male 33 females, mean CIMT in this group was 1.871 mm, which is 0.866 mm thicker than the over-weight subjects. BMI was significantly associated CIMT (P<0.01). The mean CIMT in obese subjects were 1.103 mm thicker than normal weight diabetic subjects. The mean CIMT in overweight subjects were 0.237 mm thicker compared to normal weight subjects. This was statically significant (P<0.01). Mean IMT was significantly higher in obese subjects compared with normal weight (P<0.01) and underweight (P<0.001). Mean CIMT was significantly higher in overweight subjects compared with normal weight ones (P<0.05).

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Table 1: Association between duration of diabetes and CIMT

<table>
<thead>
<tr>
<th>Duration (years) of DM</th>
<th>N</th>
<th>Male</th>
<th>Female</th>
<th>Mean CIMT (mm)</th>
<th>Level of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed</td>
<td>20</td>
<td>6</td>
<td>14</td>
<td>0.794±0.26</td>
<td></td>
</tr>
<tr>
<td>0.1 to 3.0</td>
<td>12</td>
<td>6</td>
<td>6</td>
<td>1.083±0.13</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>3.1 to 7.5</td>
<td>20</td>
<td>8</td>
<td>12</td>
<td>1.574±0.19</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>7.5 to 15.5</td>
<td>28</td>
<td>16</td>
<td>12</td>
<td>1.778±0.36</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>15.6 to 31.0</td>
<td>20</td>
<td>12</td>
<td>8</td>
<td>2.123±0.46</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION
It was observed that as the duration of diabetes increases the mean CIMT is also increasing. In Table 1, the association between the duration
of diabetes and mean CIMT was observed statistically significant (P<0.02) (Table 1), which has a similar result of another researcher. Mitsuhashi and Takayanagi [21] reported a close association between carotid atherosclerosis, which measured as intima-media thickness (IMT), and cardiovascular morbidity in type 2 diabetic Japanese patients. They suggested higher prevalence of IMT in type 2 DM patients detect urgently the progression of coronary artery disease.

Table 2: Association Between FBS and CCA-IMT and ICA-IMT

<table>
<thead>
<tr>
<th>FBS (mg/dl)</th>
<th>N</th>
<th>Male</th>
<th>Female</th>
<th>CCA-IMT (mm)</th>
<th>ICA-IMT (mm)</th>
<th>Level of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;134</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>0.633</td>
<td>0.607</td>
<td></td>
</tr>
<tr>
<td>135 – 225</td>
<td>35</td>
<td>19</td>
<td>16</td>
<td>1.163</td>
<td>1.142</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>226 – 300</td>
<td>21</td>
<td>8</td>
<td>13</td>
<td>1.632</td>
<td>1.685</td>
<td></td>
</tr>
<tr>
<td>301 – 400</td>
<td>30</td>
<td>15</td>
<td>15</td>
<td>1.919</td>
<td>1.956</td>
<td></td>
</tr>
<tr>
<td>&gt;401</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td>2.069</td>
<td>2.169</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Association between Albuminuria and CIMT

<table>
<thead>
<tr>
<th>Urinary albumin</th>
<th>N</th>
<th>Male</th>
<th>Female</th>
<th>CIMT (mm)</th>
<th>Level of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>39</td>
<td>15</td>
<td>24</td>
<td>1.020</td>
<td></td>
</tr>
<tr>
<td>Micro albuminuria</td>
<td>41</td>
<td>22</td>
<td>19</td>
<td>1.615</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>1.901</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Association between HbA1c and CIMT

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>Male</th>
<th>Female</th>
<th>CIMT (mm)</th>
<th>Level of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 – 7.5</td>
<td>7</td>
<td>8</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>7.6 – 8.0</td>
<td>19</td>
<td>15</td>
<td>1.648</td>
<td></td>
</tr>
<tr>
<td>8.1-8.5</td>
<td>17</td>
<td>19</td>
<td>1.707</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>8.6 – 9</td>
<td>3</td>
<td>7</td>
<td>2.011</td>
<td></td>
</tr>
<tr>
<td>&gt;9</td>
<td>2</td>
<td>3</td>
<td>2.41</td>
<td></td>
</tr>
</tbody>
</table>

Table 5: Association between obesity and CIMT

<table>
<thead>
<tr>
<th>BMI</th>
<th>N</th>
<th>Male</th>
<th>Female</th>
<th>CIMT (mm)</th>
<th>Level of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese</td>
<td>65</td>
<td>32</td>
<td>33</td>
<td>1.871</td>
<td></td>
</tr>
<tr>
<td>Over weight</td>
<td>22</td>
<td>10</td>
<td>12</td>
<td>1.005</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Normal</td>
<td>13</td>
<td>6</td>
<td>7</td>
<td>0.768</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSION

CIMT is an objective measure of subclinical atherosclerosis. It is a non invasive, relatively less expensive, less time taking and reproducible way of demonstrating subclinical atherosclerosis. Thus, it can serve as a window for atherosclerosis status in other major arteries like coronary artery and cerebral arteries. Patients suffering from sequel of atherosclerosis (e.g. coronary artery disease, myocardial infarction, cerebro-vascular disease), which come in contact with the clinician at a time when the only treatment option is to minimize the debility already incurred. The present challenge is to identify the process of sub clinical atherosclerosis by methods like measurement of CIMT, which can provide us with an opportunity to halt the process of atheroma formation and development of plaque vulnerability. CIMT may be an indicator of endothelial dysfunction and can well become in future an independent risk factor for coronary heart disease and cerebro-vascular accident. So, CIMT may be an objective measure of macro vascular disease in future, depending on which the future doctors will tailor therapy for atherosclerosis. In the present study, CIMT is found closely associated with surrogate markers viz. uric acid, blood sugar, HbA1c, albumen and obesity through BMI during the progression of type 2 DM.

Acknowledgement

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Conflict of interest

Authors declare none.

Ethical approval

The ethical approval has been given by Institutional Ethical Committee, Calcutta National Medical College and Hospital, Kolkata, India. The ethical committee have given the written
permission with Memo No. CNMC/ETHI/1653/P dated 13/02/2007 for conducting the present research work.

REFERENCES