Review Article

Carotid intima–media thickness: Current evidence, practices, and Indian experience

Ravi R. Kasliwal, Manish Bansal, Devang Desai[1], Maya Sharma[2]

Division of Clinical and Preventive Cardiology, Medanta, The Medicity, Gurgaon, Haryana, [1]Interventional Cardiologist, Mahavir Cardiac Hospital, Surat, Gujarat, [2]Medical Affairs, Astra Zeneca India, Bangalore, Karnataka, India

ABSTRACT

As the developed and developing nations cope up with increasing predisposition to cardiovascular diseases (CVD) by adopting lifestyle changes the burden of coronary artery disease continues to rise globally. The presence of modifiable risk factors, which account for more than 90% of the cardiovascular (CV) risk, cannot always be interpreted as the presence of atherosclerotic heart disease and absence of modifiable risk factors do not guarantee absence of atherosclerotic changes in the arterial tree. Increasing awareness about primordial prevention and primary prevention of CVD is of vital importance in such scenarios. Ultrasonographic measurement of intima media thickness has been reported as a procedure to detect the early stages of atherosclerosis. Carotid intima media thickness (CIMT) testing is a safe, noninvasive and cost effective method to detect early atherosclerotic vascular diseases. This method of CV risk evaluation drew attention worldwide and of Indian physicians because of its feasibility in Indian population. Hence, detection and management of atherosclerosis in asymptomatic individuals will go a long way in preventing atherosclerotic diseases and prolonging survival and improving quality of life.

Key words: Atherosclerosis, atherosclerotic disease, coronary artery disease, carotid intima-media thickness

Introduction

The burden of coronary artery disease (CAD) continues to rise globally, as developing nations, including India, are adopting to lifestyle changes with predisposition to cardiovascular diseases (CVD).[1] In India, incidences of CAD have doubled over the last three decades. By 2015, CVDs alone would amount to 1.5 million deaths, including 34% of male and 32% of female global deaths.[2] According to a study, presence of modifiable risk factors account for more than 90% of the cardiovascular (CV) risk. Their presence cannot always be interpreted as the presence of atherosclerotic heart diseases, nor their absence guarantees atherosclerotic lesion-free arterial tree.[3] Atherosclerosis, the precursor of CV events, keeps progressing insidiously without symptoms, afflicting large sections of arterial tree including carotid and coronary arteries. Hence, increasing the population awareness about factors causing CVD and recognizing novel screening modalities to evaluate subclinical atherosclerosis is of paramount importance for prevention of CAD, stroke, and peripheral vascular disease.

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Intimo-medial thickness (IMT) is a measure of the combined thickness of intima and media layers of carotid artery, most commonly assessed by B-mode ultrasound. Increase in carotid intima–media thickness (CIMT) may result from hypertrophy of intimal or medial layers or both because cellular/molecular mechanisms that increase CIMT are also the factors responsible for development and progression of atherosclerosis.[4]

CIMT has been reported as representative of subclinical and asymptomatic atherosclerotic vascular diseases, shown in several large ultrasonographic measurement

Corresponding Author: Dr. Maya Sharma, Cardiovascular Division, Medical affairs, Astra Zeneca India, Bangalore, Karnataka, India.
E-mail: ashish.gulati@astrazeneca.com

of IMT, and therefore a procedure to detect primordial atherosclerosis. The amount of lesion in the common carotid artery (CCA) has been reported to correlate to the extent of atherosclerotic lesions elsewhere in the body. Over more than two decades, CIMT has been extensively researched and explored for its medical and clinical viability, and available in clinically since 2002. Several large, research-based cohort studies have clearly indicated a relationship between CIMT and CV events and emphasized its use.[4,5]

The purpose of the present review is to summarize emerging need and utilities of CIMT testing and its application in relation to primary prevention of CV events in India. CIMT testing is a safe, noninvasive, and cost effective method to detect early atherosclerotic vascular diseases.

Conventional Diagnostic Modalities and their Limitations

Coronary angiography (CAG) is still a procedure of choice to stratify patients with risk of coronary and cerebrovascular diseases. However, the procedure is invasive and costly, involves fewer but definite risk of death and disability, and is unable to detect early atherosclerosis. These drawbacks severely influenced the use of CAG, and hence its use had limitations.[6] Other diagnostic modalities with similar limitations were exercise electrocardiography, stress echocardiography, and thallium scanning. Another conventional diagnostic modality, computed tomography coronary artery calcium (CT-CAC) testing method, was considered superior to Framingham Risk Score (FRS) in the risk prediction.[7,8] However, its use is limited due to 1) lack of sensitivity in younger populations; 2) heavy radiation exposure (up to 100 times a plain chest X-ray); 3) requirement of radiocontrast media; and 4) its high cost. Hence, CT-CAC was not considered as a general screening tool for routine use.

Noninvasive assessment of myocardial perfusion imaging (MPI) has been an important diagnostic test for risk stratification in patients with suspected or clinically manifested CAD. Other noninvasive techniques were single-photon emission computed tomography (SPECT), positron emission tomography (PET), myocardial contrast echocardiography (MCE), cardiac magnetic resonance imaging (CMRI), and cardiac computed tomography (CT). All these noninvasive techniques are promising but present with diverse range of limitations. The SPECT-MPI has long acquisition protocols and poor spatial resolution resulting in inability to detect subendocardial perfusion defects.[9] It involves lot of imaging artifacts (interfering signals) and possessed low sensitivity to detect left main disease or three-vessel disease related to balanced ischemia and radiation exposure. Increased cost and need for a cyclotron for Rb-82 imaging or imaging agents labeled with F-18 impede widespread clinical use of PET imaging. Further, negligible interference of motion artifacts during scan makes it difficult to interpret their influence on imaging.[9] The MCE technique has an added advantage that it does not involve radiation exposure and thus is preferred over other modalities. However, its use was limited due to suboptimal image quality, increased variability, decreased reproducibility, requirement of trained operators, and absence of Food and Drug Administration approved contrast agents. CMRI is preferred in perfusion stress testing due to its high spatial resolution which permits absolute quantification of perfusion. The major limitation for its widespread use was its high cost. It may also invoke claustrophobia in patients and therefore was not performed on critically ill patients. The gadolinium contrast agents used for imaging in CMRI have been reported to cause nephrogenic systemic fibrosis in patients with low creatinine clearance (less than 30 mg/dL).[10] In spite of advances in CT imaging, high exposure to ionizing radiation could not be avoided and remained its biggest limitation.

The resistive index (RI) test is a measure of impedance to blood flow and is done to measure subclinical atherosclerosis in the carotid arteries. A study compared RI and CIMT progression over a period of 6 years and found CIMT to be a better modality in the detection and assessment of subclinical atherosclerosis.[11] Coronary artery inter-adventitial distance was a relatively new test that was found to be promising in the prediction of CV risk, but its effectiveness remained to be confirmed.[12] Brachial artery reactivity testing and ankle brachial pressure index (ABPI) were the other alternative modalities for atherosclerosis detection and evaluation. ABPI was biased in the detection of more severe disease and its utility in patients with low-grade stenosis and with high-risk of heavy arterial calcification was unreliable.[13,14] All these techniques were limited primarily because of the non-linear relationship between CV risk factors and the actual development of disease, their high cost, invasiveness, limited availability, advanced setup requirements, exposure to radiation and contrast, and decreased sensitivity and specificity. These factors posed a greater challenge in diagnosing atherosclerosis in low-risk individuals who may otherwise not require aggressive treatment. Therefore, in the recent years, focus has shifted to 1) More feasible, noninvasive, and cost-effective modalities for screening low-risk individuals with atherosclerotic vascular diseases and 2) tools that can directly detect vascular disease itself at

a primordial stage and do not rely on indirect risk prediction through these risk factors.

CIMT: A Promising Approach to Primary Prevention of Atherosclerotic Diseases

Atherosclerosis is observed to be more or less present equally in the coronary, cerebral, and carotid arteries. In 1986, Pignoli and colleagues[15] for the first time reported ultrasound imaging to measure IMT of carotid arteries. In 1991, Salonen and colleagues[16] showed for the first time the *in vivo* use of ultrasound imaging for the evaluation of atherosclerotic changes in the carotid arteries. They demonstrated close histological relationship between coronary, cerebral, and carotid atherosclerotic diseases. Since then, the ultrasonographic assessment of easily accessible arteries has become a surrogate marker for evaluation of less accessible vessels such as coronary and cerebral arterial systems. Ultrasound imaging provided information on IMT, the presence and type of plaque, calcification, and wall diameter. These information enabled assessment of presymptomatic lesions, atherosclerotic burden, and reduced death and disabilities from CVD.

Metabolic syndrome (MS) constitutes risk factors that considerably increase the risk for heart disease and other health problems. It is associated with subclinical atherosclerosis and is evident by increased CIMT; with the spontaneous recovery from MS, low CIMT was observed correlating well with slow atherosclerosis progression.[17-19]

MS is associated with aberration in apolipoprotein metabolism and has elevated levels of apolipoprotein B (Apo B), C-reactive proteins, and type II secretory phospholipase A2 (sPLA2), and low levels of apolipoprotein A1. In 2010, Mattsson *et al*.[18] used cross-sectional and 6-year prospective data from the cardiovascular risk in the Young Finns Study (YFS) and investigated the association between MS and carotid atherosclerosis in relation to Apo B, Apo A1, and other inflammatory markers in young adults aged 24-39 years. The CIMT was assessed from the posterior wall of left CCA and ≈ 10 mm proximal from the bifurcation. Both Apo B and MS were reported to be independently associated with increased CIMT (defined as CIMT more than 90th percentile and/or plaque), and CIMT was attenuated by ~40% after adjustment with Apo B. However, in the study, this association was not influenced after adjustments with the Apo A1, CRP, or sPLA2 levels. Individuals with MS and high Apo B levels possessed more than three times higher relative risk of incident IMT than those without MS and with normal Apo B. Hence, Apo B plays a significant role in the assessment of increased burden of future atherosclerosis. In a previous YFS, Apo B and Apo B/Apo A1 ratio were found to be directly related and Apo A1 was inversely related with adulthood IMT in patients aged 12-18 years. They also suggested Apo B/Apo A1 ratio in adolescence as the best lipoprotein variable predicting increased CIMT in young adults.[19]

Definition

CIMT is defined as the area of tissue starting at the luminal-intimal interface and the media-adventitia interface of CCA. Since B-mode (bright-mode) ultrasonography is a safe, noninvasive, and cost-effective to measure CIMT, a recent study more precisely defined CIMT as the double-line pattern visualized by B-mode vascular ultrasound formed by two parallel echogenic lines representing junction of the vessel lumen with intima and media-adventitia interface.[20]

Positive and negative predictive values

In real clinical situations, an ideal or truly accurate test always gives a positive result with disease and a negative result without disease. Positive predictive value (PPV) refers to the proportion of patients with a positive test result who actually have disease. Likewise, negative predictive value (NPV) refers to the proportion of patients with a negative test result who do not have disease.

In 2002, Belhassen *et al*.[21] in a pilot study reported the value of CIMT and aortic intima-media thickness (AoIMT) in ruling out significant CAD in patients awaiting heart valve surgery. They demonstrated the values of CIMT and AoIMT as less than 0.55 and less than 3 mm, respectively, and both of them excellently predicted the absence of CAD. In addition, the NPV of CIMT and AoIMT were reported as 100% and 99%, respectively, and the specificity as 50% and 65%, respectively, for ruling out of CAD. However, they reported that CIMT had the sensitivity of 100% for detecting CAD and concluded that both CIMT and AoIMT may help in selecting patients not requiring CAG before heart valve surgery.[21]

In 2006, Modi *et al*.[22] in a prospective study reported PPV and NPV for CIMT as 0.73 and 0.92, respectively, in patients with end-stage renal disease (ESRD). The sensitivity and specificity of using CIMT >0.75 mm to predict CAD was reported as 90.47% and 73%, respectively. They concluded that CIMT could predict CAD in patients with ESRD and could also help in avoiding the need for pretransplant CAG in asymptomatic patients with CIMT <0.75 mm.[22]

In 2010, Tessitore *et al*.[23] investigated the association between CIMT and aortic arch plaque (AP) in 138 asymptomatic elderly men and women. The authors

showed that only CIMT at the bifurcation was associated with large AP after adjustment for atherosclerotic risk factors. The PPV and NPV for AP ≥4 mm of CIMT at the bifurcation above the 75th percentile (≥0.95 mm) was 42% and 80%, respectively. The NPV increased to 87% after considering median CIMT value (0.82 mm). The strong NPV of CIMT for large AP indicated that it might be used as initial screening test to rule out severe arch atherosclerosis in the general population.

Guidelines for CIMT measurements

The American Society of Echocardiography (ASE) in a consensus statement has standardized the technique for CIMT assessment.[4] Adherence to the prescribed imaging protocol and close attention to instrumentation are critical in CIMT measurement as small errors can classify patients in different risk categories. Ultrasound imaging in CIMT uses transducers that produce acoustic or sound waves. Two types of transducers, sector phased-array and linear phased-array, are used in ultrasound imaging. Linear phased-array transducers (version A and version B) have an advantage over sector phased-array because of its improved image quality. Presently, these transducers are helping clinicians in making accurate diagnosis with improved image quality, ergonomics, and trapezoid imaging formats.[24] The current guidelines recommend the use of state-of-the art linear-array ultrasound transducers that can operate at a fundamental frequency of at least 7 MHz to scan carotid arteries. Depending on scanning protocol, the specific predetermined bilateral sites in the vicinity of carotid bifurcation are selected for taking CIMT measurements. Other segments of the carotid artery used for CIMT measurement are CCA and the internal carotid artery (ICA). CIMT of the CCA has better reproducibility than ICA or carotid bifurcation due to its ease of access and proximity to the surface and runs relatively parallel to the skin.

The consensus statement on use of CIMT from ASE has recommended adhering to carotid ultrasound scanning technique and procedures to facilitate high-quality, reproducible images, and requires both sonographer and patient to be positioned properly to obtain high-quality images. CIMT testing is conducted in supine position on scan bed with head of the patient resting comfortably, and neck slightly hyper-extended and rotated in direction opposite to the probe. A wedge pillow at an angle of 45° standardizes lateral rotation. Optimization of images is done by adjusting patient's neck position especially in anterior scanning planes, and rolled towels are given under neck and legs for comfort. With the use of external landmarks such as the Meijer arc or similar device, transducer angle is standardized. Height and location of ultrasound system keyboard and monitor, examination bed, and chair are adjusted accordingly to avoid any musculoskeletal injuries to patients.[4]

The six values of mean CIMT (three on each side) are obtained and averaged to get mean CIMT.[25] Reliance on a single absolute threshold abnormality will result in under-detection of diseases in younger individuals and over-detection in older individuals.[26]

In healthy middle-aged adults, CIMT values between 0.6 and 0.7 mm have been considered normal, while CIMT of 1 mm or more has been associated with significant increased absolute risk of CHD.[27] In healthy Indian adults, the average and maximum CIMT values reported were 0.67 and 0.70 mm, respectively.[28] The measurement of CIMT varies with age and values >1.0 mm are considered abnormal in younger population and confer increased absolute risk of CHD.[26,29] In a cross-sectional study, apparent age-related increase in common CIMT was observed in both the genders (approximately 0.010 mm/year in seemingly healthy men and ~0.014 mm/year in seemingly healthy women), whereas it is 0.010 mm for both genders in the ICA. Patients with known CAD had three times higher rate of CIMT progression than patients without known CAD (0.030 mm/year vs. 0.010 mm/year, respectively).[30]

According to the ASE guidelines,[4] patients at intermediate CVD risk [Framingham Risk Score (FRS) 6%-20% without established coronary heart disease (CHD)], peripheral arterial disease, cerebrovascular disease, diabetes mellitus, or abdominal aortic aneurysm) were the potential candidates for CIMT measurement. The carotid plaque was identified by ultrasound to refine CVD risk assessment. Other patient categories that were considered for CIMT measurement and carotid plaque detection included (1) patients with family history of premature CVD in a first-degree relative (men less than 55 years old, women less than 65 years old); (2) patients with severe abnormalities in single risk factor (e.g., genetic dyslipidemia) aged less than 60 years who otherwise would not serve as the candidates for pharmacotherapy; and (c) women aged less than 60 years old with at least two CVD risk factors.

The present consensus on echocardiography reported CIMT values ≥75th percentile as the upper limit of normal across age, gender, and race/ethnicity, and served as the indicators of increased CVD risk. CIMT values increase with age and are generally more in men than women. Thickness of CIMT has been reported to be the highest in African Americans, least in Hispanics, and intermediate in Whites.[26] In 2010, Liviakis *et al.* also supported recommendation of the ASE

guidelines to use CIMT in 75th percentile as the upper cut-off limit.[20] Patients with these elevated CIMT values were considered for aggressive treatment for atherosclerosis. The CIMT values between 25th and 75th percentiles were considered as average and indicative of unchanged CVD risk. At these CIMT values, physicians might consider treatment initiation. The guidelines suggested that patients with CIMT values ≤25th percentile may be considered to have lower CVD risk. But lowering treatments than standard care in such patients remained to be confirmed, and therefore recommended reporting of these broad levels of risk based on CIMT values.[4]

IMT was calculated based on the protocol incorporating all three carotid segments (i.e., distal common carotid, carotid artery bifurcation, and proximal internal carotid arteries). A strong correlation between incident CVD and increasing CIMT has been reported in the age group of 42-74 years. But comparatively strong relationship between increasing risk factor burden, emerging risk factors, and CIMT has been observed in young adults aged 18-42 years. The finding of the Carotid Atherosclerosis Progression Study with 2436 individuals younger than 50 years reported that CIMT predictive value for future vascular events was at least as high in younger subjects as in older subjects, and the relative risk associated with the increased CIMT were considerably higher in individuals younger than 50 years.[31]

CIMT for Prediction of CV Risk

Asymptomatic individuals

Presently, there are growing consensus for the use of CIMT in risk prediction in asymptomatic individuals or patients at risk of coronary diseases, especially type 2 diabetics. American Heart Association (AHA) prevention conference V in 2001 recognized that traditional risk factors alone were insufficient in categorizing risk of patients and had recommended the use of CIMT for risk stratification.[32] In 2004, Wackers *et al*.[33] also suggested that two or more risk factors failed to identify large proportion of patients (41%) with silent ischemia as revealed from baseline analysis of the SPECT data. Two years later, the task force Screening for Heart Attack Prevention and Education (SHAPE) recommended all asymptomatic middle-aged and older men and women to be screened using noninvasive imaging to detect and treat patients with subclinical atherosclerosis.[34] A large European prospective study called the Carotid and Femoral Ultrasound Morphology Screening and Cardiovascular Events (CAFES-CAVE)[35] trial demonstrated significant predictive values in low-risk subjects. The recent consensus statement from the ASE in 2008 reiterated results of previous studies and recommended the use of carotid ultrasound for identifying subclinical atherosclerosis and in evaluating the CVD risk in asymptomatic individuals at intermediate risk.[4]

Computed tomography coronary angiography (CTCA) is a new test available for diagnosis of CAD. The procedure uses intravenous dye containing iodine injected through an arm vein to image the coronary arteries. Though the procedure is noninvasive as it does not require the use of catheters, it still involves some risks. In individuals allergic to iodine, pre-treatment with anti-allergy medications is necessary to prevent allergic reactions to the dye. The dye may also worsen kidney function in people with impaired renal function and diabetes. Finally, risk of radiation exposure is similar to or greater than that received with a conventional coronary angiogram. Apart from these issues, patients most often need to take a beta blocker to slow the heart rate to allow production of clear pictures. CTCA has a limitation in patients who have irregular pulse or are unable to take a beta blocker. CTCA can be used as a screening tool for CAD, and evaluates subclinical vascular disease by measuring coronary artery calcium (CAC). The Multi-Ethnic Study of Atherosclerosis (MESA) with 6814 adults aged 45-84 years in four ethnic groups reported CAC to be a better predictor of CVD events than CIMT, but CIMT was better predictor of stroke than CAC.[36] In 2009, Lester *et al*.[37] suggested CIMT to be more predictive and accurate than CAC score in young and middle-aged patients. Based on the CAC score, large proportions (47%) of patients with zero CAC score (low risk) were at substantially elevated risk of atherosclerosis and had high CIMT values more than75th percentile (per age, sex and race category). However, only a small fraction (15%) of patients possessing high CAC score were at high risk and had low CIMT values less than 50th percentile. It was reported that 50% of the people experiencing first episode of coronary events remain unidentified by FRS.

The ASE guidelines emphasize CAC assessment in older individuals with intermediate CVD risk.[4] In comparison to CT-CAC, CIMT has been observed to be more effective in detecting early non-calcified subclinical atherosclerotic changes as CT-CAC identifies the presence of more calcified artery predictive of advanced disease state. Moreover, CIMT does not involve the use of ionizing radiations and is used as a continuous measure to stratify risk in women and younger individuals. It also offers an added advantage in identifying the CV risk in African American population where CT-CAC was observed to be of limited use due to zero CAC score.[38]

In a study by Postley *et al*.,[39] they reported that ultrasound

evaluation of the carotid and femoral arteries can identify people with substantially high risk and may need aggressive CVD risk factor modification but are at low and intermediate risk for CAD as per FRS. Further, a review in 2009 by Nguyen and Benzaquin[40] suggested the use of CIMT for reclassification of primary prevention patients into high- and low-risk categories. The potential of CIMT testing for the prediction of CAD in 150 asymptomatic type 2 diabetics was further explored using B-mode ultrasound and was considered useful in identifying diabetic patients at higher risk for CAD by Djaberi and colleagues.[41] In 2010, another study was conducted on 98 asymptomatic type 2 diabetics to investigate the use of CIMT in the diagnosis of abnormal myocardial perfusion.[42] The study showed that categorization of patients based on CIMT inputs helped in referring asymptomatic type 2 diabetes patients who may require further test or intensification of the therapy. Sibal and colleagues[43] recently suggested that routine assessment of CIMT might add value to risk stratification and would facilitate better use of various treatment strategies in people with diabetes. In a systemic review, asymptomatic individuals with intermediate risk mostly benefited from additional evaluation of risk with CIMT and other noninvasive B-mode ultrasound approaches.[44]

Individuals with existing CVD

Several large prospective clinical studies that included Atherosclerosis Risk in Communities (ARIC) study,[45] Cardiovascular Health Study (CHS),[46] and the Rotterdam study[47] reported correlation of increased CIMT with the risk of CV events. These trials involved long-term follow-up of patients with existing CAD, including young and middle-aged patients at risk of CAD. CIMT was not only reported to be higher in patients with CAD, but was also shown to have a significant linear relationship with the number of involved coronary arteries.

The ARIC Study involved 7289 female and 5552 male participants aged 45-70 with no history of CHD and followed them for a period of 4-7 years. The hazard ratio for MI or CHD death for high versus low tertiles was 6.69 and 2.88 for females and males, respectively. The CHS studied 5858 participants aged more than 65 without clinically apparent CHD for a median of 6.2 years. After adjustment for age and sex, patients who were in the highest quintile of CIMT had 3.87 relative risk of MI or stroke than those in the lowest quintile. In 2004, Kablak-Ziembicka *et al.*[48] reported a correlation of CIMT and extent of CAD in 558 consecutive patients with mean age of 58.8 years. They showed that there was an increase in CIMT as the CAD progressed and patients with CIMT value of 1.15 mm had 94% higher risk of CAD. Every 0.1 mm increase of CIMT was reported to increase the risk of myocardial infarction (MI) by 11%.

In 2007, a meta-analysis of eight clinical trials by Lorenz *et al.*[44] showed that CIMT was a robust predictor of CV events. They showed that an absolute CIMT difference of 0.1 mm increased the future risk of stroke and MI by 13-18% and 10-15%, respectively. In 2008, Li *et al.*[49] demonstrated threefold higher risk of ischemic stroke than those without carotid artery atherosclerosis, despite adjustment for traditional risk factors in patients with normal blood pressure (140/90 mm Hg) but with carotid artery atherosclerosis (defined as CIMT ≥ 0.81mm) and/or presence of plaque (CIMT more than 1.2 mm) over a mean of 10.7 years.

Overall, all prospective studies concluded CIMT to be a marker of severe symptomatic CAD and increase in CIMT was strongly correlated with the presence and extent of abnormal myocardial perfusion.[46,50] As a traditional risk factor, it was also reported as a strong predictor of CV events after adjustment for other traditional risk factors and had strong association with the development of cardiac events. Presently, there are no randomized studies which demonstrate measurement of CIMT in clinical practice to improve CV outcomes except The Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin (METEOR) study.[50] In this study, rosuvastatin reduced progression of CIMT in 984 middle-aged adults at apparently low to intermediate CVD risk. The magnitude of reduction in the rate of CIMT progression with rosuvastatin was similar to that observed in secondary prevention trials that were associated with reduction in CV events. This indirectly implied that statin therapy could potentially benefit these individuals who otherwise would not have qualified for it based on current treatment guidelines. Thus, this study, for the first time, demonstrated potential of CIMT-based treatment strategy to improve clinical outcomes.[50]

CIMT for Monitoring Response to Therapy

Atherosclerotic vascular changes are known to precede cardiovascular death and disability. CIMT has gradually become a choice among clinicians for detection of subclinical or accelerated atherosclerotic disease by virtue of being cheap and unsophisticated. In clinical practices, it was reported to be useful in evaluating the effectiveness of prevention therapy.[50] Hence, clinicians may make therapeutic decision based on CIMT reports.

Lifestyle changes, including smoking cessation, regular exercise, healthy diet choices, and weight loss have been observed to profoundly influence initiation, development, and progression of atherosclerosis. The landmark study reporting the influence of lifestyle changes on atherosclerosis progression was Monitored Atherosclerosis Regression Study which directly correlated various lifestyle modifications with annual reduction of CIMT.[4] The CIMT progression was annually reduced by 0.065, 0.0033, and 0.028 mm after reduction of body weight index by 5 kg/m^2, dietary cholesterol intake by 100 mg/day, and by quitting smoking of 10 cigarettes/day, respectively. Cumulatively, changes in these lifestyle measures had led to an annual decrease in CIMT by 0.13 mm.[48,51]

A smoker may have a vascular age of 60 years based on the reports of CIMT even if his original chances of survival were low, and hence would motivate patient to stop smoking.

Physical activity and good cardiorespiratory fitness imposes a favorable effect on risk factors for atherosclerosis. In 2001, Lakka *et al*.[52] reported that cardiorespiratory fitness [maximal oxygen uptake (ml/kg/min)] was associated with the progression of early carotid atherosclerosis in middle-aged men. In a 4-year controlled study,[53] obese patients treated with gastroplasty showed reduction in several CVD risk factors (blood pressure, high-density lipoprotein-cholesterol, triglycerides, and insulin) than obese control group subjects. In addition, their CIMT progression rate was also similar to lean subject groups. However, CIMT progression rate in obese controls subjects was three times higher than in lean subjects. This study importantly highlighted the role of weight reduction on retardation of atherosclerosis progression.[53]

In addition, CIMT progression was prevented with improved glycemic control in type 2 diabetics. In 2003, Wu *et al*.[54] reported the relationship between progression of atherosclerosis and dietary intake. They showed that progression of CIMT was retarded with intake of pectin (a viscous fiber) and with increased physical activity.[54,55]

In a recent review, Cobble and Bale suggested CIMT to be an important tool for day-to-day clinical practice to detect CV risk in patients and also that laboratory reports of CIMT would act as motivator for patients to reduce CV risk.[51]

Advantages of CIMT

Ultrasonographic assessment of CIMT has several advantages in clinical practice over angiography in observing atherosclerotic vascular changes and development of atherosclerosis.[45,56,51]

- CIMT can be used repeatedly and reproducibly with no adverse effects on the patients. It can be performed noninvasively with no risk of vessel dissection, vessel closure, or coronary spasm
- CIMT scanning protocol can detect atherosclerotic diseases in early and asymptomatic stages
- CIMT directly visualizes vasculature unlike indirect biomarkers such as low-density LDL-C or even the more advanced biomarkers like high-sensitivity C-reactive protein or lipoprotein-associated phospholipase A2 (Lp-PLA2)
- CIMT with plaque interrogation can be performed in any basic ultrasound ambulatory setting with favorable speed and cost factors
- CIMT can be easily quantified via automated boundary detection software, and the carotid interrogation is radiation free and thus safer than other imaging tests such as coronary calcium scoring or CT-CAG
- CIMT allows for observation of the arterial wall, the actual site of the atherosclerotic disease, rather than the lumen
- CIMT is not dependent on calcification of the plaque as are some of the other assessment tools such as coronary artery calcification score.

Challenges of CIMT testing

In addition to several advantages of CIMT, there are also a few shortcomings of this procedure; however, some of them were resolved.[43,52]

- There is no standardized protocol for measurement of CIMT, which might lead to inaccurate estimation of the progression and regression of the CIMT during the follow-up studies or in the evaluation of any therapeutic intervention on the measured CIMT
- *Resolution:* Implementation of edge detection software programs improved reproducibility and reduced reader variation[57]
- Different portions of the carotid artery have been used to measure the CIMT, common carotid, bifurcation, internal carotid, and combined CIMT, which may influence the value of the measured CIMT
- *Resolution:* Iglesias del Sol and colleagues measured CIMT at the common carotid, bifurcation, internal carotid, and combined CIMT, and they found that all the measurement sites had the same ability to predict future cardiovascular events[58]
- Measurement of CIMT involves a combined measure of the intimal and medial layers of the arterial wall, whereas the atherosclerotic process is restricted in the intimal layer, particularly in its early phase
- CIMT is only an indirect assessment of the possible atherosclerotic burden in the coronary arteries, as

in CIMT, carotid arteries and not coronary arteries are visualized since CAD is the commonest cause of cardiovascular-related deaths. The detection of atherosclerosis in the carotids by CIMT may not represent atherosclerosis in the carotid artery

- *Resolution:* Atherosclerosis has been reported to be more or less present equally in the coronary, cerebral, and carotid arteries, and autopsy study showed close histological relationship between coronary, cerebral, and carotid atherosclerotic disease.[16]

CIMT in Indian Clinical Scenarios

Asian Indians have been an ethnically vulnerable race for developing metabolic syndrome and diabetes, both of which are well-known contributors to the pathogenesis of atherosclerotic vascular disease.[58] The subclinical diabetes is reported as an important vascular risk for Asian Indians.[59] Additionally, atherosclerosis is known to develop in patients of hypertension, chronic autoimmune vasculitides or arthritis, polycystic ovarian syndrome, and in patients receiving dialysis.

Several studies on Indian population have reported various clinical scenarios using CIMT as endpoint of the study.[27,59,60] In 2003, Hansa *et al*.[28] reported association of CIMT with CAD and CV risk factors in the Indian population which included 101 patients with established CAD and 140 control subjects with no CAD. CIMT, as measured at three predefined sites (carotid bifurcation, CCA, and ICA) on each side, was significantly higher in the coronary disease group compared to the controls. The results of this study indicated that increased values of average and maximum CIMT were significantly associated with the presence of CAD and this association was independent on the presence of other conventional CV risk factors.[28]

The Chennai Urban Rural Epidemiology Study (CURES-2), an epidemiological study published in 2004, reported association of CIMT and arterial stiffness with retinopathy in Asian Indians who were at a high risk group for diabetes and CAD.[61] The data from this study showed an association between early atherosclerosis and diabetic retinopathy in urban South Indian population. A prospective study in 2006 reported efficacy of CIMT in predicting the prevalence of CAD in a patient population of end-stage renal disease (ESRD) using CAG as standard. The study reported that CIMT can be used as a screening tool for the evaluation of CAD in patients with ESRD, and in the absence of other risk factors, patients with IMT less than 0.75 mm may not need a pre-transplant CAG.[22]

In 2008, Agarwal *et al*.[62] published a study in the current issue of JAPI, which reported examination of the CIMT in Indian diabetic patients. The study reported higher CIMT in diabetics who had CAD, even when the CAD was not clinically overt, and suggested that the CIMT was a reliable surrogate marker for subclinical CAD in diabetic patients. In 2008, Mahajan *et al*.[63] published a study that was regarded as the second only Indian study examining the extent of atherosclerosis in rheumatoid arthritis (RA) patients. The study reported that RA patients had significantly greater CIMT values than age-sex-matched controls, indicating the association of RA with premature atherosclerosis. A recent study by Madhuri *et al*.[64] reported relation of the CIMT with age and found a significant association between advancing age and CIMT. Another group studied association between CIMT and prevalent CAD in Indian subjects and found significantly increased CIMT in patients with established CAD.[28] In another study from the same group, CIMT was found to predict the presence of left main CAD with reasonable accuracy. Mean CIMT value more than1.0 mm had 92% specificity for the presence of left main CAD.[65]

Conclusion

CIMT testing as a marker of atherosclerotic vascular disease generated considerable interest among physicians globally including India because of its simplicity, safety, and reproducibility. India has a population with a high incidence of diabetes, a high prevalence of dyslipidemia, and with increasing urbanization, an ever increasing population with adverse lifestyle changes. Among the different tools for subclinical atherosclerosis assessment, CIMT offers distinct advantages such as CIMT is associated with CVD risk factors, with prevalent and incident CVD, and is an independent predictor of CV events in a variety of populations. Due to its ease of use and reproducibility, CIMT would be the ideal choice for assessing subclinical atherosclerosis in clinical practice. CIMT as a reliable marker of atherosclerosis and harbinger of CV risk appears to be feasible in low-risk Indian population where cost effectiveness is of paramount importance.

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