

COMMENTARY - SOUTH ASIANS AND RISK OF CARDIOVASCULAR DISEASE: CURRENT INSIGHTS AND TRENDS

Patients from the Indian subcontinent have a distinct cardiovascular risk profile with profound health consequences. South Asians tend to develop more severe coronary artery disease at a younger age, and may also suffer from earlier myocardial infarction and heart failure. The genesis of this risk is multi-factorial. One important culprit is increased insulin resistance, possibly due to recently identified genetic polymorphisms. Another possible explanation is subclinical inflammation and a prothrombotic environment, as evidenced by increased levels of homocysteine, plasminogen activator inhibitor-1, and fibrinogen. The lipid profile of South Asians may play a role, as this population is known to have elevated levels of lipoprotein (a), as well as lower levels of HDL. In addition, this HDL may be dysfunctional, as this population may have a higher prevalence of low levels of HDL2b, as well as an increased preponderance of smaller HDL. Current guidelines for primary and secondary prevention have not reflected our growing insight into the unique characteristics of the South Asian population, and may need to evolve to reflect our knowledge. (*Ethn Dis.* 2010;20:474-478)

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INTRODUCTION

Patients from the Indian subcontinent, including India, Pakistan, Bangladesh, Sri Lanka and Nepal, present evolving challenges to internists and specialists alike. Constituting one fifth of the world's population, these individuals have a distinct cardiovascular risk profile with an increased risk of developing atherosclerotic coronary artery disease.¹

The most prominent manifestation of this risk is premature death from cardiovascular causes.^{2,3} This increased risk has been found not only in South Asians living in their countries of origin,⁴ but in immigrants as well.^{5,6} Early studies from the United Kingdom found up to a 50% increased risk of mortality in individuals from the Indian sub-continent vs England.⁷ These conclusions are supported by research from around the globe, including the Caribbean,⁸ and other parts of Asia.^{9,10} More recent population studies from Canada and the United States have provided further information confirming this increase in risk. For example, a comparative analysis from California found that South Asian Indian men and women had the highest proportional mortality for coronary heart disease when compared with six other racial groups.¹¹ In Canada, the Study of Heart Assessment and Risk in Ethnic Groups (SHARE) found that South Asians have a greater prevalence of atherosclerosis, and more ominously, that South Asian ethnicity was an independent predictor of cardiovascular risk, even after adjusting for conventional risk factors such as the lipid profile.¹²

The increased risk of cardiovascular disease (CVD) in South Asians manifests itself in other ways. South Asians tend to develop coronary artery disease at a younger age than other ethnic groups, often before the age of forty.¹³ Furthermore, despite their younger age, coronary angiography demonstrates that they may have more severe disease.¹⁴ South Asians also suffer from premature morbidity, including earlier myocardial infarction,¹⁵ and heart failure.¹⁶

PREVALENCE OF INSULIN RESISTANCE AND OTHER RISK FACTORS

A growing body of research suggests that the genesis of the excess cardiovascular risk of South Asians is multi-factorial. The increased risk of cardiovascular events in South Asians is associated with a decreased prevalence of many traditional risk factors, but a higher prevalence of type 2 diabetes mellitus (T2DM). A pro-inflammatory state also appears to play a unique role in this ethnic group.

Of the traditional risk factors for CVD, insulin resistance appears to play the most significant role. Though there is certainly evidence to suggest an increased prevalence of overt diabetes mellitus in South Asians,¹⁷ this may be merely the endpoint of underlying problems with glucose homeostasis. Even in the absence of diabetes, numerous studies have demonstrated that South Asians have decreased sensitivity to insulin when compared to other ethnic groups.^{18,19} This is likely due to comparatively increased levels of visceral

fat resulting in a blunted response to insulin.^{20–22}

There is also evidence to suggest that South Asians may have a susceptibility to insulin resistance and obesity due to recently identified genetic polymorphisms for this phenomenon.^{23–26} Genes such as (PC-1) K121Q, and PPARGC1A may have increased prevalence in South Asians, resulting in a possible genetic predisposition to these ailments.

The effect of insulin resistance on this population group appears to be profound. Despite evidence that South Asians may have lower levels of cholesterol,²⁷ tobacco use,²⁸ and body mass index (BMI), they suffer from an increased rate of mortality from cardiovascular causes.²⁹ Thus, one plausible explanation is that, in South Asians, glucose intolerance is a risk factor which tends to overwhelm all others.

The role of another risk factor, hypertension, may be more difficult to identify. Some data suggest that this population suffers from elevated blood pressure when compared to other ethnicities;³⁰ other data suggest quite the opposite.³¹ These differences may be age-dependent; younger South Asians may have lower comparative blood pressure to Caucasians, while the blood pressure of older South Asians may be higher.³² An alternate explanation is that there is significant heterogeneity within the South Asian population, with some groups such as Bangladeshis maintaining low blood pressure relative to Asian Indians.³³ In fact, blood pressure may be one of several risk factors whose prevalence varies depending on the specific country of origin.³⁴

Of particular interest for immigrants, environmental factors may also play a role in the excess cardiovascular risk. There is ample evidence suggesting that a Western diet and lifestyle, and lower socio-economic class, increase risk in immigrants from South Asia.^{35–37} A recent study comparing immigrants to the United Kingdom to their counter-

parts in India identified increases in dietary fat and energy intake as a primary culprit for increased coronary disease.³⁸

However, the disparity in cardiovascular risk between South Asians and other ethnic groups appears to begin at a young age, undermining the contention that environment alone is to blame.^{39,40}

SUBCLINICAL INFLAMMATION MAY INCREASE CARDIAC RISK IN SOUTH ASIANS

Another possible explanation for increased cardiovascular risk in the South Asian population is increased levels of subclinical inflammation, as measured by high sensitivity C-reactive protein (hs-CRP) levels. Clearly, this may be related to increased insulin resistance in South Asians, as inflammation is a known consequence of T2DM. However, there is ample evidence demonstrating higher relative CRP levels at baseline (ie, pre-T2DM) in this ethnic group.^{41,42} One recent study found CRP levels to be more than 100% higher in South Asian children in England as compared to their European counterparts.⁴³ Other studies have demonstrated that elevated CRP levels in adult South Asians are associated with a 14% increase in coronary heart disease compared with Europeans.⁴⁴

C-reactive protein is not the only pro-inflammatory marker found in increased prevalence in this group. An increase in prothrombotic markers such as homocysteine, plasminogen activator inhibitor-1,⁴⁵ and fibrinogen⁴⁶ are also found in South Asians, suggesting the presence of a prothrombotic environment that increases cardiovascular events. Underlying vascular dysfunction in South Asians may also play some role. Recent evidence suggests this ethnicity may suffer from increased arterial stiffness,⁴⁷ and endothelial cell dysfunction,^{48,49} both of which may contribute to cardiac risk.

DO SOUTH ASIANS HAVE A UNIQUE LIPID PROFILE?

There is a growing body of literature suggesting that South Asians have a different lipid profile than other ethnic groups, increasing their risk for atherosclerotic vascular disease. These factors may act synergistically with other genetic and environmental factors to make this population particularly susceptible.

Some aspects of the lipid profile appear similar to those in other ethnic groups. For example, it appears that South Asians have similar levels of low density lipoprotein as Caucasians,⁵⁰ and may in fact have a lower prevalence of smaller, denser LDL particles compared with Caucasians.^{51,52}

In other respects, the lipid profile of South Asians appears unique. This group may have elevated baseline lipoprotein (a) levels; these levels are associated with increased cardiovascular risk and may be genetically determined. One study, for example, found that South Asians in both London and India have significantly higher baseline lipoprotein (a) levels than Caucasians, in some cases by more than two-fold.⁵³ Further research has shown these comparatively elevated levels persist in South Asians immigrants to the United States as well.⁵⁴ One study suggested that these differences may be limited to women.⁵⁵ Other studies have demonstrated genetic polymorphisms in the gene for apolipoprotein B (the major protein of LDL) that may also increase cardiovascular risk for this ethnicity,⁵⁶ and have demonstrated elevated Apo B100/Apo A-I (the major protein of high density lipoproteins) ratios, a confirmed marker for predicting cardiovascular risk.⁵⁷

Of particular interest is the role of high density lipoprotein (HDL) in increasing cardiovascular risk in South Asians. Decades of research have confirmed the strong inverse relationship between plasma HDL levels and the

risk of coronary atherosclerosis, likely due to the reverse cholesterol transport, anti-inflammatory, and anti-oxidant effects of HDL.⁵⁸ Low HDL levels have been associated with increased risk of coronary artery disease,⁵⁹ myocardial infarction,⁶⁰ restenosis after angioplasty,⁶¹ and death from cardiovascular causes.⁶² Conversely, incremental increases in HDL have resulted in measurable reductions in cardiovascular risk.^{63–67}

SOUTH ASIANS AND HDL

Though the important cardio-protective benefit of HDL is clear, its role in the South Asian population remains to be clarified. Research has shown lower levels of HDL in South Asians when compared with the general population.⁶⁸ Furthermore, even when levels of HDL are comparable, they appear to lack cardio-protective benefits, as measured by carotid intima media thickness,⁶⁹ and may in fact be dysfunctional.⁷⁰ However, these differences may be complicated by variations due to the country of origin; for example, a far higher proportion of Bangladeshis suffer from low HDL when compared to similar Indians or Pakistanis.⁷¹

For South Asians, a key difference may lie in HDL subtypes. Specifically, there is emerging evidence that South Asians may have impaired reverse cholesterol transport, as Asian Indian males have a higher prevalence of low levels of HDL2b, even in patients with normal levels of overall HDL.^{72,73} Furthermore, South Asians may have an increased preponderance of smaller, less cardio protective HDL than their Caucasian counterparts.⁷⁴ However, the precise clinical impact of particle size on cardiovascular risk remains to be determined, as recent data has suggested that increased risk may be associated with larger HDL particle size.⁷⁵

AREAS FOR CONTINUED RESEARCH AND IMPLICATIONS FOR CLINICIANS

For clinicians, patients of South Asian origin present a challenge for screening and management of CVD. While many traditional risk factors such as insulin resistance may inform treatment decisions, the absence of other risk factors may underestimate overall risk. Furthermore, differences among subgroups of South Asians may add further layers of complexity. Current research is beginning to demonstrate the contours of that complexity, and suggest that this ethnic group has many unique characteristics that require yet more investigation.

Consideration of ethnicity when determining preventative health guidelines is not without precedent. For example, the World Health Organization has recognized the benefit of different obesity cutoffs for BMI based on ethnicity, noting that Asian populations have high risk of disease even when not obese by European standards.⁷⁶

To date, current guidelines for primary and secondary prevention have not reflected our growing insight into the unique characteristics of the South Asian population. For the US population, the desirable target levels for LDL are well known, though there is currently no official ACC/AHA or ATP III target value for HDL. It is mentioned in the ATP III guidelines that treatment for isolated low HDL is reserved for persons with CVD and CVD equivalents, and is included as an estimate of 10 year risk for CVD in the Framingham assessment for CVD.⁷⁷ Ultimately, guidelines for primary and secondary prevention may need to evolve to reflect our growing understanding of the unique risks of this population.

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