

Can Conventional Risk Factors Explain Excess Coronary Artery Disease Risk in South Asians: Dyslipidemias and Dysfunctional High Density Lipoprotein (HDL)

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Abstract: Over the past several years, the overall prevalence and incidence of cardiovascular diseases in general and coronary artery diseases (CAD) in particular have declined in the United States (US). However, among South Asian in general and South Asian immigrants in particular, a disturbing trend toward high rates of CAD has been noted. This trend is associated with a high prevalence of conventional risk factors and metabolic syndrome in this population, yet these conventional risk factors may not account for the greater CAD risk among SAIs. A search for additional markers is warranted, to enable early detection and prevention of CAD in this high risk group. High density lipoprotein (HDL) is one of the predictor of CAD and is considered to be cardio-protective. However, some of the recent studies have shown that HDL is not only *ineffective* as an antioxidant but, paradoxically, appears to be pro-oxidant, and has been found to be associated with CAD. Such HDL is called dysfunctional HDL. More research is required in South Asians to explore associations with CAD and to enhance early detection and prevention of CAD in this high risk group. We present here an overview on risk factors of CAD in general and dyslipidemias in particular in South Asians. In addition, concepts on dysfunctional HDL and its impact on CAD are also presented. At the end, recommendations are made to improve and prevent CAD morbidity and mortality in the South Asian communities.

INTRODUCTION

Among cardiovascular diseases, coronary artery disease (CAD) is the leading cause of death in the United States (US), and certain populations, such as South Asians, African Americans, and Hispanics, carry a disproportionately larger burden of CAD [1-3]. Even though CAD event rates have decreased by 50% in the US and other developed countries over the past 30 years, rates have doubled in South Asians-people with ancestors from the Indian subcontinent (i.e. India, Pakistan, Bangladesh and others), and have risen even more among South Asians who immigrate to the US [2]. The mortality rates from CAD in South Asians are reported to be two to three times higher than those for Caucasians, irrespective of gender, religion, social class, dietary practices or country of residence [3, 4]. This higher prevalence is seen in South Asians living in the United States, as well as, in those living in India, and rates are similar among vegetarians and non-vegetarians [3-8]. South Asian Indian women in California have the highest death rate from CAD in the United States, higher than Caucasians, Blacks, Hispanics, and Native Americans [9]. Specifically, 33% of all deaths among Indian women are due to CAD compared with 11% among Japanese, 16% among Chinese, and 20% among Hispanics, Blacks, and Caucasians [9]. In California, South Asian immigrants have the highest rate of hospitalization for CAD, and Chinese have the lowest rate. Intermediate rates have been reported for Caucasians, Japanese, and Filipinos [9].

The high rates of CAD among South Asian immigrants are not limited to the United States and appear to be part of a global phenomenon [10]. Further, CAD risk factors are present in South Asians at a younger age compared to other populations, resulting in CAD at a younger age than in other populations [3]. The reasons for early development of CAD risk factors at a relatively young age in South Asian immigrants are still unclear.

More than 3.6 million South Asians live in the United States, and although this group represents the second fastest growing Asian immigrant population, little is known regarding their increased risk for CAD [2]. There has been much speculation about what causes the increased occurrence of and mortality from CAD in South Asian immigrants. Differences in CAD and stroke mortality between South Asians in other countries and those in South Asian countries could be due to either the effect of a new environment triggering latent susceptibilities that weren't triggered in the home country, or merely an effect of environmental and behavioral changes due to immigration on the incidence of these diseases. Not uniform groups, South Asians include ethnic subgroups with different cultures and practices, and the prevalence of recognized risk factors for CAD varies among the subgroups [8, 10-12]. As a whole, however, South Asians and South Asian immigrants have a much higher prevalence of diabetes, insulin resistance, central obesity, dyslipidemias (increased lipoprotein [a], higher triglycerides), increased thrombotic tendency (increased plasminogen activator inhibitor-1 and decreased tissue plasminogen activator levels), decreased levels of physical activity, and lower birth weights, commonly known as "fetal origins hypothesis syndrome" [3, 8, 11-17].

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predictive value. Here we present the review of HDL role in preventing CAD and theories underlying dysfunctional HDL concepts. In this paper, dysfunctional HDL (Dys-HDL) and pro-inflammatory HDL terms are used inter-changeably

HDL ROLE IN CAD

HDL is a heterogeneous lipoprotein, containing several surface apolipoproteins (Apo A-I, AII, C, E, AIV, 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) -acetylhydrolase, lecithin cholesterol acyltransferase (LCAT), and cholesteryl ester transfer protein (CETP). Differences 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 [30].

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 (Table 1).

1. 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 [40, 41]. 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 [42].
2. 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 [44-49]. 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 [45].
3. 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 [44, 45, 50].

EVIDENCE THAT HDL MAY NOT BE PROTECTIVE: PRO-INFLAMMATORY HDL

According to several recent studies, in patients with CAD, HDL is not only *ineffective* as an antioxidant but, paradoxically, appears to be pro-oxidant, promoting LDL oxidation and monocytes chemotactic activity in the human artery wall as well as increase in HDL lipid hydroperoxides,

as assessed by its lipid peroxide content [51-55]. In addition, HDL from patients with a history of CAD enhances the oxidation of LDL and of phospholipids in LDL [51, 53]. 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 [55]; (Figs. 2, 3). The mechanisms underlying this phenomenon are not completely understood. One of the hypothesized mechanisms involves myeloperoxidase [56]. Apo A-I is targeted by myeloperoxidase, and, when oxidized and nitrated, impairs ABCA1-dependent cholesterol efflux [56]. Furthermore, exposing HDL or Apo A-I to myeloperoxidase almost entirely prevents ABCA1-dependent reverse cholesterol transport [55]. It has been hypothesized that a certain variant of Apo A-I is susceptible to oxidation and nitration [57].

Table 1. Pleiotropic Effects of HDL

	HDL	Key References
Cell proliferation	↑ proliferation, ↓apoptosis	[41, 42]
Vascular tone	↑ NO, ↑ PGI ₂	[43, 44]
Inflammation	↑ VCAM-1, ↑ ICAM-1, ↓ E-selectin, ↑ TGF-β2	[40, 44, 45, 50]
Coagulation, fibrinolysis	↑ TF, ↓ PAF, ↑ activated protein C, ↑ protein S	[40]
LDL oxidation	↓ metal ions mediated oxidation	[39, 40, 4144]
	↓ 12-Lox mediated oxidation	
	Scavenge of lipid peroxides and LPC, PON, PAF-AH and GPX	

CETP= Cholesteryl ester transfer protein, GPX= Glutathione peroxidase, HL= Hepatic lipase, HPETE = Hydro-peroxy eicosatetraenoic acid, HPODE = Hydroperoxyoctadecadienoic acid, PON = Paraoxonase, PAF-AH = Platelet activation factor acetyl hydrolase, PS = Phosphatidylserine, PC = Phosphatidylcholine, PLTP= Phospholipid transfer protein, LCAT= Lecithin-cholesterol acyltransferase, SR-BI= Scavenger Receptor type BI, Lox= Lipoxigenase.

The diagnosis of dysfunctional HDL has historically been made with a cell-based assay that requires endothelial cells, smooth muscle cells, and monocytes. However, the use of a cell-based assay is not practical for large-scale studies. Recently, a cell free assay was developed to detect HDL that is dysfunctional in preventing the formation or inactivation of oxidized phospholipids [58, 59]. This is a rapid test for HDL function that does not require cells and gives results highly comparable to those of the previously described cell-based assay [58]. Using this assay, investigators determined that HDL from patients with documented CAD was pro-inflammatory, while HDL from normal subjects was anti-inflammatory. These patients had normal levels of blood lipids, had no major risk factors for CAD, and therefore, would not have been predicted to be at risk for atherosclerosis by conventional risk factor analysis. In short, the new cell-free assay has the potential to allow wide-spread testing for HDL that is dysfunctional and identification of individuals at risk for CAD.

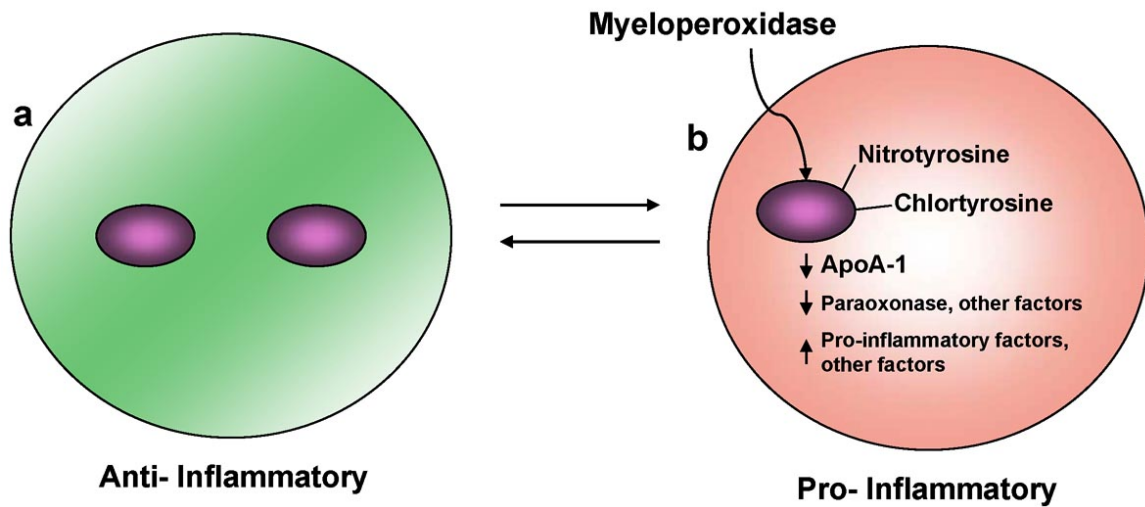


Fig. (2). Dysfunctional HDL and it's adverse effects.

Fig. (3). Model of bidirectional conversion of high-density lipoprotein (HDL) from anti-inflammatory (a) to pro-inflammatory (b) Modified from Fogelman *et al.* Nat Med 2004 Sep; 10(9): 902-3.

The inflammatory/anti-inflammatory properties of HDL can be determined by calculating HDL inflammatory index [58, 59]. This index is calculated by normalizing the cell-free assay values obtained for a standard LDL alone to <1.0. Using normalization procedure, a test HDL is classified as pro-inflammatory (dysfunctional) when addition of the test HDL along with an LDL standard to the assay results in a normalized value of 1.0 or greater. Conversely, a value less than 1.0 classifies the test HDL as anti-inflammatory. In recent studies of Caucasians and Chinese Asians with CAD, HDL was not only found to be *ineffective* as an antioxidant but, paradoxically, appeared to be pro-oxidant [58, 60]. The Association of Dys-HDL has also been seen in metabolic syndrome, diabetes, systemic lupus erythematosus and other diseases causing systemic infection [61-68]. This pro-inflammatory HDL or Dys-HDL accumulates oxidants that inhibit HDL-associated antioxidant enzymes, render Apolipoprotein A-I (Apo A-I), the main protein component of HDL unable to promote ABCA1 mediated cholesterol efflux (Fig. 3), and promotes the formation of LDL-derived oxidized lipids [58, 59]. Association of Dys-HDL with CAD has been seen in small scale studies of Caucasians [58, 59, 69].

PRO-INFLAMMATORY (DYSFUNCTIONAL) HDL IN SOUTH ASIAN IMMIGRANTS?

The current data indicates that a 1% increase in HDL serum concentration can decrease cardiovascular risk by 2-3%, independent of LDL levels [30]. However, HDL can have this protective effect only if it is functional. The incidence of pro-oxidant or pro-inflammatory HDL (dysfunctional HDL) in South Asian immigrants is not known.

A small study done on South Asian immigrants without CAD showed inflammatory index values of ≥ 1.00 in 50 percent (95% CI 0.8772, 1.4333) suggesting pro-inflammatory HDL [70, 71]. In addition, pro-inflammatory HDL (≥ 1.00) was associated with sub-clinical CAD, using IMT values ≥ 0.80 mm as surrogate marker for CAD ($p=0.04$) [42]. The mean HDL inflammatory Index was 0.8772 in the group with CAD and 0.6269 in the group without CAD.

Given that animal and small-scale human studies suggest that measures of the quality and functionality of HDL can provide an improved means of identifying subjects at increased risk for atherosclerotic events, compared with the current practice of only measuring the level of HDL [32], the level of dysfunctional HDL and its association with CAD in South Asian immigrants needs to be explored in bigger studies. Given the results of small studies, we can hypothesize that South Asian immigrant populations have a high prevalence of dysfunctional HDL and that this could be related to their excessive risk of CAD. Similarly, South Asian immigrants carry an increased prevalence of metabolic syndrome and diabetes (sub-clinical chronic inflammation) as compared to other groups, therefore, we predict that this population has increased dysfunctional HDL that could be related to coronary events [16, 18, 19]. Patients with metabolic syndrome tend to have dysfunctional HDL (pro-inflammatory HDL) more often than controls [62]. Identification of dysfunctional HDL and its association with CAD and metabolic syndrome in South Asian immigrants will help to identify high risk individuals; high risk that cannot be explained by

traditional risk factors. Patients found to have dysfunctional HDL and no other CAD risk factors can be targeted for early lipid lowering treatment which has been shown to improve HDL anti-inflammatory function [59, 60, 69].

APO A-I AND GENE POLYMORPHISMS

Apo A-I (APOAI gene, Apo A-I protein) is the major protein of HDL and consists of 243 amino acid long peptide, synthesized mainly in the liver and to some extent in the small intestine. The inverse relationship between HDL plasma levels and CAD has been attributed to the role that HDL and its major constituent Apo A-I play in reverse cholesterol transport (RCT). The efficiency of RCT depends on the specific ability of Apo A-I to promote cellular cholesterol efflux, bind lipids, activate lecithin: cholesterol acyl-transferase (LCAT), and form mature HDL that interacts with specific receptors and lipid transfer proteins [72-78]. The APOAI gene is present along with the APOC3 and APOA4 genes, on chromosome 11(11q23.3-qter). It has also been shown that the A allele of the APOAI gene contributes to the severity of CAD and low levels of HDL among Northern Indians [75].

Epidemiological studies have shown that HDL and Apo A-I levels are inversely correlated with the risk of developing CAD [57, 67, 68, 72]. Although various factors such as genetic variations, diet, exercise, alcohol, smoking, hormones, and certain drugs can significantly influence the levels of HDL and Apo A-I [76], family and twin studies have demonstrated a strong genetic heritability, accounting for up to 66% of the variability of HDL and Apo A-I levels [77-79]. Furthermore, 40-60% of the inter-individual variation in HDL concentrations is controlled at the genetic level [80, 81] and the strong positive correlation between plasma levels of Apo A-I and HDL suggests that Apo A-I gene polymorphisms may be linked to variability in HDL levels as well as to dysfunction [57, 67, 72].

More than 40 mutations in Apo A-I have been identified in several ethnic populations [82-88] each producing differing HDL activity and levels. Apo A-I gene mutations are separated into three classes. Class I includes mutations that prevent the formation of Apo A-I; class II defects lead to expression of a truncated Apo A-I protein; and class III defects result in an altered functional state of Apo A-I. Not surprisingly, class I mutations are associated with CAD, xanthomatosis, and corneal opacifications, whereas class II mutations exhibit variable phenotypes [84-88]. Mutations affecting the structure of Apo A-I (nonsense mutations with premature stop codons or large genomic deletions) result in an absence of Apo A-I in plasma and a marked reduction in HDL levels [88]. Interestingly, of the 12 mutations that truncate Apo A-I, not all are associated with CAD. Further, several point mutations have been identified [80-83], and one in particular is associated with low levels of HDL but not with an increased CAD risk and is, instead, associated with a reduction in CAD risk [84]. This Apo A-I mutation is called Apo A-I milano (Apo A-I_{Arg 173 Cys}).

APO A-I POLYMORPHISMS IN SOUTH ASIAN IMMIGRANTS

A majority of the studies on Apo A-I polymorphisms and their association with HDL level and CAD have been carried

out in Caucasian and other populations. The association of Apo A-I gene polymorphisms with carotid IMT as a surrogate marker for atherosclerosis has been examined, but not fully. For example, Apo A-I (L178P) was found to be associated with high IMT measurements ($p < 0.001$) in a European population, however due to the small sample size, results can not be generalized [86]. Similarly, Apo A-I/C-III/A-IV SstI polymorphism was found to be associated with high carotid IMT measurements in a study of a young Finnish population [87]. However, the role of Apo A-I polymorphisms in individuals with metabolic syndrome and its association with dysfunctional HDL has not yet been fully studied. A few studies have examined Apo A-I polymorphisms in native populations of South Asians from India, however, to our knowledge, no study has examined Apo A-I polymorphisms in South Asian immigrants and its association with dysfunctional HDL, IMT, or CAD. Polymorphisms in Apo A-I and other lipid metabolism-related genes have been suggested to be clinically useful in assessing an individual's risk for cardiovascular disease and in conducting genetic-epidemiological evaluations [85].

Given that South Asian immigrants are significantly under-represented in major clinical trials, evidence-based management strategies for treatment and prevention of CAD specifically in this population is seriously lacking. A literature search for Apo A-I gene mutations in South Asian populations yielded a small solo study that showed polymorphisms in the Apo lipoprotein C-III promoter gene that were associated with features of metabolic syndrome in South Asian Indians, however, the relationship of these polymorphisms to CAD was not examined [86-89]. A recent small study conducted on Pakistanis suggested that the promoter region of the Apo A-I gene may play a role in determining blood pressure [90]; however, due to insufficient power, these results cannot be generalized. Chhabra and colleagues [91] found a correlation between the expression of the Apo A-I G-75A polymorphism in northern Indians, the severity of CAD, and low levels of HDL; however this study was restricted to one ethnic group and relationship was not examined in other ethnic groups. Studies have shown that South Indians carry more CAD risk as compare to North Indians [35].

In small study on South Asian immigrants, six novel polymorphisms were identified, one of which, G4 (C938T), was significantly associated with low (< 40 mg/dl) HDL levels ($p=0.03$) [92]. Further research is required to explore Apo A-I polymorphisms in South Asian immigrants and correlate possible associations with dysfunctional HDL and CAD. Moreover, the identification of these genes may lead to screening tests that will allow persons at risk for developing CAD to be identified early enough that prevention/intervention strategies can be implemented to prevent or ameliorate the disease process, and may also lead to the development of gene therapy mechanisms useful in the treatment of CAD in South Asian immigrants.

CONCLUSION

South Asian immigrants are the second fastest growing Asian immigrant population in the United States, constituting a large, visible minority, and are known to be at heightened risk for premature CAD. Conventional risk factors clearly confer risk in South Asians but do not adequately

explain their excess risk compared with other populations. New risk factors and markers like dysfunctional HDL, known genetic polymorphisms though shown to be linked with CAD; however greater research is required in South Asians. The rates of CAD have accelerated dramatically amongst South Asians, driven to an important extent by the atherogenic dyslipidemia and type 2 diabetes that have become so common amongst them. South Asians may have a genetic predisposition to CAD; however, environmental, nutritional, and lifestyle factors may also be responsible. South Asians have a much higher prevalence of metabolic syndrome, diabetes, insulin resistance (and resultant hyperinsulinemia), central obesity, dyslipidemias (lower high-density lipoprotein, increased lipoprotein[a], higher triglyceride levels), increased thrombotic tendency (increased plasminogen activator inhibitor-1 and decreased tissue plasminogen activator levels), decreased levels of physical activity, and low birth weights. In addition, the dietary indiscretions and sedentary lifestyle practiced by most South Asians puts them at a higher risk. A multidisciplinary approach involving the population at risk, healthcare personnel, and the government is required to diminish the incidence.

The key to combating the increasing incidence of CAD among South Asians is early diagnosis and treatment of CAD risk factors to prevent future CAD morbidity and mortality. An aggressive treatment of known risk factors through both an individual-based as well as a population-based approach aimed at comprehensive risk factor reduction is needed. The Assessment of dysfunctional HDL and its association with coronary artery diseases in a larger South Asian immigrant population is under way. In addition, further research is needed to discover new risk factors like dysfunctional HDL that can be responsible for an excess CAD risk not explained by conventional risk factors.

ACKNOWLEDGEMENTS

I would like to thank Ms. Cathey Ellis, my Office Specialist for her help in editing and format this manuscript.

AUTHORS' CONTRIBUTIONS

SD conceived the idea and wrote whole paper including literature search.

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Received: July 22, 2008

Revised: September 3, 2008

Accepted: January 15, 2009

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