Correlation of Coronary Angiographic Severity with Carotid intima Media Thickness and Flow mediated dilatation of brachial Artery in Patients with Ischemic Heart Disease

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Key words:
Ischaemic Heart Disease, Carotid intima media thickness (CIMT), Flow mediated dilatation (FMD), Coronary angiography.

Abstract :

Background: *Ischemic Heart Disease which encompasses Acute Coronary Syndrome and Chronic Stable Angina is the most common cause of worldwide mortality and morbidity. Carotid intima media thickness (CIMT) is a non-invasive ultrasonographic technique to image the carotid arteries which measures the thickness of the intima and media of these vessels. It is a marker of atherosclerotic process. Flow mediated dilatation (FMD) is a marker of endothelial function of arteries. Ischemic heart disease can be predicted long before its actual occurrence by observing these two phenomenons.*

Methods: *This cross sectional study done in the Department of Cardiology, Dhaka Medical College Hospital during the period of Oct 2010- Sept 2011.We enrolled 102 patients admitted with IHD by purposive sampling. We assessed FMD of brachial artery, CIMT by vascular duplex. Coronary artery disease severity was assessed by vessel score, stenosis score and extent score from angiography.*

Results:*The mean (±SD) age of the patients was 50.9(±11.3) years. The male- female ratio was 5:1. CIMT has significant negative correlation with FMD (r=-.407, p=<.001). Flow mediated dilatation of brachial artery has weak but significant negative co-relation with vessel score(r=-.609, p=<.001), stenosis score(r=-.493, p=<.001) and extent score (r=-.477, p=<.001). However, carotid intima media thickness has weak but positive correlation with vessel score (r=.447, p=<.001), stenosis score (r=.417, p=<.001) and extent score(r=.412, p=<.001).*

Conclusion: *The present study concludes CIMT has significant negative correlation with flow mediated dilatation of brachial artery. FMD has weak but significant negative co-relation and CIMT has weak but positive correlation with vessel score, stenosis score and extent score of coronary arteries.*

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Introduction:

Endothelial dysfunction plays a crucial role in the process of atherosclerotic diseases and has been accepted as an early stage of atherosclerosis.[1,2,3] A noninvasive ultrasound technique to evaluate brachial artery flow–mediated dilatation (FMD) has recently been much used in the study of arterial physiology. The dilatation response with increased blood flow is mainly mediated by nitric oxide released from arterial endothelial cells. Brachial artery FMD response is correlated with coronary endothelial function as tested by invasive methods. Impaired brachial FMD is related to the prevalence and extent of coronary atherosclerosis and predicts cardiovascular events.[4] Carotid intima media thickness (CIMT) and flow-mediated dilatation (FMD) of the brachial artery have been recommended as noninvasive methods to assess endothelial and smooth muscle function. While an increase in CIMT is an early morphological change in atherosclerosis, FMD reflects a functional impairment of the endothelium before morphological changes can be detected. [5]

These noninvasive procedures are regarded as surrogate markers for, and means of measuring atherosclerosis.[1,4,6]Angiographic properties of patients with acute coronary syndrome (ACS) are closely associated with cardiovascular events.[7,8,9]The number of significantly diseased coronary vessels is also a predictive variable of survival and properties of stenotic lesions are

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one of the major predicting factors for cardiac events and mortality.[5]

In this study, we investigated the relation of atherosclerotic properties of coronary, carotid and brachial arteries with Coronary Angiography, CIMT, FMD respectively in patients with IHD.

Material and Methods:

This cross sectional study was done in the Department of Cardiology, Dhaka Medical College Hospital, Dhaka; during the period of Oct 2010- Sept 2011. The Study population was the patients with IHD admitted in the cardiology department undergoing CAG.

Patients having previous history of PCI, CABG, carotid surgery, unfit for CAG or CIMT or FMD study, getting lipid lowering drugs in the last 3 months, renal dysfunction, hepatic dysfunction, major non cardiovascular disease and systemic infection were excluded from the study.

The sample size was 102. Initial evaluation of the patients by history and clinical examination was performed and recorded in the preformed data collection sheet. Demographic profile and Pulse, BP, Body weight, BMI were measured. Risk factors of ischaemic heart disease like hypertension, diabetes mellitus, smoking, dyslipidaemia, obesity and family history of premature CAD were noted. Drug history was taken regarding anti hypertensive, anti diabetic and lipid lowering drugs. Baseline laboratory investigation e.g. CBC, chest x-ray, serum creatinine, serum electrolytes, blood sugar, ECG, Echocardiography were done for each patient. Coronary angiography was done in all patients who fulfilled the criteria. Interpretations of coronary angiogram were reviewed by at least two cardiologists.

Assessment of Angiographic severity of coronary arteries in IHD patients was done by (1) **Vessel score:** This is the number of vessels with a significant stenosis. For left main coronary artery 50% or greater and for others 70% or greater reduction in luminal diameter.[10] Score ranges from 0 to 3, depending on the number of vessel involve. Left main artery was scored as single vessel disease [11] (2) **Stenosis score:** For stenosis score a modified Gensini score was used. The reduction in the lumen diameter and the roentgenographic appearance of concentric lesions and eccentric plaques were evaluated (reductions of 25%, 50%, 75%, 90%, 99%, and complete occlusion are given Gensini scores of 1, 2, 4, 8, 16, and 32, respectively). Each principal vascular segment was assigned a multiplier in accordance with the functional significance of the myocardial area supplied by that segment: the left main coronary artery, ×5; the proximal segment of left anterior descending coronary artery (LAD), ×2.5; the proximal segment of the circumflex artery, ×2.5; the mid-segment of the LAD, ×1.5; the right coronary artery, the distal segment of the LAD, the posterolateral artery and the obtuse marginal artery, ×1; and others, ×0.5. This score therefore, places emphasis on the severity of stenosis, while including some of the extent of CAD[12]. (3) **Extent score:** The proportion of each vessel involved by atheroma, identified by luminal irregularity was multiplied by the factor for each vessel. Left main artery, 5; left anterior descending, 20; main diagonal branch, 10; first septal perforator, 5; left circumflex artery, 20; obtuse marginal and posterolateral vessels, 10; right coronary artery, 20; and main posterior descending branch, 10. When a vessel was occluded and the distal vessel not fully visualized by collateral flow, the proportion of vessel not visualized was given the mean extent score of the remaining vessels. When the major lateral wall branch is a large obtuse marginal or intermediate vessel, this was given a factor of 20 and the left circumflex artery a factor of 10. The score for each vessel or branch were added to give a total score out of 100 that was the percentage of coronary intimal surface area involved by atheroma [11].

Carotid Intima Media Thickness (CIMT)

Carotid intima media thickness (CIMT) was measured by B-Mode ultrasonography and carotid Doppler. The sonographers recorded image sequences for twenty seconds from each of three standardised probe angles (posterior, lateral and anterolateral) in both the left and right common carotids arteries[7,9].

Calculation of CIMT and lumen diameter

When edge detection is complete, automated display of a magnified area of interest marks the lumen margins and the far wall media-adventitia interface with coloured lines. CIMT is expressed in millimetres.

Calculation of FMD

The examination requires the patients to be supine, at rest, in a quiet air conditioned room. A longitudinal section of the brachial artery is analyzed; it is essential that the probe is held in the same position during the scan. After a baseline measurement, a cuff, which can be placed above the transducer position, is inflated to suprasystolic pressure to produce ischemia in the forearm. The cuff is deflated after some minutes (usually 5) thus causing a reactive hyperemia which in turn produces a shear stress stimulus that induces the endothelium to release NO, a vasodilator. FMD, which reflects endothelium dependent vasodilatation, is calculated as the percentage increase or decrease in diameter from baseline to the maximum value which is obtained after the cuff deflation.[13, 14]

In this study our patients underwent automatic assessment of the endothelial function from B-mode images of the brachial artery in Center for Nuclear Medicine (CNMU), Dhaka Medical College. Here the system works in real-time and is based on a fast and robust edge detector which is used to locate the two borders of the artery. All the information was properly noted in the preformed data sheet.

Data analysis:

Data was analyzed by using SPSS version 12. Test statistics to be used to analyze the data are descriptive statistics, Student's t- test and Pearson correlation. Level of significance was set at 0.05.

Ethical implications:

Prior to commencement of this study the respective authority approved the research protocol. All the patients included in this study were informed about the nature, risk and benefit of the study and then written informed consent was taken from each patient. Proper permission was taken from the department and institution concerned for this study.

Results and Observations:

Table-I

Age distribution of the study subjects (n=102)

Age group (years)	Frequency (%)
20-29	6 (5.9%)
30-39	5 (4.9%)
40-49	31(30.4%)
50-59	33(32.3%)
60-69	21(20.6%)
70+	6 (5.9%)
Mean±SD	50.9±11.3
Range	22-75

The mean (±SD) age of the patients was 50.9(±11.3) years with a range of 22-75 years (table-I). Distribution of patients by age shows that the highest number of patients (32.3%) are in the age group '50-59 years' followed by '40-49 years' age group (30.4%) and '60-69 years' age group (20.6%). 5.9% patients belong to '20-29 years' age group and 4.9% to '30-39 years' age group. 5.9% patients were 70 or more years old (table-I).

Table-II

Sex distribution of the study subjects (n=102)

Sex	Frequency (%)
Male	85(83.3%)
Female	17(16.7%)
Total	102(100%)

Among the participants 85(83.3%) were male and 17(16.7%) were female with a male- female ratio of 5:1(table-II).

Table-III

Distribution of study subjects by cardiac risk factors (n=102)

Cardiac risk factors	Frequency (%)
Hypertension	49(48.0%)
Diabetes mellitus	32(31.4%)
Dyslipidemia	97(95.1%)
Smoking	54(52.9%)
Family history of premature CAD	23(22.5%)

Among the cardiac risk factors hypertension was present in 49(48.0%) patients, diabetes mellitus in 32(31.4%) patients, dyslipidemia in 97(95.1%) patients, and family history of premature CAD in 23 (22.5%) patients. Fifty four (52.9%) patients were smoker (table-III).

Table-IV

Clinical diagnosis of study subjects (n=102)

Clinical diagnosis	Frequency (%)
Unstable angina	23(22.5%)
Stable angina	28(27.5%)
STEMI	47(46.1%)
NSTEMI	4(3.9%)
Total	102(100%)

The clinical diagnosis of patients were STEMI in 47(46.1%) patients, stable angina in 28(27.5%), unstable angina in 23(22.5%), NSTEMI in 4(3.9%) (table-IV).

Table-V

Distribution of study subjects by vessel score (n=102)

Vessel score	Frequency (%)
No significant lesions	8(7.8%)
Single vessel disease	44(43.1%)
Double vessel disease	33(32.4%)
Triple vessel disease	17(16.7%)
Total	102(100%)

Forty four (43.1%) of the participants had single vessel disease, 33 (32.4%) patients had double vessel disease and 17(16.7%) had triple vessel disease. No significant lesions were demonstrated in 8(7.8%) patients (table-V).

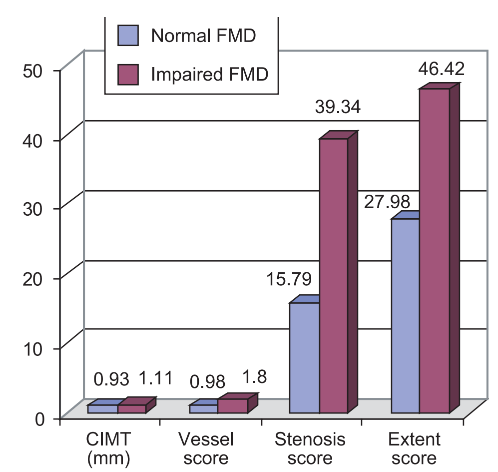

Fig.-1: *Bar diagram showing mean CIMT (mm) and vessel score, stenosis score and extent score of study subjects with normal and impaired FMD*

Table-VI

Comparison of study subjects with impaired and normal CIMT (N=102)

CIMT	Normal CIMT (<0.9 mm) (n=31)	Increased CIMT (≥0.9) (n=71)	p value
FMD	7.91±6.42	3.00±8.49	.005^{s}
Vessel score	1.00±0.63	1.66±0.88	<.001^{s}
Stenosis score	12.82±11.20	36.99±30.86	<.001^{s}
Extent score	28.55±15.82	43.31±20.92	<.001^{s}

s=Significant; ns=Not Significant

Patients were divided into two groups according to the measurement of CIMT: Increased CIMT group with thickness equal to or greater than 0.9 mm (n=71) and normal CIMT group (n=31). 69.6% patients with IHD had increased CIMT. The mean±SD FMD of increased CIMT group was significantly lower than normal CIMT group (3.00±8.49 vs 7.91±6.42; p=.005). The mean±SD vessel score, stenosis score, and extent score of increased CIMT group were significantly higher than normal CIMT group (vessel score: 1.66±0.88 vs1.00±0.63; p<.001, stenosis score: 36.99±30.86 vs 12.82±11.20; p<.001and extent score: 43.31±20.92 vs 28.55±15.82; p<.001) (Table-VI).

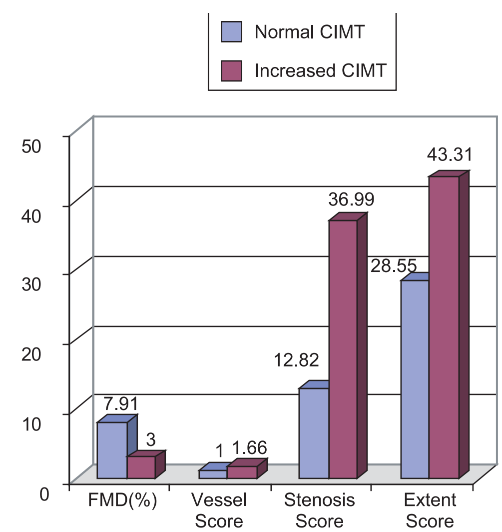

Fig.-2: *Bar diagram showing mean FMD (%) and vessel score, stenosis score and extent score of study subjects with normal and increased CIMT*

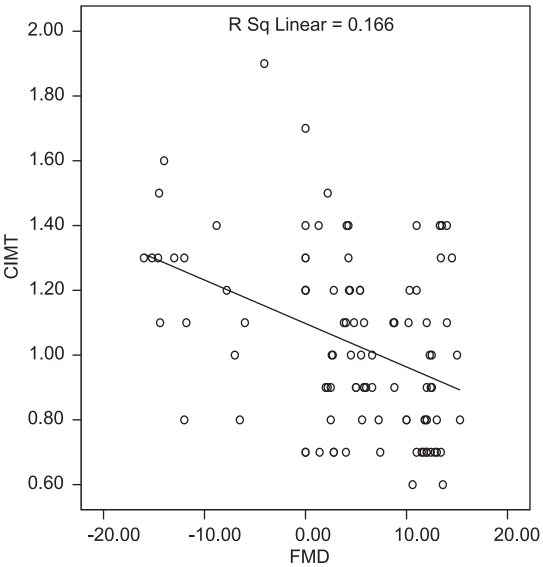

Fig.-3: *Scattered plot diagram showing negative correlation between FMD and CIMT*

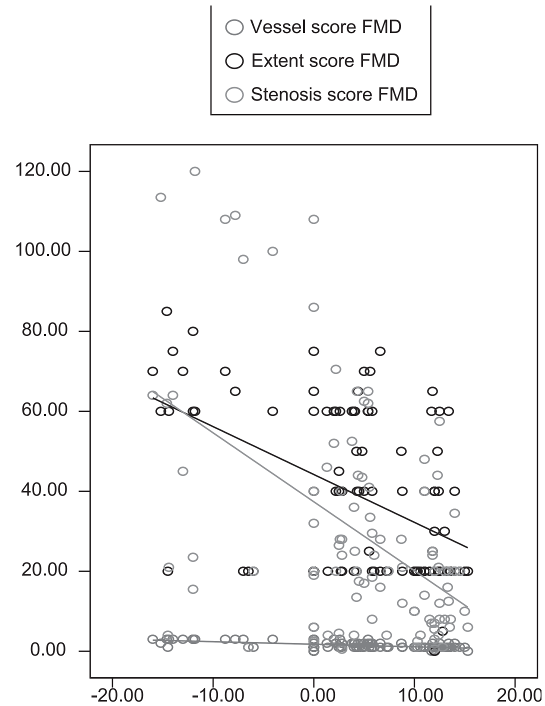

Fig.-4: *Scattered plot diagram showing negative correlation between FMD and vessel score, stenosis score and extent score.*

Table-VII

Comparison of study subjects with impaired and normal FMD (N=102)

FMD (%)	Normal FMD (≥7%) (n=42)	Impaired FMD (<7%) (n=60)	P value
CIMT(mm)	.93±0.24	1.11±0.27	.001^{s}
Vessel score	.98±.52	1.80±0.90	<0.001^{s}
Stenosis score	15.79±13.30	39.34±32.44	<0.001^{s}
Extent score	27.98±14.98	46.42±20.69	<0.001^{s}

s=Significant; ns=Not Significant

Patients were first divided into two groups: Impaired FMD group with FMD value lesser than <7% (n=60) and normal FMD group with FMD value equal to or above 7% (n=42). 58.8% patients with IHD had impaired FMD. The mean±SD CIMT of impaired FMD group was significantly higher than normal FMD group (1.11±0.27 vs .93±0.24; p=.001). The mean±SD vessel score, stenosis score, and extent score of impaired FMD group were significantly higher than normal FMD group (vessel score: 1.80±0.90 vs .98±.52; p<.001, stenosis score: 39.34±32.44 vs 15.79±13.30; p<.001and extent score: 46.42±20.69 vs 27.98±14.98; p<.001) (Table-VII).

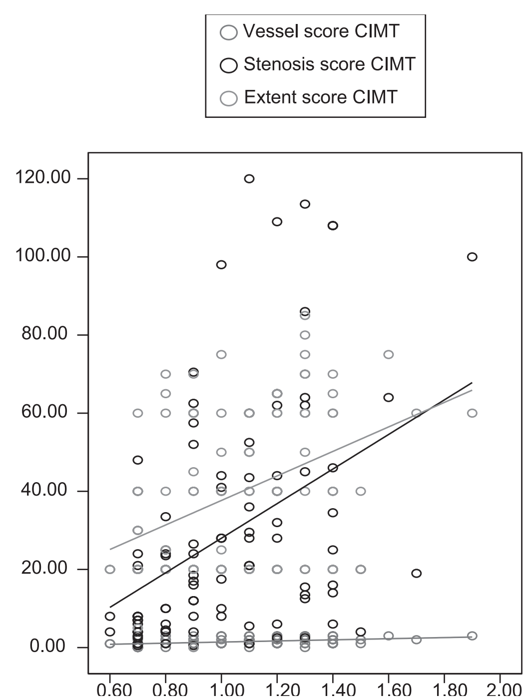

Fig.-5: *Scattered plot diagram showing positive correlation between CIMT and vessel score, stenosis score and extent score.*

Table-VIII

Correlation between angiographic severity, CIMT and FMD

	FMD (%)	Vessel score	Stenosis score	Extent score
FMD (%)	-	r=-.609 p<.001[s]	r=-.493 p<.001[s]	r=-.477 p<.001[s]
CIMT(mm)	r=-.407 p<.001[s]	r=.447 p<.001[s]	r=.417 p<.001[s]	r=.412 p<0.001[s]

s=Significant; ns=Not Significant

Pearson's correlation statistics shows that CIMT has significant negative correlation with %FMD (r=-.407, p=<.001). Flow mediated dilatation of brachial artery has significant negative correlation with vessel score(r=-.609, p=<.001), stenosis score(r=-.493, p=<.001) and extent score (r=-.477, p=<.001). However, carotid intima media thickness has positive correlation with vessel score (r=.447, p=<.001), stenosis score (r=.417, p=<.001) and extent score(r=.412, p=<.001) (table-VIII).

Discussion:

The mean (±SD) age of the patients of the present study was 50.9(±11.3) years with a range of 22-75 years and the highest number of patients (32.3%) were in the age group '50-59 years' followed by '40-49 years' age group (30.4%) and '60-69 years' age group (20.6%). IHD is most common in middle aged group population. Studies done by some other authors also selected patients of this age. The mean (±SD) age of the patients selected by Kalay et al was 59.7 ± 11.8 years.[5] O'Leary [17] selected patients with a mean (±SD) age 72.5 ±5.5 years. Among the participants male- female ratio was 5:1 as coronary arterial disease is more prevalent in male than female. Kalay et al found 86.2% male among their participants.[5]

The mean (±SD) BMI of the patients was 24.42 (±4.29) with a range of 18.55-40.14 and most of the participants of the study had normal weight (64.7%). Kalay et al [5] found mean (±SD) BMI 26.9 ± 3.6 and Jounala et al[4] found mean (±SD) BMI 25 ± 4 among their participants which is very similar with BMI of the present study.

In this study the traditional risk factors was evaluated and found that dyslipidaemia 95.1% was the most common risk factor, followed by smoking in 52.9%, HTN in 48.0% and diabetes mellitus (DM) in 31.4% among the study patients. Family history of premature CAD was present in about one fifth of the whole study patients. Jounala et al [4] found smoking 46.6%, family history of premature CAD 15.4% in their study. O'Leary et al18 studied 5201 patients. Among the participants diabetes was present in 12.9%, Hypertension 39.9%, smoker 12.2%.

The Clinical diagnosis of patients were STEMI in 47 (46.1%) patients, stable angina in 28 (27.5%), unstable angina in 23 (22.5%), NSTEMI in 4 (3.9%). Our findings are similar with the study of Adams et al[19] who studied 350 consecutive subjects. The indications for coronary angiography were stable angina in 146 (42%), unstable angina in 94 (27%), prognosis after myocardial infarction in 32 (9%), important valvular disease in 32 (9%), atypical chest pain in 22 (6%), and other reasons in 24 patients (7%).

The mean±SD vessel score, stenosis score, and extent score of impaired FMD group were significantly higher than normal FMD group (vessel score: 1.80±0.90 vs .98±.52; p<.001, stenosis score: 39.34±32.44 vs 15.79±13.30; p<.001and extent score: 46.42±20.69 vs 27.98±14.98; p<.001). The mean±SD vessel score, stenosis score, and extent score of increased CIMT group were significantly higher than normal CIMT group (vessel score: 1.66±0.88 vs1.00±0.63; p<.001, stenosis score: 36.99±30.86 vs 12.82±11.20; p< .001and extend score: 43.31±20.92 vs 28.55±15.82; p<.001). Pearson's correlation statistics shows that CIMT has significant negative correlation with FMD (r=-.407, p<.001). FMD of brachial artery has significant negative correlation with vessel score(r=-.609, p<.001), stenosis score (r=-.493, p<.001) and extent score (r=-.477, p<.001) and carotid intima media thickness is positively correlated with vessel score(r=.447, p<.001), stenosis score(r=.417, p=<.001) and extent score(r=.412, p<.001).

The findings of the present study is supported by several other contemporary studies.[4,5,18-20] The findings of Bots et al [20] indicated that an increased CIMT is associated with future cerebrovascular and cardiovascular events in older subjects. Juonala et al [4] measured FMD and carotid artery IMT in 2109 healthy adults. They concluded that brachial FMD is inversely associated with carotid IMT. These results are in line with the concepts that impaired systemic endothelial function is an early event in atherosclerosis and that the status of systemic endothelial function may modify the association between risk factors and atherosclerosis. O'Leary and co-workers [18] concluded in a study that the intima–media thickness of the common carotid artery and the internal carotid artery is strongly associated with the risk of myocardial infarction and stroke in asymptomatic older adults O'Leary et al.[18]

Kalay et al [5] found increased CIMT in 33% patients with acute coronary syndrome. Number of diseased vessels was significantly higher in patients with increased CIMT. Significant but weak correlations were found between CIMT, FMD and angiographic severity of coronary atherosclerosis. Angiographic properties and lesion morphology were similar between CIMT and FMD groups. They concluded that there is a relationship between CIMT, FMD and severity of coronary atherosclerosis in patients with ACS Kalay et al.[5]

Matsushima et al [1] studied 103 patients with clinically suspected CAD. FMD and CIMT correlated to coronary stenosis index (CSI) to a similar degree and there was a significant correlation between FMD and CIMT.[1]

However, Adams et al stated that mean CIMT was weakly but significantly correlated with CAD severity, extent, and modified Gensini score. This may be due to the different underlying pathological processes of IMT and atherosclerosis and/or to differential effects of the traditional vascular risk factors on the carotid and coronary circulations.[19]

Adams et al described the explanation of weak correlation of atherogenesis of different arteries [19]. The pathological processes leading to intima-media thickening in the distal CCA and to eccentric coronary plaque formation are not similar. Furthermore, there are territorial differences in vascular beds and their responses to risk factors, and even coronary arteries within the same individuals are not uniformly affected by atheroma. For example, the carotid and coronary circulations are differently associated with some of the traditional vascular risk factors, with hypercholesterolemia being more strongly associated with coronary atheroma than with carotid disease, and carotid atheroma often appearing later in life than coronary plaques. Although the major risk factors were significantly associated with both IMT and CAD scores in the present study, there was a differential effect of some of these factors on IMT compared with coronary disease extent and severity, and this may have contributed to the weak correlation observed between these two measures of arterial disease Adams et al.[19]

Bots et al [20] also stated that whether increased CIMT itself reflects local atherosclerosis is still a subject of debate. It may merely reflect an adaptive response of the vessel wall to changes in shear stress, tensile stress, and blood flow and subsequent changes in lumen diameter. Atherosclerosis is a disorder of the intima, and ultrasound imaging cannot discriminate between the intimal and medial layers of the vessel wall Bots et al.[19]

In the current study we found a negative correlation between the coronary angiographic severity and flow mediated dilatation of brachial artery and a positive correlation between CAG severity and carotid intima media thickness in patients with IHD. FMD of brachial artery and CIMT have a significant negative association between them too. The last finding is very important for the fact that both these tests are non-invasive in nature which can be employed almost instantly to any patient and the result is readily available for use.

Conclusion:

The present study concludes CIMT has significant negative correlation with flow mediated dilatation of brachial artery. FMD has weak but significant negative co-relation and CIMT has weak but positive correlation with vessel score, stenosis score and extent score of coronary arteries. A multicentric study with large sample size should be undertaken to generalize the finding.

Limitations of the study

Sample is small. Study was conducted in a tertiary hospital which does not represent the general population.

Conflict of Interest - None.

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