Original Article

A Study to derive distribution of carotid intima media thickness and to determine its CORrelation with cardiovascular Risk factors in asymptomatic nationwide Indian population (SCORE-India)

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ABSTRACT

Background: There is presently no data to describe normal distribution of carotid intima-media thickness (CIMT), an established measure of subclinical atherosclerosis, in Indian subjects.

Methods: In this multi-centric study, 1229 subjects with age ≥30 years and no previous cardiovascular disease (CVD) underwent CVD risk factor assessment and CIMT measurement. Mean far wall common carotid artery IMT was measured on both sides and averaged.

Results: Mean age of the subjects was 48.0 ± 12.0 years and 54.2% were men. CIMT measurement was feasible in 1157 subjects. Mean, median and 75th percentile values of CIMT for different age-groups were derived for men and women separately. There was a progressive increase in CIMT with increasing age (P < 0.001) and men had higher CIMT values than women (0.608 ± 0.12 mm vs. 0.579 ± 0.11 mm, P < 0.001). The CIMT values were also higher in diabetics (0.635 ± 0.10 mm) and hypertensives (0.624 ± 0.10 mm) as compared to non-diabetics (0.589 ± 0.12 mm, P < 0.001) and non-hypertensives (0.592 ± 0.12, P 0.02) respectively. Among continuous variables, age, systolic blood pressure and fasting blood glucose had strong to modest correlation with CIMT (Pearson’s r 0.524, 0.282 and 0.192 respectively, all P values <0.001), whereas body mass index, diastolic blood pressure and serum triglycerides exhibited weak but still statistically significant relationship (Pearson’s r 0.069, P 0.019; Pearson’s r 0.065, P 0.026; and Pearson’s r 0.054, P 0.001, respectively).

Conclusions: This is the first study to provide age- and gender-specific distribution of CIMT in Indian subjects free from CVD. This information should help facilitate further research and clinical work involving CIMT in India.

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1. Introduction

Early detection of atherosclerosis, when still in its preclinical stage, has emerged as a promising approach to facilitate optimum cardiovascular disease (CVD) risk stratification of asymptomatic individuals.1-4 Although definitive outcome data is lacking, preliminary evidence suggests that addition of atherosclerosis imaging to conventional risk assessment tools may help better determine the nature and aggressiveness of the required preventive measures and can thus improve clinical outcomes.5-10 In addition, limited evidence also suggests that detection of structural evidence of atherosclerosis may improve patient compliance toward therapeutic measures.5-10

Numerous tools have been developed for preclinical atherosclerosis assessment, such as carotid intima media thickness (CIMT), coronary calcium score (CCS), brachial artery flow-mediated dilatation, pulse wave velocity, ankle brachial index, etc. Of these, CIMT is one of the most extensively utilized modalities. A large number of clinical trials involving several thousand patients have shown that increased CIMT is associated with increased risk of vascular events, independent of conventional CVD risk factors or...
Framingham risk score.\textsuperscript{4,11–16} Compared with other modalities for atherosclerosis imaging, CIMT has the advantages of being less expensive, widely available and being free from ionizing radiation.

However, CIMT is significantly influenced by ethnicity and therefore ethnic-specific reference values are needed for interpreting CIMT values in a given individual. Although numerous small scale studies have evaluated associations of CIMT in Indian subjects,\textsuperscript{17–22} there is unfortunately no large-scale study to provide normal values of CIMT in Indian subjects. Therefore, this study was sought with the primary objective of defining normal distribution of CIMT in Indian subjects and to also explore the relationship of CIMT values with various demographics characteristics and CVD risk factors in Indians.

2. Methodology

2.1. Study design and procedure details

This was a non-interventional, observational, cross-sectional study, conducted at 15 sites across India. The study was performed in accordance with the ethical guidelines of the Declaration of Helsinki. Institutional review board and the local ethics committee approval was obtained at each site (the core ethics committee: Medanta Independent Ethics Committee, study no. MIRC-208/2012). A written informed consent was obtained from all the participants.

A total of 1229 asymptomatic subjects with age \(\geq 30\) years and no pre-existing CVD were enrolled in the study. The subjects were recruited from participating clinics/hospitals and included healthy volunteers or those undergoing preventive health checks. The absence of significant coronary artery disease (CAD) was confirmed on the basis of history and normal exercise stress test. The subjects were excluded if they (1) had any acute or chronic systemic illness, (including gastro-intestinal, renal, hepatic, central nervous system, respiratory, infectious, or psychiatric diseases), (2) were already taking lipid lowering drug for more than three months, (3) had known hypersensitivity to carotid bulb, (4) were suffering from any medical condition that, in the opinion of the investigator, would have interfered with safe completion of the study, or (5) were already participating in any other clinical study. In addition, pregnant or lactating women were also not allowed to take part in this study. A urine pregnancy test was performed for all female participants with childbearing potential to exclude pregnancy.

Each site was encouraged to recruit subjects in an age-stratified manner with nearly equal number of subjects in each of the following four age groups:

- \(30–39\) years,
- \(40–49\) years,
- \(50–59\) years, and
- \(60\) years and above.

Once recruited in the study, all participants underwent clinical assessment, biochemical investigations and CIMT measurement. All the study procedures were completed in a single day. However, due to any reason, if any study variable was not captured on the same day, the subject was asked to come back for a second visit within 7 days of the first visit.

Clinical assessment included a detailed medical history about CVD risk factors, concomitant medications and symptoms suggestive of CVD, if any; height, weight and blood pressure (BP) measurement; and examination of the cardiovascular system. BP was measured in the right arm in supine position, using a standard sphygmomanometer. Laboratory investigations included fasting blood glucose and lipid profile estimation; and estimation of spot urinary albumin concentration. For the purpose of the present study, hypertension was defined according to Joint National Committee (JNC) 7 guidelines as systolic BP \(\geq 140\) mmHg or diastolic BP \(\geq 90\) mmHg or previous history of hypertension or self-reported use of anti-hypertensive medications.\textsuperscript{23} Diabetes mellitus was defined as fasting blood glucose \(\geq 126\) mg/dL or 2-hour postprandial blood glucose \(\geq 200\) mg/dL or pharmacological treatment for diabetes or previous history of diabetes mellitus.\textsuperscript{24} Family history was considered positive if a coronary event had occurred in a male first degree relative before the age of 55 years or a female first degree relative before the age of 65 years.\textsuperscript{25} Smoking or tobacco use in any form during the preceding month was also considered to be a CVD risk factor.

2.2. CIMT measurement

The measurement of CIMT was performed following the recently published guidelines of the American Society of Echocardiography (ASE).\textsuperscript{4} The images were obtained at the participating study sites and were then transferred to the core lab for offline CIMT measurement.

2.2.1. Image acquisition

Imaging was performed using a linear-array transducer with minimum fundamental frequency of 7 MHz attached to Sonosite M-turbo 1.5 color Doppler ultrasound system.

The subjects were asked to lie supine with head resting comfortably. The neck was slightly hyperextended and rotated in the direction opposite to the side of measurement. ECG was connected for obtaining R-wave gated images. The default scan depth was kept at 4 cm but could be changed depending on the built of the person. Common carotid artery (CCA) was imaged in longitudinal plane and optimal angle of incidence was identified. The optimal angle of incidence is defined as the plane in which the bifurcation of the carotid bulb into the internal and external carotid arteries can be visualized simultaneously with the bulb and distal CCA (Fig. 1). Once this view was created, finer adjustments in the transducer position were done to ensure that distal CCA was perfectly horizontal on the screen and ‘double lines’ of intima and adventitia were clearly visualized in the far wall of the CCA (Fig. 1).

After optimizing the image, a cine-loop with 3–5 beats was stored. The CCA was then imaged from two additional complimentary angles, approximately 45° anterior and posterior to the first image.
and a cine-loop was stored for each of these views. All images were transferred to a CD in DICOM format for offline analysis.

2.2.2. Image analysis

The image analysis was performed at the core lab, using the semi-automated software provided by SonoSite Ltd. (Fig. 2). All images were analyzed by a single observer. Only the far wall CIMT of distal 1 cm of CCA was measured, as recommended by the ASE.4

For analysis, the images were transferred from the CD to the workstation and were first reviewed for overall image quality. Each loop was then played individually and the R-wave gated still frame showing the best image of distal 1 cm of CCA far wall was selected for CIMT measurement.

A region-of-interest box with 1 cm length was placed at the distal end of the CCA, just before bifurcation. The software then automatically traced lumen-intima and media-adventitia interfaces using leading edge-to-leading edge method. Manual adjustments were done to ensure optimum tracing. If a plaque was present in the segment where CIMT measurement was being performed, it was traced as part of CIMT. The software then provided mean and maximum values of CIMT over 1 cm length of CCA (Fig. 2), which were recorded. The same process was then repeated for all the three angles on both sides. Thus, six (three for each side) values of mean and maximum CIMT were obtained for each subject. The six mean CIMT values were averaged to provide composite ‘mean CIMT’ which was used for subsequent analysis.

2.3. Statistical methods

The data were managed on Microsoft excel spreadsheet (version 2007, Microsoft Corp., Seattle, Washington) and analyzed using SPSS for Windows (release 15.0, SPSS Inc., Chicago, IL, USA). Standard descriptive analysis was performed to analyze the baseline characteristics of the study population. Continuous values were expressed as mean with standard deviation and the categorical values as actual numbers with percentages. For obtaining CIMT distribution, mean, median and 75th percentile values of mean CIMT were derived for each age-group, for men and women separately.

For assessing the relationship between various CVD risk factors and CIMT, Student’s independent samples t-test was used for dichotomous risk factors and Pearson’s correlation coefficient for continuous variables. Spearman’s rank correlation was used for assessing the statistical significance of CIMT trend across the age-groups. Multiple regression analysis was used for determining the relative strength of association between various CVD risk factors and CIMT. A P value <0.05 was considered statistically significant for all the analysis performed.

2.3.1. Measurement variability

As mentioned above, all the CIMT measurements in the present study were performed by a single observer. The same observer repeated measurements in 20 randomly selected studies. Coefficient of variation was calculated and Bland–Altman plot constructed to assess the intra-observer variability.

3. Results

Table 1 summarizes the clinical characteristics of the study population. Mean age of the study subjects was 48.0 ± 12.0 years and 54.2% (666 of 1229) were men. Of all the subjects, 11.1% were

| Parameter                                | Value       |
|------------------------------------------|-------------|
| Age (years)                              | 48.0 ± 12.0 |
| Male gender, n (%)                       | 666 (54.2)  |
| Body mass index (kg/m²)                  | 26.0 ± 4.1  |
| Hypertension, n (%)                      | 96 (7.8)    |
| Diabetes, n (%)                          | 131 (11.1)  |
| Smoking, n (%)                           | 129 (10.5)  |
| Family history of premature CAD, n (%)   | 121 (9.8)   |
| Systolic BP (mmHg)                       | 125 ± 16    |
| Diastolic BP (mmHg)                      | 78 ± 11     |
| Fasting blood sugar (mg/dL)              | 104.9 ± 37.8|
| Total cholesterol (mg/dL)                | 182.0 ± 39.7|
| Serum triglycerides (mg/dL)              | 141.9 ± 80.1|
| HDL-cholesterol (mg/dL)                  | 43.6 ± 12.1 |
| LDL-cholesterol (mg/dL)                  | 114.4 ± 31.9|
| Urinary albumin concentration (mg/L)     | 37.3 ± 56.9 |

All values are mean ± standard deviation or actual number with percentages in parenthesis.
BP, blood pressure; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
diabetics. 7.8% had hypertension, 10.5% were current smokers and 9.8% had family history of premature CAD. Mean body mass index was 26.0 ± 4.1 kg/m².

3.1. CIMT distribution

Of the 1229 subjects, 1203 (98.0%) completed the study and therefore had carotid scanning done. Of these 1203 subjects, 46 subjects (3.8%) had to be excluded because of the poor image quality. Thus, CIMT measurement was performed in the remaining 1157 subjects (94.1% of total).

The ASE has recommended using age- and gender-specific 75th percentile values of CIMT as the upper limits of normal.⁴ Accordingly, mean, median and 75th percentile values of mean CIMT for men and women in each age-group are provided in Table 2. As is evident, there was progressive increase in CIMT with increasing age (P < 0.001, Fig. 3) and men had higher CIMT values than women in each age group (overall mean CIMT 0.608 ± 0.12 mm in men vs. 0.579 ± 0.11 mm in women, P < 0.001).

Table 2 summarizes age and gender specific CIMT values in individuals without diabetes, those without diabetes and hypertension and those without diabetes, hypertension, smoking and family history of premature CAD.

3.2. Relationship between various CVD risk factors and CIMT (Table 4)

As already mentioned above, men had higher CIMT values than women. The CIMT values were also higher in diabetics...
(0.635 ± 0.10 mm) and hypertensives (0.624 ± 0.10 mm) as compared to non-diabetics (0.589 ± 0.12 mm, P < 0.001) and non-hypertensives (0.592 ± 0.12 mm, P = 0.02) respectively. However, family history of premature CAD and smoking did not demonstrate any significant relationship with CIMT. Among continuous variables, age, systolic BP and fasting blood glucose had strong to modest correlation with CIMT (Pearson’s r=0.524, 0.282 and 0.192 respectively, all P values <0.001), whereas body mass index, diastolic BP, serum triglycerides and urinary albumin concentration exhibited weak but still statistically significant relationship (Pearson’s r=0.065, P=0.026; Pearson’s r=0.094, P=0.001; and Pearson’s r=0.127, P < 0.001, respectively) (Table 4). On multivariate analysis, age and gender demonstrated strongest association with CIMT among the risk factors included in the analysis (Table 5).

### Table 4
Relationship between mean carotid intima-media thickness and various cardiovascular risk factors.

| Categorical variables                  | Mean CIMT (mm) | P value
|----------------------------------------|----------------|---------|
| Male gender                            | 0.579 ± 0.11   | <0.001  |
| Hypertension                           | 0.592 ± 0.12   | 0.02    |
| Diabetes                               | 0.589 ± 0.12   | <0.001  |
| Smoking                                | 0.594 ± 0.12   | 0.38    |
| Family history of premature CAD        | 0.596 ± 0.12   | 0.282   |

### Table 5
Multivariate regression analysis to assess determinants of carotid intima-media thickness.

|         | Unstandardized coefficients | Standardized coefficients | P value |
|---------|-----------------------------|---------------------------|---------|
|         | β                             | Std. Error                | t       |         |
| (Constant) | 0.259 | 0.030 | 8.59 | <0.001 |
| Age (years) | 0.004 | <0.005 | 0.502 | 14.37 | <0.001 |
| Male gender | 0.033 | 0.007 | 0.166 | 5.03 | <0.001 |
| Body mass index (kg/m²) | 0.002 | 0.001 | 0.068 | 2.044 | 0.041 |
| Systolic blood pressure (mmHg) | <0.001 | <0.001 | 0.046 | 1.302 | 0.194 |
| Fasting blood glucose (mmHg) | <0.005 | <0.005 | 0.135 | 4.041 | <0.001 |
| Urinary albumin concentration (mg/L) | <0.001 | <0.001 | 0.003 | 0.101 | 0.920 |

### Fig. 4
Bland–Altman limits of agreement for intra-observer reproducibility of carotid intima-media thickness measurement in the present study.

#### 3.3. Intra-observer variability

Fig. 4 depicts Bland–Altman limits of agreement for intra-observer reproducibility of mean CIMT. The average difference between repeat measurements was -0.011 mm with standard deviation 0.032 mm and coefficient of variation 5.2%. These values are consistent with those previously reported in the literature. 26–28

### 4. Discussion

The rapid increase in the prevalence of CVD world over has necessitated development of aggressive strategies for its prevention. One of the key requirements for any CVD preventive strategy to be effective is the ability to accurately identify the individuals who are at high risk of developing CVD. Focusing on these 'high risk' individuals is expected to result in the most effective utilization of the limited healthcare resources. Additionally, the knowledge of the anticipated CVD risk may also help improve patients’ health-related behaviors and improve the compliance to the treatment.

Traditionally, assessment of the CVD risk is performed by taking into consideration the presence or absence of various CVD risk factors and subsequently using one of the several risk algorithms currently available.26 A major limitation with these risk algorithms is that they only provide probabilities of developing a CVD event but cannot identify the individuals who are actually going to develop the disease. Thus, while these algorithms work well at the population level, their accuracy at the individual level is suboptimal. To overcome this limitation, detection of subclinical atherosclerosis has been proposed as an alternate strategy with the premise that the presence of an early evidence of atherosclerosis in a given individual will confirm his/her susceptibility to develop atherosclerosis regardless of the presence or absence of various CVD risk factors.

A number of tools for detection of subclinical atherosclerosis are now available, such as carotid ultrasound imaging for CIMT and carotid plaque assessment, CCS, brachial artery flow-mediated dilatation, pulse wave velocity, ankle brachial index, etc. Of these, CCS and CIMT are the most extensively utilized modalities and a large number of studies have documented their incremental value in predicting CVD risk over conventional risk factors.14,11–16,29–34 Although CIMT has relatively less robust evidence base as compared to CCS, it has the advantages of being less expensive, widely available, simpler to perform, and the most
importantly, being free from radiation exposure. These attributes make CIMT an attractive option for incorporation in to routine clinical practice. Although various authorities have provided different recommendations for clinical use of CIMT, it is already being increasingly adopted for CVD risk stratification in clinical practice.

However, a major challenge with CIMT, just as with all other atherosclerosis imaging modalities, is that it varies with age, gender and ethnicity. Accordingly, ethnic-specific normative data needs to be used for interpreting CIMT results in a given population. Unfortunately, while a number of studies have evaluated the association of CIMT with CVD risk factors and prevalent CVD in Indian subjects,17–22 no large-scale study has so far provided normal distribution of CIMT in this population. This has remained a major factor limiting wider use of CIMT in clinical practice in India. The present study was conducted as an attempt to fill this knowledge gap. Using a fairly large study sample of men and women free from existing CVD, we derived age- and gender-specific normative data for CIMT in Indians.

While deriving normative data, most of the previous large studies had included all subjects, regardless of the presence or absence of CVD risk factors,11,12,15,34 and therefore we have also followed the same approach. The reason for not excluding individuals with CVD factors is that the actual incremental value of CIMT is only when it is added to conventional CVD risk factors. As is well established, and was observed in our study too, CIMT values are much lower in individuals who are completely free from all major CVD risk factors. Using these values as reference will result in most of the subjects with one or more CVD risk factors being considered to have increased CIMT, thus defeating the very purpose of risk stratification. Nevertheless, for the benefit of the readers, we have also provided CIMT values in individuals who were free from various specific CVD risk factors.

It is noteworthy that in our study we found significant relationship of CIMT with various CVD risk factors such as age, gender, diabetes, hypertension, urine albumin concentration etc. These findings are consistent with the existing literature on CIMT and provide an indirect validation of our data.

4.1. Limitations

Our study had certain limitations that merit attention. Although this is the largest study to describe normal distribution of CIMT in Indians, it is still small given the overall size and the diversity of our population. For this reason, the present study findings cannot be described as true normative values of CIMT in India. Nevertheless, our study still is an important step toward filling this huge knowledge gap and should be of help in future research and clinical work in India, until larger data is generated.

Second, due to logistic reasons, we did not specifically look for carotid plaques in this study. Previous studies have shown that carotid plaques have stronger association with the presence of obstructive CAD and the future CVD risk as compared to CIMT17–40 and therefore, detection of carotid plaques (along with CIMT measurement) forms a part of carotid ultrasound examination for CVD risk stratification. However, it should be noted that in apparently healthy young individuals carotid plaques are seen in only <10% subjects.28 Thus, while the presence of a carotid plaque signifies high CVD risk, absence of a plaque does not help clinicians in assessing CVD risk. For this reason, we believe, lack of information about carotid plaques is unlikely to have appreciably affected the significance of our findings. Moreover, the primary purpose of the present study was to describe distribution of CIMT and not to evaluate the comparative predictive accuracy of CIMT and carotid plaques. This was also the reason (coupled with logistic challenges) why we did not look for other novel CVD risk factors and other measures of subclinical atherosclerosis in this study.

5. Conclusions

To the best of our knowledge, this is the first large-scale study to provide age- and gender-specific distribution of CIMT in Indian subjects free from pre-existing CVD. This information should help facilitate further research and clinical work involving CIMT in India.

Conflicts of interest

The authors have none to declare.

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Appendix A

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