Atherothrombosis in South Asians: Implications of Atherosclerotic and Inflammatory Markers

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Abstract: South Asian immigrants (SAIs) have a higher prevalence of cardiovascular (CV) morbidity and mortality compared with other populations. The major challenge associated with primary prevention of cardiovascular to coronary artery diseases (CAD) in SAIs involves early and accurate detection of CAD in asymptomatic individuals at high cardiovascular risk. Inflammatory processes are now recognized to play a central role in the pathogenesis of atherosclerosis and are found to be associated with future CV risk in a variety of clinical settings. Imaging measures, such as common carotid artery intima-media thickness (CCA-IMT), are being applied as surrogate markers for end-points, such as myocardial infarction (MI) and death in clinical trials. Considering high CAD risk in SAIs and knowing that conventional risk factors may not fully explain the excess CAD risk in this group, studies on the role of CCA-IMT in CAD prediction have been discussed. Also, C-reactive protein (CRP) validity in risk prediction, the role of dysfunctional high density lipoprotein (HDL) as a CAD risk marker in SAIs have been presented.

Keywords: Coronary artery disease, Cardiovascular disease, Dysfunctional HDL, South Asians, C-reactive protein.

INTRODUCTION

Cardiovascular diseases (CVDs) account for more than 15 million deaths each year in the world [1]. Many who die are under the age of 65 and given today's increased life span, these deaths are premature. South Asians are individuals whose ethnic roots originate from the Indian subcontinent, a large geographic area that includes India, Pakistan, Sri Lanka, Nepal, and Bangladesh. Collectively, South Asians represent one fifth of the global population [2-4]. In North America, more than 3.6 million South Asians live in the US, and although this group represents the second fastest growing Asian immigrant population, little is known regarding their increased risk for CAD. It is important to recognize that the term "South Asian" refers to a heterogeneous population, with important differences in diet, culture, and lifestyle among different South Asian populations and religions. Multiple studies of migrant South Asian populations have, however, confirmed a 3- to 5-fold increase in the risk for myocardial infarction (MI) and cardiovascular death as compared with other populations [4-6]. Studies in the United Kingdom (UK) have found that South Asian Immigrants' (SAIs) risk of CAD death is as much as 40% above whites' [7,8]. In the US, South Asian Indian men have been found to have a rate of heart attacks that is nearly double than the general US population i.e. 7% vs. 3% [9]. Studies comparing CAD risk factors amongst Indians living in India to immigrants in Britain [10] highlight that CAD risk factors are markedly higher amongst Indian Punjabi [11] and Gujarati [12] migrants than their counterparts in India. Traditional CV risk factors like hypertension, smoking or high cholesterol do not fully account for the increased CAD risk in SAs. Insulin resistance is thought to be a contributory factor, but the exact patho-physiological mechanism for these increased incidences in SAs awaits further insight. A study comparing SA men to European Caucasian men showed elevated systemic arterial stiffening in SA men that could be partly responsible for the high CVD burden in this population. Increased insulin resistance may lead to arterial stiffening. Vessel wall composition in SAs may be another factor playing a role [13]. Knowing the high prevalence of CAD and its risk factors in South Asian immigrants, a major challenge associated with primary prevention of CAD involves early detection of CAD in those individuals who are at risk but are asymptomatic. Inflammatory mechanisms play a prominent role in mediating all stages of atherosclerosis, and measurement of inflammatory biomarkers provides a method for detecting individuals at future vascular risk. Advances in cardiovascular imaging, especially with reference to common carotid artery intima media thickness (CCA-IMT), have the potential to improve the early detection of atherosclerotic vascular disease and quantify its progression. Clinicians and their patients are challenged with how best to integrate these emerging modalities into clinical practice and understand their implications as surrogate markers for clinical end points in trials.

We therefore, present here a review of literature and updates on studies examining the role CCA-IMT in CAD prediction. In addition, we have briefly touched upon implications of C-reactive protein (CRP) and its validity in CAD risk prediction especially in SAIs. At the end of the review, we have provided insights on the dysfunctional HDL, and its potential role as CAD risk marker.

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COMMON CAROTID ARTERY INTIMA-MEDIA THICKNESS (CCA-IMT)

Assessment of CCA-IMT is well-recognized as a surrogate marker of atherosclerosis [14-20]. Moreover, CCA-IMT is a strong and independent predictor of death, stroke and myocardial infarction (MI) in hypertensive patients with CAD referred for coronary angiography. CCA-IMT is one of the methods for the detection of early stages of atherosclerotic disease and has been chosen as a surrogate marker over other non-invasive methods because it is a high-resolution, noninvasive technique that is readily available, allows to visualize the vessel wall structure with high resolution [21]. Pignoli and others established that the distance measured between two lines separated by a hypoechogenic space visible in an ultrasound image of the carotid distal wall correlated with the thickness of the intima-media (IMT) layers of the artery measured *in vitro* and *in vivo* [22]. Later studies extended this measurement to the thickness of the focal carotid plaque, and this "composite thickness" was used as a marker of atherosclerotic burden. This method has been widely used since its introduction, and validated in many cross-sectional and longitudinal epidemiologic and clinical studies. In addition, carotid atherosclerosis (IMT >1.0 mm) was associated with severe coronary disease (odds ratio, 2.2; 95% confidence interval, 1.2 to 4.0) in subjects undergoing elective coronary angiography [23]. The American Society of Echocardiography's (ASE) 2008 consensus statement on CCA-IMT defines it as the combined thickness of the intimal and medial layers of the far arterial wall of the carotid artery [24]. Carotid plaque is defined as focal arterial wall thickening 50% greater than the surrounding wall or a focal region of CCA-IMT >1.5 mm [25]. Although standard carotid duplex ultrasonography is primarily used to identify occlusive carotid plaque (advanced atherosclerosis), CCA-IMT assessment measures arterial wall thickening (pre-atherosclerosis) and non-occlusive plaque formation (subclinical atherosclerosis).

According to data published after the completion of major epidemiologic studies as the Atherosclerosis Risk in Communities (ARIC) Study [25, 26], the European British Heart Study [27] and the Rotterdam Study [28], the increase in IMT not only correlates with most of the known atherosclerotic risk factors such as systolic hypertension, total and Low Density Lipoprotein (LDL) cholesterol levels, cigarette smoking, high-sensitivity C-reactive protein (hsCRP) levels, diabetes, and others, but also increases the risk of cardiovascular events. The results of the ARIC Study show that with an increase of 0.19 mm of the IMT, the risk of coronary disease increases by 69% in women and 36% in men [25, 26]. The risk of stroke is 8.5 times higher for women and 3.6 times higher for men with IMT > 1 mm, compared with those with IMT <0.6 mm.

In classic screening procedures, there is a strong tendency to concentrate on modifiable risk factors, especially when the data collection is relatively simple and easily available (*e.g.,* blood samples or blood-pressure measurements). However, when patients are treated actively, those classic risk factors can lose their predictive value. Although levels of known CV risk factors vary in South Asians, they do not fully explain the differences in CAD rates [29]. The traditional approach to CAD risk assessment is based on identifying and to a certain extent quantifying established CV risk factors. Several algorithms based on this approach are used [30, 31]. Among these, the Framingham Risk Assessment Model is the most widely accepted. Although used extensively and generally accepted, this model (as well as other algorithms based on similar approaches) has limitations. It is derived from a white Caucasian population in the US and may be less applicable to other ethnic groups. Family history, abdominal adiposity, inflammation, CCA-IMT and other factors shown to predict CV risk [31-33] are not incorporated in the Framingham risk score (FRS). Diabetes and smoking are identified only as present or absent, although current evidence supports a continuous relationship between glycemia and tobacco exposure to CAD risk [34, 35]. Age is the overriding FRS determinant, ignoring the greater inter-individual variation in atherosclerotic burden at older ages and often providing false reassurance at younger ages. Importantly, the FRS only predicts short-term (10-year) risk, although from a clinical perspective the life-long risk of developing CAD events is equally relevant [36]. Early detection of sub-clinical CAD in high risk South Asian at a young age could help prevent CV events and substantially reduce the level of death and disability attributable to CAD. Imaging of arteries to identify and quantify the presence of subclinical atherosclerosis has been suggested to further refine CV risk assessment. Limited published data is available looking into the associations of CV factors with CCA- IMT in South Asians, especially in SAI groups. Anand *et al.* performed a cross-sectional population study in 1015 Canadian adults of Caucasian European, South Asian, Chinese and Aboriginal ancestry [35]. This study showed that 22% of SAIs who were categorized as low risk based on FRS had CCA IMT values of ≥75th percentile for age, sex and ethnicity. Furthermore, CCA-IMT has been shown to be independently associated with CAD in South Asians [36] and is a reproducible clinical tool to evaluate atherosclerosis, predict coronary artery disease and show the effectiveness of medical therapies [30, 37, 38]. We have shown in several of our studies on SAIs in the US that even without CAD or diabetes, positive CCA-IMT (≥ 0.8 mm) was seen in 40% of homogeneous multi-ethnic SAI groups [39]. Moreover, positive CCA-IMT was also found to be associated with dysfunctional HDL (Dys-HDL) after adjusting for age, family history of cardiovascular disease, and hypertension (p=0.030) [40].

Increased CCA- IMT measurements have been employed to predict the extent and severity of CAD and have been found to be strongly associated with an increased risk of CV morbidity and mortality [41]. Similarly, reductions in CCA-IMT thickness have been correlated with decreased CAD morbidity and mortality and used as an end point surrogate marker of atherosclerosis regression and dyslipidemias improvement in patients on lipid lowering therapy including SAIs [42]. There is need to identify sub-clinical CAD using atherosclerosis surrogate markers like CCA-IMT in SAIs that will help identify high-risk population for early preventive strategies to reduce future risk of CAD.

Normal CCA-IMT values have been defined on the basis of age and gender distribution curves within a general healthy population, as reported in the ARIC study [43]. The ASE consensus statement concludes that CCA-IMT values

that are ≥75th percentile suggest risk higher than that predicted by the FRS and should be regarded as "high" values [24]. Values that fall within the 25th to 75th percentile range are considered "average" and should not affect traditional risk estimates. Values that are ≤25th percentile are "low" and suggest risk lower than that predicted by the FRS. One of the biggest challenge faced by cardiologists and vascular physicians is how best to interpret the results of trials using CCA-IMT as the primary end point. Another challenge is how to integrate new imaging measures such as CCA-IMT into clinical practice. The ASE concluded that measuring CCA-IMT and identifying carotid plaque may be useful in evaluating CV risk in the following patient populations [24]; (1) patients with intermediate cardiovascular disease risk (6% to 20% 10-year risk for myocardial infarction by the FRS), (2) patients with family histories of premature CVDs in first-degree relatives; (3) patients aged <60 years with severe single–risk factor abnormalities (i.e., genetic dyslipidemia), who would otherwise not be candidates for pharmacotherapy; and (4) women aged <60 years with ≥2 cardiovascular disease risk factors. In addition, consensus statement also suggests that CCA-IMT can be used if the "burden of subclinical vascular disease" is unclear or if evaluation for the degree of aggressiveness of therapy is needed [24] CCA-IMT measurement has not been recommended for patients in whom the results would not change treatment, such as patients with established CAD.

It is important to recognize that current recommendations for the clinical use of CCA-IMT are based on observational studies. The use of CCA-IMT ultrasound measurement visualizes the long-term effects of different risk factors on the arterial wall and on the development of atherosclerotic changes in a given patient. It allows the presence of atherosclerosis to be detected almost directly and, to some extent, semi-quantitatively. Due to slow changes, CCA-IMT demonstrates the "overall atherosclerotic burden" and reflects the risk of death and of other CV events, even when classic risk factors are successfully corrected by therapeutic interventions. Ultimately, prospective trials comparing the effectiveness of CCA-IMT as a predictive tool of CV risk with that of other novel markers would best direct clinical recommendations for this imaging measure

INFLAMMATORY BIOMARKERS

SAIs have higher CAD morbidity and mortality rates and conventional risk factors do not explain this excess risk. Thus, much attention has focused on whether plasma levels of circulating markers of vascular inflammation may help identify SAIs at high risk for future CV events. Inflammation plays a central role in mediating all phases of atherosclerosis, from initial recruitment of circulating leucocytes to the arterial wall to the eventual rupture of the unstable plaque. I hereby present recent updates on C-reactive protein (CRP) and dysfunctional HDL with special focus on SAIs in determining vascular events and the potential use of inflammatory bio-markers for cardiovascular risk prediction.

C - Reactive Protein (CRP)

C-reactive protein (CRP) is a classical acute phase reactant and a member of the pentraxin family of innate immune response proteins [44, 45]. CRP is mainly produced in the liver in response to interlukin 6 IL-6 and thus has been thought of as an inactive downstream, by-stander marker of the inflammatory cascade. However, recent data suggest that CRP may play a direct role in atherogenesis. CRP is a prototypic marker of inflammation. Numerous prospective studies in healthy volunteers have confirmed that high-sensitivity CRP (hsCRP) predicts CV events, and hsCRP seems additive to an elevated total cholesterol level and a total/high-density lipoprotein (HDL) cholesterol ratio in men and women [46]. In smokers and people with metabolic syndrome, hsCRP levels are elevated; in elderly people, there seems to be a relationship between hsCRP and CV events and mortality [47]. Several properties of CRP make it proatherogenic; however; pending further studies, it should be considered as a risk marker [48]. In people with acute coronary syndromes, hsCRP measurement may be valuable [46]. Elevated levels in the highest quantile seem to predict greater mortality and poorer prognosis in patients with unstable angina and MI. While hsCRP is a strong independent predictor of risk of future MI, stroke, peripheral arterial disease, and vascular death, the validity of hsCRP as a risk marker needs to be assessed in all populations. Weight loss, statin drugs, aspirin, and high-dose alpha tocopherol therapy could affect hsCRP [48]. It has its greatest validity as an adjunctive measure in the primary prevention of cardiovascular disease. Data from two large statin trials suggest that testing for CRP may identify many patients without hyperlipidaemia who are at high risk for future cardiovascular events and who may benefit from statin therapy [49]. Once confirmed in ongoing large-scale prospective trials, screening for inflammation using CRP as a biomarker could prove an important adjunctive method for identifying individuals at increased risk who would benefit most from targeted preventive interventions. Research on CRP is even more relevant in South Asians in general and SAIs in particular, since they are at high risk for the development of metabolic syndrome, type 2 diabetes and CAD [50]. Sub-clinical inflammation is a recent addition to the long list of risk factors in SAIs. CRP levels in SAIs were reported to be higher than in Europeans [51, 52]. However, the precise significance of high CRP levels in SAIs is not known and definitive answers would be provided by the prospective studies correlating CRP levels in SAIs to the CV endpoints and glucose intolerance in long-term prospective studies. Further, whether high CRP levels alone in young SAIs would influence future CV risk is not known. In summary, emerging evidence suggests that CRP is a robust marker for the prediction and prognosis of CAD and type 2 diabetes however its impact remains to be ascertained. However, the significance of elevated CRP levels as a marker for CAD in populations exposed to repeated and persistent infections in childhood is not clear. There is ongoing debate about the added value of measuring CRP concentrations to improve risk prediction, and that it may be premature.

Dysfunctional HDL (Dys-HDL)

High density lipoprotein (HDL) is a heterogeneous lipoprotein, containing several surface apolipoproteins (Apo AI, AII, AIV, C, E, J, and D). Apolipoprotein A-I (Apo A-I) is the principle protein of HDL, which also carries enzymes, such as paraoxonase 1 (PON 1), platelet activating factor (PAF) –acetyl hydrolase, lecithin cholesterol acyl transferase (LCAT), and cholesteryl ester transfer protein (CETP). Dif-

ferences in HDL particle size result mainly from the number of apolipoprotein molecules and the volume of the cholesterol ester in the core of the particle [53].

1. HDL has antioxidant, anti-inflammatory, and anti-thrombotic properties that contribute to its function as an anti-atherogenic agent. Although our understanding of how HDL protects against CAD is still incomplete, evidence supports at least three major athero-protective mechanisms of HDL.
2. HDL is an integral component of the reverse cholesterol transport process, functioning as a carrier of excess cellular cholesterol from peripheral tissues to the liver, where it is excreted from the body as bile acids and cholesterol. More specifically, HDL mediates efflux of cholesterol from cholesterol-loaded macrophages by passive diffusion, through scavenger receptor B1 (SR B1), and, most significantly, *via* the protein Apo A-I [54, 55]. Apo A-I functions through an ATP-binding cassette transporter A1 (ABCA1) in the vessel wall, where it accepts free cholesterol, forming pre-beta HDL that matures after esterification to cholesteryl esters (CE) and then by lecithin-cholesterol acyltransferase to alpha migrating HDL [55].
3. A series of antioxidant enzymes which protect LDL from oxidation are associated with HDL. Oxidized lipids are transferred to HDL from LDL and are hydrolyzed by HDL-associated PON1, LCAT, and platelet activating factor (PAF) acetylhydrolase enzymes [56-58].file:///C:/HDL study/understanding hDL.htm - R26-3425 The activities of these enzymes destroy oxidized lipids and also inhibit their formation. Removing the oxidized lipids initiates a positive feedback loop that results in further activation of the enzymes and further destruction of the oxidized lipids. In addition, Apo A-I reduces lipid peroxides within LDL, independent of PON1 [59].

HDL may protect against CAD by selectively decreasing endothelial cell adhesion molecules, which facilitate the binding of mononuclear cells to the vessel wall and promote lesion development [60].

However, according to several recent studies, in patients with CAD, HDL is not only ineffective as an antioxidant but, paradoxically, appears to be pro-oxidant, as assessed by its lipid peroxide content [61-64]. In addition, HDL from patients with a history of CAD enhances the oxidation of LDL and of phospholipids in LDL [62]. This pro-inflammatory HDL, which is dysfunctional, accumulates oxidants that inhibit HDL-associated antioxidant enzymes, render Apo A-I unable to promote ABCA1 mediated cholesterol efflux, and promotes the formation of LDL-derived oxidized lipids. What makes HDL become dysfunctional is not clearly understood, however it has been hypothesized that a certain variant of Apo A-I susceptible to oxidation and nitration could be the culprit [65]. Current data indicates that a 1% increase in HDL serum concentration can decrease cardiovascular risk by 2-3%, independent of LDL levels [53]. However, HDL can have this protective effect only if it is functional. The incidence of dys-HDL in SAIs is not known, however several of the recent studies have shown prevalence of Dys-HDL in SAIs upto 50% in a group without CAD [40]. Moreover, small available data have shown Dys-HDL association with CCA-IMT [37]. Considering Apo-A-I polymorphisms as a hypothesized cause of Dys-HDL, data in SAIs found six novel single nucleotide polymorphisms (SNPs) in Apo-A-I gene. One of those showed association with low HDL in SAIs [65], however association of Apo-A-I polymorphism with Dys-HDL is still work under progress and needs larger prospective studies.

CONCLUSIONS

Given that SAIs are known to carry a disproportionately high risk for CAD and that traditional CAD risk factors may not fully explain the excess risk, there is a need to explore and understand other non-traditional risk factors. SAIs are under-represented in major clinical trials, and evidence-based management strategies of CAD in this population are lacking. Most clinicians are aware of the low HDL levels in this group, but whether this is due to isolated low HDL levels, high total cholesterol/HDL ratio, or an elevated non-HDL level, is not known. Moreover, the quality of HDL and its role in CAD protection is rapidly emerging. The time has now come for CAD to be considered the number one public health problem in SAIs, the second largest Asian immigrant population in the US. Emerging data from some well-planned community-based investigations have emphasized the gravity of this rapidly increasing epidemic. The good news is that the epidemiologic studies have already shown that the bulk of the CAD can be prevented or at least its manifestations can be delayed. A multidisciplinary approach towards improving lifestyle methods involving the population at risk, healthcare personnel, and the government is required to diminish the incidence. From SAIs' perspective, there is a need for implementation of newer guidelines as well as lowering the threshold for initiating therapeutic interventions. IMT may be helpful in predicting the occurrence of CV events in SAs that are asymptomatic but at a high risk due to additional factors after controlling for factors such as sex, age, any other clinical conditions and drug treatment the patient may be undergoing. IMT would be a good tool for therapeutic intervention, for monitoring the efficacy of statins, ACE inhibitors and other drugs in SAs. However, the assessment needs to take into account long term effects in IMT for the same patient, to control for any pre-existing conditions that may cause inflammation [66]. With respect to the potential value of novel risk factors for CV risk prediction, we illustrate why this work is very much in its infancy and currently not guaranteed to reach clinical utility. Indeed, the existence of several more powerful and easily measured predictors of diabetes, suggests that the additional value of novel markers may be limited. Ultimately, prospective trials comparing the effectiveness of CCA-IMT as a predictive tool of CV risk with that of other novel markers would best direct clinical recommendations for this imaging measure. Nevertheless, several suggestions to improve relevant research are given. CCA-IMT is a noninvasive surrogate marker of atherosclerosis and proven to be helpful in detecting sub-clinical CAD by stratifying populations at highest risk for CAD. In addition, determining the presence of Dys-HDL in SAIs will answer several questions related to the presence of altered HDL level and function. This information will not only help to stratify this high risk asymptomatic group, but will also be useful from a disease management point of view.

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