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REVIEW

Lipoprotein abnormalities in South Asians and its association with cardiovascular disease: Current state and future directions

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Abstract

South Asians have a high prevalence of coronary heart disease (CHD) and suffer from early-onset CHD compared to other ethnic groups. Conventional risk factors may not fully explain this increased CHD risk in this population. Indeed, South Asians have a unique lipid profile which may predispose them to premature CHD. Dyslipidemia in this patient population seems to be an important contributor to the high incidence of coronary atherosclerosis. The dyslipidemia in South Asians is characterized by elevated levels of triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, elevated lipoprotein(a) levels, and a higher atherogenic particle burden despite comparable low-density lipoprotein cholesterol levels compared with other ethnic subgroups. HDL particles also appear to be smaller, dysfunctional, and proatherogenic in South Asians. Despite the rapid expansion of the current literature with better understanding of the specific lipid abnormalities in this patient population, studies with adequate sample sizes are needed to assess the significance and contribution of a given lipid parameter on overall cardiovascular risk in this population. Specific management goals and treatment thresholds do not exist for South Asians because of paucity of data. Current treatment recommendations are mostly extrapolated from Western guidelines. Lastly, large, prospective studies with outcomes data are needed to assess cardiovascular benefit associated with various lipid-lowering therapies (including combination therapy) in this patient population.

Key words: Dyslipidemia; South Asians; Asian Indians; Cardiovascular disease

Core tip: South Asians have a high prevalence of coronary heart disease (CHD) and suffer from early-onset CHD. Indeed, an important contributor is their unique lipid profile which is characterized by elevated levels of triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, elevated lipoprotein(a) levels, a higher atherogenic particle burden despite comparable low-density lipoprotein cholesterol levels compared with other ethnic subgroups. HDL particles also appear to be smaller, dysfunctional, and proatherogenic. Despite the rapid expansion of the current literature with better understanding of the specific lipid abnormalities in this patient population, specific management goals and treatment thresholds do not exist for South Asians because of paucity of data. Current treatment recommendations are mostly extrapolated from Western guidelines. Lastly, large, prospective studies with outcomes data are needed to assess cardiovascular benefit associated with various lipid-lowering therapies (including combination therapy) in this patient population.

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INTRODUCTION

The term "South Asian" refers to people who have ancestral origins in the Indian subcontinent (the countries of India, Pakistan, Bangladesh, Sri Lanka, and Nepal), where 1.6 billion people live. This region constitutes about 1/5 of the world's population. Nearly 3.6 million South Asians live in the United States, and the South Asian population has the highest rates of coronary heart disease (CHD) among all ethnic groups[1]. CHD in this population is usually premature and severe with 3- to 5-fold higher risk of morbidity and mortality[1-4]. The prevalence of CHD is higher in South Asian immigrants compared with the overall United States population, with similar rates among vegetarians and non-vegetarians[4-6]. Interheart, a global case-control study, was performed in 15152 cases with acute myocardial infarction (AMI) and 14820 controls in 52 countries. Of these, 1732 cases and 2204 controls were South Asian. Median age at first AMI was 53 years in South Asia compared with 63 years in both China and Western Europe. The highest proportions of cases with first AMI at age 40 years or younger were in men from the Middle East (12.6%), Africa (10.9%), and South Asia (9.7%), and the lowest proportions were in women from China and Hong Kong (1.2%), South America (1.0%), and central and eastern Europe (0.9%)[7]. These results indicate the magnitude of premature CHD risk in South Asians.

Although CHD rates in the general United States population have declined over the last few decades because of aggressive modification of risk factors and population-based interventions[8], the rates have conversely doubled in South Asian immigrants[3] and remain higher than their counterparts in their country of origin[9-11].

Given the consistent findings of increased prevalence, premature onset, and increased mortality from CHD in South Asians, there has been much interest in determining the underlying causes. Conventional risk factors such as hypertension, hypercholesterolemia, diabetes mellitus, abdominal obesity, metabolic syndrome, and tobacco use have been clearly associated with CHD risk among South Asian populations[7,12].

Other factors such as sedentary life style and dietary influences also play a role. Although a considerable percentage of South Asians are vegetarians, excess sugars and refined carbohydrates remain problematic for this population. Indeed India is among the largest consumers of sugar in the world. Diet rich in sugar and processed carbohydrates may be a considerable threat to the future health and wellness of the increasingly sedentary South Asian people with their innate genetic predisposition to CHD.

Although South Asians represent an heterogeneous population, with varied practices in terms of diet and exercise, they have a much higher prevalence of diabetes, insulin resistance, central obesity, increased thrombotic tendency, and physical inactivity than other populations[1,7,9,13-16]. Conversely, the prevalence of hypertension, smoking, and obesity (using traditional body mass index cut-offs) is lower in South Asians compared with the Western World[5]. Studies comparing South Asians with other ethnic groups have consistently shown that differences in these risk factors do not fully account for the excess incidence of CHD noted in South Asians[1,3,7,17-21]. The Study of Health Assessment and Risk in Ethnic Groups assessed conventional and novel cardiovascular risk factors among 985 participants of South Asian, Chinese, and European descent living in Canada. South Asians had an increased prevalence of glucose intolerance, higher total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride levels, and lower high-density lipoprotein cholesterol (HDL-C) levels compared with Caucasians. These abnormalities only partially explained the high atherosclerosis burden (defined by carotid atherosclerosis measured with B-mode ultrasonography) in this population[14]. Thus, other factors may apply to the increased CHD risk in South Asians. Despite these findings, the INTERHEART study reported the association of smoking, history of hypertension or diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins, and psychosocial factors with myocardial infarction in 9 ethnic populations including South Asians. Dyslipidemia appeared to be the strongest contributor of AMI in South Asians, with a population-

attributable risk of 49.2%[22]. Therefore, dyslipidemia appears to be an important determinant of increased CHD burden in South Asians.

In this article, we review the lipid and lipoprotein abnormalities in South Asian population as a potential cause of increased CHD risk. We also provide a succinct discussion on the efficacy of lipid-lowering therapy in South Asians. In Table 1, we provide references and a brief overview of studies discussed in this review. In Table 2, we summarize major lipid abnormalities in South Asians.

SEARCH STRATEGY

A PubMed/Medline search using key words "South Asian, Asian, Indian, lipids, cholesterol, cardiovascular disease, metabolic syndrome" was conducted. Studies since 1990 were included. Individual studies were initially screened using their titles and abstract content. An initial pool of studies was identified with this methodology. We subsequently reviewed references listed in the selected studies and included them in this review when relevant to the topic. Individual study references known to the authors of this review were also included.

DYSLIPIDEMIA IN SOUTH ASIANS

Total cholesterol, LDL-C and small dense LDL

Hypercholesterolemia (TC > 200 mg/dL) has been reported to have a prevalence of up to 35% in men and 36% in women from South Asian countries[23-25]. LDL-C is a well-established marker for the occurrence, recurrence, and severity of CHD. It is the co-primary target for lipid-lowering therapy as per the National Lipid Association recommendations for cholesterol management[26].

Elevated LDL-C levels clearly predict CHD risk in the South Asian population[17,22,27,28]. In various reports, LDL-C levels have been found to be either similar[5,29-32] or lower[33] among South Asians compared with Caucasians. Compared with Caucasian participants in the Framingham Offspring Study, LDL-C level and LDL particle size were similar in South Asians (LDL-C level: 139 ± 33 mg/dL *vs* 135 ± 31 mg/dL, respectively, $P < 0.10$; and LDL particle size: 20.6 nmol ± 0.7 *vs* 20.7 nmol ± 0.6, respectively, $P < 0.08$)[31]. LDL-C levels did not discriminate between Asian Indian and non-Asian Indian males[30]. On the other hand, studies have shown that CHD may appear at relatively lower LDL-C levels in South Asians. As shown in the INTERHEART study, although the overall associations between LDL-C and risk for AMI were similar among South Asians and others, South Asians had LDL-C levels that were on average 10 mg/dL lower than other groups. Interestingly, the proportion of cases and control subjects from Asia who had LDL-C levels < 100 mg/dL was 25.5% and 32.3% respectively, compared with 19.4% and 25.3% in non-Asians, with consistent results in both sexes[22]. These results indicate that although LDL-C is associated with AMI risk in South Asians, the risk is elevated even at a much lower LDL-C level compared with other ethnic groups.

Another study analyzed metabolic profile in 1066 Indian patients of whom 877 had CHD and 189 did not have CHD. The 50th percentile for TC was 205 mg/dL for the cases and 186 mg/dL for controls, while for triglycerides, the 50th percentile was 158 mg/dL for cases and 140 mg/dL for controls, thus suggesting the occurrence of CHD in this patient population at relatively lower levels of cholesterol[34].

Why South Asians carry a higher CHD risk at a given LDL-C level remains a question. One of the postulated mechanisms is that South Asians carry a higher LDL particle burden at a given LDL-C level. Smaller LDL particles are denser and may be more atherogenic[35]. A small study showed that the prevalence of small dense LDL, (defined as LDL subclasses 5 and 6 as measured by the Vertical Auto Profile test) was significantly higher in Asian Indians ($n = 39$) compared with white subjects ($n = 39$) (44% *vs* 21%, $P < 0.05$)[36]. A nonsignificant trend towards lower LDL particle size as measured by gel electrophoresis was also shown in South Asian adolescent boys compared with age-matched Caucasian adolescent boys[37]. Importantly, the INTERHEART study showed that for any LDL-C level, South Asians had higher apolipoprotein (apo) B concentration compared with other ethnic groups, indicating that for any LDL-C level, South Asians carry a higher number of atherogenic lipoproteins[22].

Therefore, although elevated LDL-C levels predict CHD risk in South Asians as in other ethnicities, the LDL-C levels in general are similar or lower in South Asians compared with other ethnicities. As shown in INTERHEART, a higher LDL-C level, although less frequent in South Asians, carries a similar risk for myocardial infarction as in other ethnic groups. In addition, at any given LDL-C level, South Asians tend to carry a higher total atherogenic burden as noted by higher levels of LDL particles and apo B in some studies as described above.

Triglycerides and HDL-C

HDL-C levels have been associated with a lower risk of CHD, and increasing HDL-C levels and augmenting HDL function have been associated with vascular protective effects[38-41]. Low HDL-C level (< 40 mg/dL) was defined as a CHD risk factor by the National Cholesterol Education Program Adult Treatment Panel Ⅲ guidelines[42]. Conversely, elevated triglycerides (> 150 mg/dL) are associated with increased CHD risk and are commonly associated with other lipid abnormalities (elevated non-HDL-C levels and increased LDL particle number) and nonlipid risk factors (diabetes mellitus and metabolic syndrome)[43].

One of the most common dyslipidemia in South Asians is low HDL-C and high triglycerides[14,23-25,44]. The rate of hypertriglyceridemia has shown to be higher in South Asians compared to Caucasians in several studies[45]. Hypertriglyceridemia (> 150 mg/dL) was observed in up to 70% of South Asian populations in studies with large

Table 1 Articles related to dyslipidemias in South Asians

Ref.	Methodology	Primary end point
Enas *et al*[5]	Cross-sectional, case-control study in Asian Indians and Caucasians (*n* = 1688)	CV risk factors
Anand *et al*[14]	Comparative population-based study in South Asians, Chinese, and Europeans (*n* = 985)	CV risk factors
Tillin *et al*[17]	Retrospective chart review (*n* = 2049 Europeans, 1517 South Asians, and 630 African Caribbeans)	CV risk factors
Karthikeyan *et al*[22]	Cross-sectional, population-based case-control study in 65 centers in Asia (*n* = 5731 cases of a first AMI *vs* 6459 controls)	CV risk factors
Gupta *et al*[23]	Cross-sectional study in South Asians (*n* = 1800)	CV risk factors
Sekhri *et al*[25]	Cross-sectional study in Indians (*n* = 10642 men and *n* = 1966 women)	CV risk factors
Hoogeveen *et al*[27]	Cross-sectional comparative study in Indians living in India (*n* = 103) *vs* those living in United States (*n* = 206)	Lipid profile
Sewdarsen *et al*[28]	Cross-sectional, case-control study in Indian men with CAD (*n* = 50) *vs* controls (*n* = 122)	Lipid profile
Lyratzopoulos *et al*[29]	Comparative study between South Asians and Caucasians (*n* = 34122 men and 37294 women)	CV risk factors
Superko *et al*[30]	Comparative study between Asian Indian men (*n* = 224) and non-Asian Indian men (*n* = 239)	Lipid profile
Bhalodkar *et al*[31]	Comparative study between Asian Indian men (*n* = 211) and Caucasian men (*n* = 1684)	Lipid profile
Joseph *et al*[32]	Descriptive study in Asian Indians (*n* = 206)	Lipid profile
Cappuccio *et al*[33]	Population-based survey in 505 South Asians, 524 Caucasians, and 549 Africans	CV risk factors
Krishnaswami *et al*[34]	Cross-sectional study in 1066 Indian male patients	Lipid profile
Kulkarni *et al*[36]	Cross-sectional study in 39 Asian Indians and 39 Caucasians	Lipid profile
Rashid *et al*[53]	Comparative study in 135 adolescent Indian and Caucasian boys	Lipid profile
Misra *et al*[45]	Comparative study in Asian Indians and Caucasians	CV risk factors
Bhardwaj *et al*[46]	Cross-sectional epidemiological descriptive study in 459 Indian subjects	CV risk factors
Gopinath *et al*[47]	Community-based epidemiological survey in 13414 Indian adults	CV risk factors
Misra *et al*[48]	Cross-sectional epidemiological descriptive study in 532 Indian subjects	CV risk factors
Ehtisham *et al*[50]	Cross-sectional community-based cohort study of 129 Caucasian European and Asian Indian boys	CV risk factors
Patel *et al*[51]	Cross-sectional comparative study in Indians (*n* = 294) and their immigrant counterparts in UK (*n* = 242)	Lipid profile
Sharobeem *et al*[52]	Cross-sectional study in South Asians with stroke (*n* = 55) and healthy controls (*n* = 85)	Lipid profile
Chow *et al*[54]	Cross-sectional comparative study in Indian (*n* = 303) and Caucasian (*n* = 1111) subjects	Association of CIMT with lipid profile
Dodani *et al*[55]	Cross-sectional study in South Asian immigrants in United States	Association of CIMT with lipid profile
Dodani *et al*[56]	Cross-sectional community-based study in 130 South Asian immigrants in United States	Association of CIMT with lipid profile
Isser *et al*[74]	Descriptive study in 50 Indian patients with premature CAD and their first-degree relatives	Lp(a) levels
Palaniappan *et al*[75]	Cross-sectional community-based study in Asian Indian American, African American, and Caucasian women (*n* = 70 each)	Lipid profile
Kamath *et al*[76]	Cross-sectional community-based study in 47 South Asian and 47 American women	CV risk factors
Anand *et al*[77]	Comparative cross-sectional study in South Asians and Americans	Lipid profile
Chopra *et al*[78]	Comparative study in 74 Indians with CAD and 53 controls	Lp(a) levels
Gambhir *et al*[79]	Comparative study in 50 Indians with CAD and 50 controls	Lp(a) levels
Gupta *et al*[80]	Descriptive study in 101 Indian subjects	Lp(a) levels
Articles related to treatment of dyslipidemias in South Asians		
Lee *et al*[89]	Rosuvastatin pharmacokinetics in White, Chinese, Malay, and Asian Indian subjects (*n* = 35 each)	
Patel *et al*[83]	Efficacy and safety of atorvastatin in 33 hyperlipidemic South Asians	
Gupta *et al*[85]	Lipid-modifying effects of atorvastatin and simvastatin in 86 South Asians and 137 Caucasians	
Gupta *et al*[84]	ACTFAST: 12 wk prospective, open-label study of atorvastatin in 1978	

AMI: Acute myocardial infarction; CAD: Coronary artery disease; ACTFAST: Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration; CIMT: Carotid intima-media thickness; Lp(a): Lipoprotein(a); CV: Cardiovascular.

sample sizes[46-48]. compared with 34% in Caucasians[49]. Low levels of HDL-C (< 40 mg/dL) were seen in up to a third of South Asians. In a cross-sectional epidemiological descriptive study with 459 Indian subjects in New Delhi, HDL-C levels < 40 mg/dL were seen in 37% of subjects[45].

Enas *et al*[5] compared HDL-C levels in 580 Asian Indian immigrants in the United States with those of native Caucasians in the Framingham Offspring Study. The mean levels of HDL-C were 38 mg/dL in Asian Indian men compared with 46 mg/dL in Caucasian men ($P < 0.001$). Similar results were seen in women, with mean HDL-C levels of 48 mg/dL in Asian Indian women compared with 56 mg/dL in Caucasian women ($P < 0.001$). Ehtisham *et al*[50] compared 64 white European with 65 South Asian healthy adolescents. Mean HDL-C levels were 65 mg/dL in European women compared with 58 mg/dL in South Asian women ($P = 0.001$), whereas they were 54 mg/dL in European men compared with 50 mg/dL in South Asian men ($P = 0.001$). Similarly, in the INTERHEART study, HDL-C levels were the lowest in the South Asian population, at 32.5 mg/dL in cases and

Table 2 Summary of lipoprotein abnormalities in South Asians

CAD occurs with relatively lower levels of LDL-C among South Asians
At any given LDL-C level, South Asians tend to carry a higher total atherogenic burden (*i.e.*, higher levels of apo B and a higher LDL particle concentration)
South Asians tend to suffer from atherogenic dyslipidemia (*i.e.*, high triglyceride and low HDL-C levels) more frequently compared with other ethnic groups
In South Asians, higher HDL-C levels may not be as protective against CAD as in other ethnic groups
In South Asians, HDL particles tend to be smaller and dysfunctional
South Asians have a genetic tendency for elevated atherogenic Lp(a) levels

Apo B: Apolipoprotein B; CAD: Coronary artery disease; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein(a).

33.5 mg/dL in controls, compared with other Asian and non-Asian groups. More than 80% of both cases and control subjects in South Asia had low HDL-C levels [HDL-C < 40 mg/dL (men) and < 50 mg/dL (women)][22]. These results indicate that the prevalence of low HDL-C levels is much higher in South Asians compared with other ethnic groups.

High triglyceride and low HDL-C levels are metabolically interlinked. This metabolic phenotype is also associated with increased levels of small LDL particles despite relatively normal levels of LDL-C among South Asians. This clinical syndrome is accompanied by insulin resistance, a condition frequently referred to as atherogenic dyslipidemia, which is a common metabolic derangement among Asian Indians[5,31,36,45,50-52]. Rashid *et al*[53] compared lipid levels among South Asians and Europeans (n = 244 and 238, respectively) and all elements of atherogenic dyslipidemia were more severe in South Asians compared to Europeans. Mean triglyceride level was 174 mg/dL *vs* 136 mg/dL (P < 0.0001), LDL-C level was 129 mg/dL *vs* 122 mg/dL (P < 0.02), and HDL-C level was 39 mg/dL *vs* 46 mg/dL among South Asians and Europeans, respectively (P < 0.0001).

These studies indicate that atherogenic dyslipidemia is more prevalent and severe among South Asians and may partially explain the increased CHD risk in this population despite relatively normal levels of LDL-C compared with other ethnic groups.

HDL PARADOX IN SOUTH ASIANS

Higher HDL-C levels have been shown to be associated with a lower risk of CHD[22,27,28,44]. In the INTERHEART study, higher HDL-C levels were associated with a decreased risk of AMI in South Asians. However, the protective effect of higher HDL-C levels seemed to be weaker for South Asians (with OR crossing unity) compared with other Asians in the INTERHEART study (OR for risk of first AMI per 1-SD increase in HDL-C in South Asians: 0.87, 95%CI: 0.72-1.06; OR for rest of Asia: 0.77, 95%CI: 0.70-0.85)[22]. Other investigators have also shown a similar lack of protective effect of HDL-C among South Asians. In a community-based cross-sectional study assessing the correlation of risk factors with carotid intima-media thickness (CIMT) among South Asians from India (n = 303) and Caucasians from Australia (n = 1111), increasing HDL-C levels were associated with decreasing CIMT in the Australian population, but the reverse was true for the Indian population (P < 0.001)[54]. Therefore, South Asians not only have low levels of HDL-C but also appear to have much less cardiovascular protection from HDL-C compared to other ethnic groups.

Why HDL loses its cardioprotective properties in South Asians is unclear. One proposed mechanism is presence of dysfunctional HDL particles. In a small study, Dodani *et al*[55] examined 30 South Asian immigrants and found that 50% had dysfunctional HDL (as determined by using HDL inflammatory index). Presence of dysfunctional HDL correlated with subclinical atherosclerosis measured by CIMT (P = 0.03)[55]. This finding was supported by recently published data from the same authors on 130 South Asian immigrants who underwent HDL function assessment and CIMT measurements; 26% had dysfunctional HDL defined as HDL inflammatory index value of 1 or greater. Presence of dysfunctional HDL correlated with CIMT measurement (P < 0.0024)[56].

It is postulated that metabolic syndrome may render HDL pro-inflammatory[57]. The association between dysfunctional HDL particles and atherosclerosis in South Asians could be potentially explained by a high prevalence of metabolic syndrome in South Asians[19]. However, this might be a noncausal association, and HDL dysfunction indeed may be the result of a diffuse atherosclerotic process[58-62]. What causes HDL to become dysfunctional in South Asians and whether dysfunctional HDL is a true risk factor for increased cardiovascular risk in South Asians is not known. In addition, how much the higher prevalence of metabolic syndrome in South Asians contributes to this effect is not entirely clear. Studies with large sample size are needed to further address this important question.

HDL SUBFRACTIONS IN SOUTH ASIANS

Another potential explanation for the apparent blunted cardioprotection of HDL in South Asians might be related to HDL particle size. Similar to LDL, HDL is composed of heterogeneous particles, with large particles performing highly efficient reverse cholesterol transport, whereas small particles might be less efficient in reverse cholesterol transport. In general, HDL particle size tends to be lower in patients with CHD and those with low HDL-C levels[55].

The role of HDL and other proteins in reverse cholesterol transport is of crucial importance for cholesterol clearance. Cholesterol is removed from vascular endothelial cells and tissue macrophages through a reverse transport process, in which receptors on the HDL surface, such as apo A-I, bind free cholesterol, which is then

carried to the liver and secreted into the bile[63-65]. HDL2b is a major HDL subfraction that is larger in size and may be more efficient in reverse cholesterol transport[30]. Superko *et al*[30] investigated the prevalence of metabolic disorders among Asian Indian and non-Asian Indian males. The standard lipid measurements did not discriminate between groups. However, the levels of HDL2b were significantly lower (12 mg/dL *vs* 14 mg/dL, respectively, $P = 0.0002$) and the prevalence of low HDL2b subfraction (< 20% of total HDL) was higher among Asian Indians compared with non-Asian Indians (92% *vs* 76%, respectively, $P < 0.0002$), suggesting impaired reverse cholesterol transport in South Asians. Bhalodkar *et al*[31] compared various lipoprotein concentrations and sizes between 211 healthy Asian Indian men and 1684 Caucasian men from the Framingham Offspring Study. Asian Indians had significantly lower concentrations of large HDL particles (21 mg/dL *vs* 24 mg/dL, respectively, $P < 0.005$), higher concentrations of small HDL particles (20 mg/dL *vs* 17 mg/dL, respectively, $P < 0.0001$), and smaller HDL particle size (8.5 nm *vs* 8.9 nm, respectively, $P < 0.0001$) compared with Caucasian men.

Therefore, small HDL particle size potentially resulting in inefficient reverse cholesterol transport may be more common in South Asians than in other populations and could partially explain the observed weaker association between HDL-C and cardiovascular events in South Asians compared with other ethnicities. As discussed previously, prospective studies with large sample size are needed to assess further the association between HDL particle size and future risk for cardiovascular disease in South Asians. It is important to note that in the studies described above, HDL particle size was used a surrogate for HDL's reverse cholesterol transport function and no direct measurement of reverse cholesterol transport (*e.g.,* HDL's efflux capacity) was performed.

Lipoprotein(a)

Lipoprotein(a) [Lp(a)] is a highly atherogenic and has been associated with premature atherosclerosis in coronary, cerebral, and peripheral arteries[66-73]. Lp(a) levels are primarily genetically determined, and South Asian immigrants have Lp(a) levels that are similar to those in their counterparts in their home country[71-74] and higher than those in Caucasians. Bhatnagar *et al*[9] compared Lp(a) levels of Indian immigrants in West London with their siblings in Punjab and found that Lp(a) concentrations were similar in both the West London Indian and Punjab populations, but were significantly higher ($P = 0.01$) than those of a white European population in London.

A comparative study of African American, Asian Indian American, and Caucasian American women ($n = 70$ for each) was performed by Palaniappan *et al*[75]. In this study, African Americans had the highest Lp(a) levels, followed by Asian Indian Americans and Caucasian Americans [(Lp(a) 0.5 g/L, 0.3 g/L, and 0.2 g/L, respectively, $P = 0.0001$]. Kamath *et al*[76] also compared Lp(a) levels in 47 South Asian women with those in 47 American women. Lp(a) levels were higher in South Asian women compared with American women [median level (range): 50.7 (2.9-323) nmol/L *vs* 18.3 (2.9-196) nmol/L, respectively, $P < 0.012$]. Anand *et al*[77] performed 3 separate studies comparing Lp(a) levels in South Asians and Caucasians living in North America. The first study included a group of South Asian physicians aged 40-57 years who attended an annual meeting in North America, whose Lp(a) levels were compared with those of their North American counterparts ($n = 141$ and 138, respectively). The mean Lp(a) concentration for South Asian physicians was 19.6 mg/dL compared with 17.5 mg/dL for Caucasian North American physicians ($P = 0.55$). The second study compared 255 South Asian churchgoers aged 22-70 years with 246 Caucasian Americans. The mean Lp(a) concentration was significantly elevated in South Asians (20.2 mg/dL) compared with Caucasian Americans (16.3 mg/dL, $P < 0.002$). In the third study, 30 South Asians and 21 Caucasians who were randomly sampled from the community in Canada were compared. South Asian Canadians had significantly higher mean Lp(a) concentrations compared with Caucasian Canadians (34.1 *vs* 17.3 mg/dL, $P < 0.013$). Therefore, Lp(a) levels in South Asian North Americans are higher than those in Caucasian North Americans but lower than in African Americans.

In an attempt to evaluate the association between Lp(a) levels and CHD risk, Lp(a) levels were compared in 74 Indian patients with CHD and 53 healthy Indian controls. Patients with CHD had almost 5-fold higher Lp(a) levels compared with controls (105 ± 565 mg/dL *vs* 23 ± 76 mg/dL, $P < 0.01$)[78]. In another study, Lp(a) levels were measured in 50 South Asian patients (< 40 years old) with angiographically documented CHD and an equal number of age-matched healthy South Asian controls. In patients with angiographically confirmed CHD, mean Lp(a) levels were significantly higher than in controls (35 mg/dL *vs* 20 mg/dL respectively, $P < 0.002$). Multiple regression analysis showed that elevated Lp(a) level was independently associated with presence of CHD among South Asians (OR = 3.06, 95%CI: 1.24-7.55; $P < 0.001$)[79]. Similarly, Gupta *et al*[80] compared Indian patients with angiographically confirmed CHD with age- and sex-matched Indian controls. Lp(a) concentration was higher in the CHD group ($n = 77$) compared to the control group ($n = 24$) (27 mg/dL *vs* 15 mg/dL, $P < 0.05$). Furthermore, Lp(a) values had a graded association with CHD. The prevalence of CHD in the first (< 5 mg/dL), second (5-25 mg/dL), third (26-75 mg/dL), and highest quartile (≥ 76 mg/dL) of Lp(a) levels was 66.7%, 69.0%, 87.5%, and 100%, respectively[80].

Overall, these studies point towards a genetic tendency for elevated Lp(a) levels in South Asians. These elevated Lp(a) levels correlate with presence of CHD and might partially explain the population-attributable risk for excessive CHD in this group.

TREATMENT OF DYSLIPIDEMIA IN SOUTH ASIANS

Data on the management of dyslipidemia in South Asian subjects are sparse despite the critical importance of dyslipidemia as a cardiovascular risk factor in this population. In the United States, the lipid management guideline developed by the American College of Cardiology/American Heart Association in 2013 is used for management of dyslipidemia[81]. Chandra *et al*[82] recently published a consensus statement regarding dyslipidemia management in Indian subjects. The vast majority of recommendations are extrapolated from the current Western guidelines, because of the paucity of primary data in South Asian populations.

Statin therapy

LDL-C-lowering therapy with statins is the mainstay in the pharmacological treatment of hypercholesterolemia in South Asians, with a suggested LDL-C goal of < 100 mg/dL in high-risk patients and < 70 mg/dL for very-high-risk patients as per a recent consensus statement[82]. There are no South Asian-specific treatment goals or thresholds, given the absence of prospective outcomes data, and thus, these goals were derived from studies mostly performed in Caucasian populations.

In a study in 33 South Asians with hyperlipidemia, a target LDL-C goal of < 77 mg/dL was achieved in 81% of patients after 4 wk treatment with 10 mg/d atorvastatin, without statin-related adverse effects being noted[83]. Similarly, a study in patients with established CHD on statins compared the efficacy and safety of atorvastatin and simvastatin in South Asians and Caucasians. Atorvastatin (median dose = 20 mg/d in both groups) produced similar decreases in LDL-C in South Asian (43%) and Caucasian (41%) patients and increased in HDL-C by 19% in South Asians and by 12% in Caucasians (P = NS). Simvastatin (median dose = 20 mg/d in both groups) reduced LDL-C by 35% in South Asians and by 37% in Caucasians while raising HDL-C by 12% in both groups (P = NS). Both medications were well tolerated[84].

The Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration study was a 12 wk prospective, open-label study in patients at high risk for atherosclerosis (European origin: n = 1978; South Asian origin: n = 64). After propensity matching, atorvastatin lowered LDL-C to a similar degree in both groups (reduction in LDL-C from baseline was 34% in South Asians compared with 38% in Europeans, P = 0.22), with no differences in safety observed[85]. Furthermore, postmarketing data for statins have not identified any particular safety issues with statins in South Asians[86].

Other studies performed head-to-head comparisons among different statins in South Asians. Jayaram *et al*[87] compared the use of rosuvastatin 10 mg/d with atorvastatin 10 mg/d in adult Indian patients with dyslipidemia (mean LDL-C > 160 mg/dL and triglyceride > 400 mg/dL). The fall in the mean LDL-C levels after 6 wk of treatment in the rosuvastatin group was 40%, compared with 30% in the atorvastatin group. This higher efficacy of rosuvastatin in terms of LDL-C lowering was further tested in the Investigation of Rosuvastatin in South Asians study. In this randomized trial, 740 patients of South Asian origin living in United States and Canada received 6 wk of treatment with either rosuvastatin (10 or 20 mg/d) or atorvastatin (10 or 20 mg/d). A total of 485 patients (66%) were categorized as being at high risk for CHD, with a National Cholesterol Education Program Adult Treatment Panel Ⅲ treatment goal of LDL-C < 100 mg/dL. LDL-C levels decreased by 45% with rosuvastatin 10 mg *vs* 40% with atorvastatin 10 mg (P = 0.002) and by 50% with rosuvastatin 20 mg *vs* 47% with atorvastatin 20 mg (P = NS). National Cholesterol Education Program Adult Treatment Panel Ⅲ LDL-C goal attainment rates in high-risk patients were 76% (79%) and 88% (89%) with rosuvastatin 10 (20 mg), respectively, compared with 70% (76%) and 81% (85%) with atorvastatin 10 (20 mg), respectively. Rosuvastatin and atorvastatin were both well tolerated[88].

In a pharmacokinetic study of rosuvastatin, both lasting time in serum and peak plasma concentrations were higher in Asian Indians compared with non-Asian-Indians living in Singapore (P < 0.0001)[89]. This lower statin metabolism has raised a concern about increased side effects of statins in South Asians, especially with higher doses. The United States Food and Drug Association-approved highest doses of statin are, therefore, lower for Asians compared with other groups[90], and it might be prudent to start a lower dose of a statin in Asian patients.

Overall, these results point to similar efficacy with statin therapy in South Asians compared with Caucasians, although, based on pharmacokinetic data, the maximum approved dose for rosuvastatin is lower for Asians (including South Asians) compared with other ethnicities. The recommended initiation dose for rosuvastatin is 5 mg once daily, with maximum recommended dose of 20 mg daily, for Asians.

Combination drug therapy

Given the plethora of lipoprotein abnormalities in South Asians, targeting non-LDL lipid fractions may be relevant. Sharma *et al*[91] studied combination therapy of lovastatin and niacin in a prospective multicenter study that included 131 Asian Indians with LDL-C levels ≥ 130 mg/dL. A significant trend was observed in LDL-C lowering (levels at baseline and weeks 4, 12, and 24, respectively: 153, 127, 109 and 95 mg/dL; P < 0.05). The percentage decrease in LDL-C from baseline was 38% at 24 wk. Similarly, HDL-C was increased by 18%, triglycerides were decreased by 21%, and Lp(a) was decreased by 44.5% (P < 0.05) at 24 wk compared with baseline. No significant changes were observed in systolic or diastolic blood pressure, blood creatinine, transaminases, or creatinine kinase, suggesting an acceptable safety profile.

Ezetimibe is a nonstatin medication that lowers plasma levels of LDL-C by inhibiting the activity of the

Niemann- Pick C1-like 1 (NPC1L1) protein. Stitziel *et al*[92] sequenced the exons of NPC1L1 in 7364 patients (844 South Asians) with CHD and in 14728 controls (1107 South Asians). Naturally occurring mutations that disrupt NPC1L1 function were found to be associated with reduced plasma LDL-C levels and a reduced risk for CHD in individuals with various ethnic backgrounds, including South Asians. This finding suggested that inhibitory drugs such as ezetimibe could reduce LDL-C level and CHD risk reduction in South Asians similar to in other populations. In another study, ezetimibe and statin combination therapy was examined in 64 South Asian Canadians with CHD or diabetes and persistent hypercholesterolemia on statin therapy. Patients were randomized to receive ezetimibe 10 mg/d coadministered with statin therapy or a doubling of their current statin dose. At 6 wk, the proportion of patients achieving target LDL-C (< 77 mg/dL) was significantly higher among the ezetimibe + statin-treated patients compared with the statin-doubling group (68% *vs* 36%, respectively; P = 0.031) with an OR (95%CI) of 3.97 (1.19-13.18), accounting for baseline LDL-C levels and adjusting for age. At 12 wk, 76% of ezetimibe + statin patients achieved target LDL-C compared with 48% of the patients in whom statin dose was doubled (adjusted OR = 3.31, 95%CI: 1.01-10.89; P = 0.047). No serious adverse effects were recorded[93]. Despite these findings, it is important to note that the current cholesterol treatment guidelines recommend the use of maximum tolerated statin dose before adding a second LDL-C-lowering agent.

Combination therapy targeting various dyslipidemias in South Asians appears to be promising. Prospective studies with large sample size and longer follow-up period are needed to assess accurately the efficacy and safety profile of these agents in South Asian populations. Importantly, data are needed to assess whether the use of combination therapy improves cardiovascular outcomes in this patient population with a specific need for combination therapy, given the high prevalence of atherogenic dyslipidemia as discussed above.

CONCLUSION

South Asians have a high CHD prevalence and suffer from early-onset CHD compared with other ethnic groups. Conventional risk factors may not fully explain the increased CHD risk in this population. Indeed, South Asians have a unique lipid profile which may predispose them to premature CHD. The dyslipidemia in South Asians is most importantly characterized by elevated levels of triglycerides, low levels of HDL-C, elevated Lp(a) levels, and a higher atherogenic particle burden despite relatively normal LDL-C levels. HDL particles appear to be smaller, dysfunctional, and proatherogenic in South Asians. Despite the rapid expansion of the current literature with better understanding of the specific lipid abnormalities in this patient population, studies with adequate sample sizes are needed to assess the significance and contribution of a given lipid parameter on overall cardiovascular outcomes in this patient population. Specific lipid management goals and treatment thresholds do not exist for South Asians due to the paucity of data. Current treatment recommendations are mostly extrapolated from Western guidelines. Lastly, large, prospective studies with outcomes data are needed to assess cardiovascular benefit associated with various combination therapies in this patient population.

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