

## ORIGINAL ARTICLE

### Value of Carotid Intima-Media Thickness in Estimating the Spread of Atherosclerosis and Its Relation to C-Reactive Protein

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<b>Background</b>	Carotid artery intima-media thickness (CIMT), a subclinical measure of atherosclerosis, is associated with coronary artery disease (CAD), and stroke. CIMT is also an important predictor of clinical cardiovascular events. Yet the relation between CIMT and the spread of atherosclerosis is not well investigated. On the other hand C-reactive protein (CRP) is considered as a marker for atherosclerosis, but there are no enough studies to investigate its direct relation to increased CIMT.
<b>Aim</b>	To Evaluate the CIMT as a predictor of atherosclerotic spread by studying the relation between the increased CIMT and the number of arterial territories affected by significant stenotic lesions and to investigate the relation between high sensitivity CRP (hs-CRP) level and increased CIMT.
<b>Methods</b>	The study included 40 patients (33 males), aged 50.5±6.8 years, referred to coronary angiography for various reasons. CIMT was measured bilaterally in common, internal carotid arteries and bifurcation and expressed as the mean aggregate value. In all patients coronary and renal arteries were assessed through angiography and femoral and carotid artery stenoses were assessed through B-mode ultrasound. CRP was measured on high sensitivity basis.
<b>Results</b>	According to the number of arterial territories involved with significant lesions, patients were subdivided into four groups; group A (10 patients) had no lesions in any arterial territory, group B (14 patients) had lesions in one territory, group C (10 patients) had lesions in two territories, and group D (6 patients) had lesions in three territories. CIMT strongly increased in relation to hypertension, diabetes mellitus, dyslipidemia, blood sugar level and increased level of high sensitivity CRP. Both CIMT and Hs-CRP were strongly correlated to the presence, extent of coronary artery disease, carotid and femoral stenosis and to the presence of multi territorial affection.
<b>Conclusions</b>	Increase in CIMT is associated with the increase in number of arterial territories affected by significant atherosclerotic lesions. CIMT is an independent predictor of multi-level atherosclerosis, with high sensitivity and specificity. CIMT is strongly correlated to the increased level of CRP.
<b>Keywords</b>	CIMT, CRP, Atherosclerosis. (Heart Mirror J 2010; 4(1): 80-85)

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## INTRODUCTION

Atherosclerosis has been a serious health epidemic in developed countries in the late twentieth century, and its rising prevalence in developing nations suggests that it will become the chief cause of morbidity and mortality worldwide by early in this century (1). It is a diffuse process that seems to begin in the aorta and spreads to its branches (2).

Numerous studies found a clear relation between ultrasonographically determined intima-media thickness

(IMT) and established risk factors of cardiovascular disease such as serum cholesterol level and blood pressure. An increased IMT is used as a marker of generalized atherosclerosis, including coronary atherosclerosis (3).

It has been demonstrated that carotid intima-media thickness (CIMT) may be the most sensitive marker for the earliest stages (4).

A non invasive technique of measuring CIMT obtained with B-mode ultrasound has recently generated

#### Abbreviations and Acronyms

CIMT	: Carotid artery intima-media thickness
CRP	: C-reactive protein
hs-CRP	: High sensitivity CRP
CAD	: Coronary artery disease

considerable interest as a marker of atherosclerosis and in the prediction of clinical coronary events and coronary artery disease (5).

The reproducibility of IMT measurements in the common carotid artery is reliable, even in patients with increased artery wall thickness. Also in other segments prone to atherosclerosis, such as the bulbous and internal carotid artery, good reproducibility was found (6).

Several epidemiological studies have shown a link between C-reactive protein (CRP) and subsequent cardiovascular disease in the general population (7-11). Moreover with respect to predict the likelihood of cardiovascular disease (12, 13) and is related to many atherosclerotic risk factors (14, 15), an association between CRP levels and the presence of carotid plaques has been shown in univariate analysis in a prospective survey conducted in general community (age range, 40 to 79 years) (16) or in healthy middle aged women with history of smoking (17).

The association between CRP and other cardiovascular risk factors complicates this issue. Changes in circulating elevated CRP levels, even within the normal range, are often involved in the interrelation of cardiovascular risk factors, such as age, smoking, obesity, and high blood pressure, all of which play a causal role in the pathogenesis of cardiovascular disease (18). There are studies suggesting a significant relationship between an elevated CRP level and cardiovascular risk factors in a large number of men and women. As such, CRP seems to be merely a graded marker for the effect of certain conventional risk factors on promoting atherogenesis (19).

This study aimed to perform a comprehensive analysis of CIMT as a predictor of atherosclerotic extent and to investigate the interrelation between CIMT and the number of arterial territories affected by significant (>50% lumen reduction) atherosclerotic lesions (Among: coronary, carotid, renal and femoral arteries) and to investigate the relation between high sensitivity CRP (hs-CRP) level and increased CIMT.

#### PATIENTS AND MEHTODS

The study was conducted on forty patients who underwent coronary angiography for variable indications; angina, either recent or post myocardial infarction, recent myocardial infarction or preoperative coronary angiography prior to valve replacement.

Patients were excluded from the study if they suffered from peripheral arterial disease, carotid sinus syndrome,

previous hip or pelvis trauma previous hip or pelvis surgery or irradiation, lost or unequal pulsations of the lower limbs, previous carotid surgery or carotid stenting, previous neck surgery or irradiation.

Each patient in this study was subjected to full history taking, full clinical examination, electrocardiography and laboratory testing for blood sugar, serum lipids, renal profile and hs-CRP measurement. Then, all patients underwent assessment of different multilevel arterial territories using angiography for the coronary and renal arterial territories and ultrasound evaluation for the carotid and femoral territories.

#### Coronary and Renal Angiography

Coronary and renal angiographies were performed to all patients at the same session via the right femoral artery approach using Seldinger's technique. Stenosis was expressed as percent diameter narrowing using the nearest normal appearing region as a reference. Coronary artery stenosis was considered significant if there was >50% reduction of the luminal diameter in one or more major epicardial arteries.

Selective renal angiography was performed at the same setting. Both the right and left renal arteries were examined for the presence of significant stenosis. Stenosis was considered significant if there was >50% reduction of the luminal diameter in at least one renal artery.

#### Carotid and Femoral Arteries Ultrasound Evaluation

Bilateral ultrasonography of the carotid and femoral artery was performed by means of a high resolution B-mode, color Doppler and pulsed Doppler ESAOTE AU3 ultrasound machine, equipped with a 7.5-10 MHz linear array transducer.

Carotid artery imaging was used to measure the CIMT, Doppler flow velocity in the common carotid artery (CCA) and the internal carotid artery (ICA). On each side of the neck, the maximum CIMT was measured at the far walls of the common carotid artery, the bifurcation, and the internal carotid arteries and was expressed as a mean aggregate value (Aggregate CIMT). Thickening of the IMC greater than 0.8 mm is considered abnormal (20).

The grade of stenosis in the carotid arteries was assessed through the increase in the peak systolic velocity (PSV) and end diastolic velocity (EDV) according to the criteria of Bluth et al (21). Stenosis was considered significant if there was >50% reduction of the luminal diameter in at least one carotid artery.

Real time B-mode is used to visualize the anatomy of the common femoral artery (CFA) bilaterally. Color flow mapping greatly aids in the identification of the artery and the vein, the color is a good pathfinder, permitting the identification of the target vessel. Significant lesions, >50% luminal reduction, in the femoral arteries were identified

with Doppler ultrasound examination according to the criteria of Kohler, et al. (22).

### High sensitivity C-reactive protein measurement

Blood samples were obtained from all patients before coronary angiography. Peripheral venous blood was drawn into collection tubes. Every blood sample was centrifuged to separate serum which was isolated in special tubes that were kept frozen. Later, hs-CRP levels were measured using Particle Enhanced Immunoturbidimetric Technique by Roche Diagnostics' COBAS INTEGRA 400 device. The reagents used were TRIS buffer with bovine serum albumin and immunoglobulins in addition to latex particles coated with anti-CRP in glycine buffer stabilized with 0.09% sodium azide. Normal value in adults is <0.5 mg/dl (23).

The distribution of cardiovascular risk factors was assessed in all patients. Definitions of hypertension, diabetes, hyperlipidemia, smoking status, stroke and myocardial infarction were adopted from the scientific statements of the European Society of Cardiology ([www.escardio.com](http://www.escardio.com)) and American Heart Association ([www.americanheart.org](http://www.americanheart.org)). Detailed group characteristic is presented in (Table 1).

### Statistical Analysis

Data were collected, coded, revised, and verified. The data were then statistically analyzed using the statistical software package SPSS version 12.0.

Comparison between quantitative variables was carried out by unpaired student T test of two independent samples, which were expressed in the form of P-value. Pearson correlation coefficient test (r test) was used to rank different parameters against CIMT and hs-CRP, and expressed as r-value and p-value. Chi-square test (X<sup>2</sup>) was used to compare qualitative variables with each other. Analysis of variance test (ANOVA test) was used for comparison among different times in the same group in quantitative data. Tukey test was used as a complementary test to ANOVA test when ANOVA test was significant to determine the degree of significance between individual groups. A p-value <0.05 was considered statistically significant.

Sensitivity, specificity, positive and negative predictive values were calculated to determine the discriminating power of different cut-off values using Receiver-Operator Characteristic (ROC) curves.

### RESULTS

According to the number of arterial territories affected with significant stenosis (>50% reduction in lumen diameter), the subjects were subdivided into four groups, as follows:

**Group A:** It included 10 patients (25%), who had no significant lesions in any arterial territory.

**Group B:** It included 14 patients (35%), who had significant stenosis in one arterial territory.

**Group C:** It included 10 patients (25%), who had significant stenosis in two arterial territories.

**Group D:** It included 6 patients (15%), who had significant stenosis in three arterial territories.

As shown in (Table 1), we found that the increase in number of arterial territories affected by significant stenosis was related to increase in age, history of diabetes, hs-CRP, and FBS, while no relation was found concerning gender, history of hypertension, history of dyslipidemia, smoking habit, TC, HDL-C, LDL-C, and TG. Analysis of the mean aggregate CIMT showed a positive correlation with the number of arterial territories affected with significant stenosis (P value 0.001).

Univariate analysis showed greater CIMT values for patients with significant CAD versus no CAD patients (1.21±0.23 mm versus 0.78±0.06 mm, P <0.001), patients with significant carotid artery stenosis versus those with no carotid stenosis (1.33±0.21 mm versus 0.95±0.21, P value <0.001), patients with significant femoral artery stenosis versus those with no stenosis (1.32±0.12 mm versus 1.06±0.27 mm, P value 0.04) (Table 2). CIMT also increased with the increase in number of coronary arteries affected with significant stenosis (P value <0.001) and was correlated positively with severity of CAD (lesions ≥90%) (P value 0.01).

Analysis of various risk factors of atherosclerosis in relation to CIMT showed that the mean aggregate CIMT correlated positively with increase in age (P value <0.001) DM (P value <0.001), HTN (P value= 0.008), history of dyslipidemia (P value= 0.001), FBS (P value= 0.002), TC (P value= 0.05), LDL-C (P value= 0.02), TG (P value= 0.03), hs-CRP (P value <0.001). On the other hand there was no significant relation between CIMT and other atherosclerosis risk factors; smoking (P value= 0.52), family history of CAD (P value= 0.13), HDL-C (P value= 0.23).

ROC curves analysis (Figure 1) showed that the optimal cut-off points of CIMT that enables us to predict number of arterial territories affected were as follows:

- 0.9 mm to distinguish between 0 versus one or more arterial territory involvement (Sensitivity 90%, specificity 100%, PPV 100%, NPV 76.9%, and accuracy 98%).
- 1 mm to distinguish 0 to one from two to three level involvement (Sensitivity 100%, specificity 70.8%, PPV 69.6%, NPV 100%, and accuracy 89%).
- 1.1 mm for prediction of three level stenoses (Sensitivity 100%, specificity 61.8%, PPV 31.6%, NPV 100%, and accuracy 82%).

Hs-CRP was found to correlate significantly with the presence of significant CAD (P value <0.001). It also increases significantly with increasing stenosis severity

(≥90% decrease in luminal diameter) of CAD (P value= 0.01). ROC curves analysis showed that the optimal hs-CRP cut-off value that enables us to distinguish subjects with severe (≥90%) stenosis was 0.26 mg/dl with sensitivity 91.7%, specificity 56.2%, PPV 75.9%, NPV 81.8%, and accuracy 77%.

Increased hs-CRP was significantly correlated with the extent of CAD as presented in (Table 3) (P value <0.001), presence of significant carotid artery disease (P value <0.001), and the presence of femoral artery disease (P value <0.005).

Moreover, as shown in (Figure 2), hs-CRP levels showed a highly significant relation with the number of arterial territories affected with significant stenotic lesions (P value <0.001).

ROC curves analysis (Figure 3) showed that the optimal hs-CRP cut-off values that enable us to predict number of arterial territories affected were as follows:

1. >0.26 mg/dl to distinguish between 0 versus one or more arterial territory involvement (Sensitivity

93.3%, specificity 90%, PPV 100%, NPV 96.6%, and accuracy 93%).

2. >1.15 mg/dl to distinguish 0 to one from two to three level involvement (Sensitivity 66.7%, specificity 90.9%, PPV 85.7%, NPV 76.9%, and accuracy 84%).
3. >1.15 mg/dl for prediction of three level stenoses (Sensitivity 100%, specificity 74.3%, PPV 35.7%, NPV 100%, and accuracy 89.4%).

Studying the relation between hs-CRP and CIMT, revealed a highly significant relation between the increased level of hs-CRP and the increase in CIMT (P value <0.001).

Using both hs-CRP and CIMT together for predicting the presence of CAD did not add to the accuracy of prediction offered by CIMT alone (Accuracy= 98%), but it showed higher accuracy compared to using hs-CRP alone (Accuracy= 77%).

**Table 1:** Distribution of the main demographic, clinical, laboratory, and radiological findings among the different study groups:

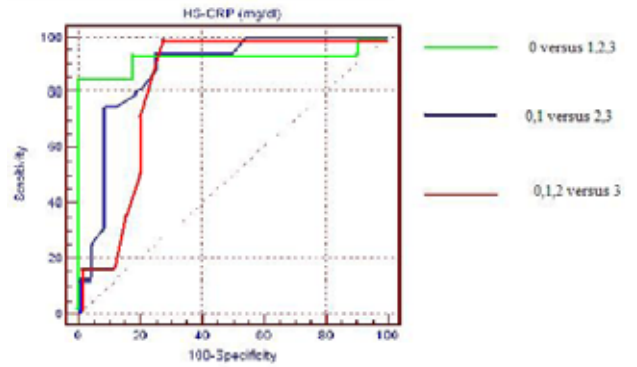
	Group A (n= 10)	Group B (n= 14)	Group C (n= 10)	Group D (n= 6)	P value
Age (Mean±SD)	46.1±6.79	49.93±8.41	51.8±2.44	56.5±2.07	0.02
Male n, (%)	7 (70)	12 (85)	8 (80)	6 (100)	0.41
Hypertension n, (%)	4 (40)	8 (57.14)	7 (70)	6 (100)	0.104
Diabetes n, (%)	1 (10)	3 (21.4)	4 (40)	5 (83.33)	0.015
Dyslipidemia n, (%)	4 (40)	10 (71.4)	6 (60)	6 (100)	0.096
Smoking n, (%)	6 (60)	10 (71.4)	9 (90)	6 (100)	0.196
MI n, (%)	0 (0)	4 (28.6)	5 (50)	5 (83.33)	0.005
CVS or TIA n, (%)	0 (0)	2 (14.3)	2 (20)	5 (83.33)	0.001
SBP (mmHg±SD)	133.5±20.01	126.79±19.96	134.5±16.74	146.67±11.26	0.19
DBP (mmHg±SD)	86.5±10.01	79.29±12.69	83±10.85	90±70.75	0.2
FBS (mg/dl±SD)	98.7±14.92	113.5±23.66	136.3±59.36	155.17±41.65	0.022
TC (mg/dl±SD)	178.2±43.14	191.07±29.36	194±60.02	232.17±24.2	0.11
HDL-C (mg/dl±SD)	33.8±2.7	34.07±3.39	38.7±8.88	34±6.45	0.17
LDL-C (mg/dl±SD)	106.3±22.29	124.29±26.39	114.6±30.93	131.5±12.03	0.2
TG (mg/dl±SD)	127.8±38.45	177±78.9	221.5±214.06	247±51.86	0.2
hs-CRP (mg/dl±SD)	0.2±0.07	0.78±0.55	1.25±0.49	1.57±0.76	0.001
CIMT (mm±SD)	0.78±0.06	1.08±0.17	1.33±0.26	1.32±0.12	<0.001
<b>Territories affected:</b>					
Coronary n, (%)	0 (0)	14 (100)	10 (100)	6 (100)	<0.001
Carotid n, (%)	0 (0)	0 (0)	10 (100)	6 (100)	<0.001
Femoral n, (%)	0 (0)	0 (0)	0 (0)	6 (100)	<0.001
Renal n, (%)	0 (0)	0 (0)	0 (0)	0 (0)	-
Mean	0	1	2	3	

**Table 2:** Correlation between CIMT and the presence of significant stenotic lesions in different arterial territories:

	CIMT Mean ± SD	P value
Patients with no significant coronary artery disease (10 patients)	0.78±0.06	0.01
Patients with significant coronary artery disease (30 patients)	1.21±0.23	
Patients with no significant carotid artery stenosis (24 patients)	0.95±0.21	<0.001
Patients with significant carotid artery stenosis (16 patients)	1.33±0.21	
Patients with no significant femoral artery stenosis (34 patients)	1.06±0.27	0.04
Patients with significant femoral artery stenosis (6 patients)	1.32±0.12	

**Table 3:** Correlation between hs-CRP and the extent of coronary artery disease:

	Hs-CRP Mean ± SD	P value
Patients with no significant coronary artery disease (12 patients)	0.2 ± 0.07	<0.001
Patients with single vessel disease (13 patients)	0.85 ± 0.57	
Patients with two vessel disease (12 patients)	1.05 ± 0.44	
Patients with three vessel disease (3 patients)	1.81 ± 0.82	



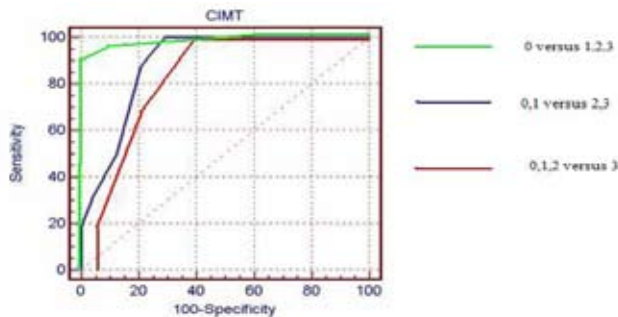
**Figure 3:** ROC curves for Hs-CRP in studied groups.

**DISCUSSION**

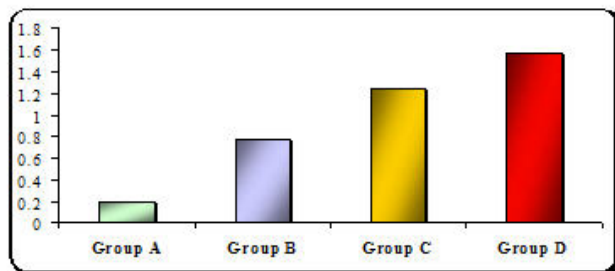
One principal finding of our study is that the CIMT can predict the spread of the atherosclerotic process. Moreover, we show that CIMT can predict, with high degree of sensitivity and specificity, the number of arterial territories affected by significant atherosclerosis. The other principal finding of our study is that the increasing level of hs-CRP is positively correlated with the increase in thickness of CIMT and also with number of arterial territories affected by significant atherosclerotic lesions.

It has been shown before that the mean aggregate CIMT is related to both the cardiovascular risk and prevalence of CAD (24-27). In the present study, we showed that the increase in thickness of the CIMC is related not only to CAD presence, severity, and extent of CAD, but it also correlates positively to the whole atherosclerotic burden, within all the major arterial beds.

We believe that our findings are of an important clinical value as they can indicate patients who are likely to have carotid, renal, lower limb and coronary artery stenoses simultaneously. Patients with multi-level stenoses are frequently aged, have a high risk profile and multiple vascular atherosclerotic distributions, suggesting the usefulness of a more global and comprehensive cardiovascular approach (28, 29). As demonstrated by Caprie trial, approximately 26% of patients have ischemic vascular disease in at least two vascular beds, supporting the generalized nature of atherosclerosis (30). The results of the Framingham Heart Study clearly demonstrate that atherosclerosis reduces life expectancy (31). History of angina pectoris, myocardial infarction or stroke reduced life expectancy by 7, 9 or 12 years, respectively, as compared to average lifetime of 80 years in healthy subject. In addition, life expectancy-in patients with history of both myocardial infarction and stroke is reduced by nearly 16 years (31). The diffuse atherosclerotic process-as showed in our study can be well deduced from CIMT observation throughout carotid artery tree. Thus, prompt diagnosis of multi-level stenoses in these patients, followed by wise procedural management is of utmost importance.



**Figure 1:** ROC curves For aggregate CIMT in studied groups.



**Figure 2:** Relation between hs-CRP and the number of arterial territories affected with significant stenotic lesions.

Our principal finding that with an increase in CIMT there is an increase in the number of territories with significant stenoses can provide an insight into the mechanism of previous population studies looking at the association between CIMT and cardiovascular risk (32-34). In particular, several prospective studies that included both asymptomatic individuals and symptomatic patients indicated that the patients with CIMT values in the highest tertile (Quartile or quintile) had the highest risk of cardiovascular events during the follow-up (32-35). For example, Wattanakit, et al. showed a two-fold increase in cardiovascular risk for patients in the highest versus lowest quartile of CIMT (34).

Our study indicates also that CIMT measurement appears superior to routine atherosclerotic risk factors assessment in prediction of systemic significant atherosclerosis. Consistent with other studies, we demonstrated that major cardiovascular risk factors independently contribute to intima-media thickening. As evidenced by Framingham score, multiple risk factors act additively on atherosclerosis progression. This is associated with an increase in CIMT, which is strongly related to the overall cardiovascular risk in individual subject (36-38). Similarly, hs-CRP level is a predictor of cardiovascular events (39-43). In accordance with the work done by Makita, et al. (28) and Lorenz, et al. (29) our data show a positive correlation between the level of hs-CRP and the aggregate CIMT.

In view of large body of evidence supporting prognostic role of CIMT, both American Heart Association and Food and Drug Administration decided to recognize CIMT as a risk factor for future cardiovascular events in their scientific statements (44). Principal findings from our study reinforce the role of CIMT by showing that CIMT is a powerful indicator of significant multi-level atherosclerosis and show the consistent relation between hs-CRP and CIMT.

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