South Asians and Cardiovascular Risk

What Clinicians Should Know

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Case presentation: A 36-year-old nonsmoking, normotensive South Asian man presented to the emergency department of a community hospital with retrosternal chest pain of ≈60 minutes' duration. His 12-lead ECG demonstrated 10 mm of ST-segment elevation in leads V_2 through V_6, and he received fibrinolytic therapy within 90 minutes of symptom onset. His pain resolved, but his ST segments only partially normalized; he had a peak creatine kinase of 4564 IU/L, and he showed signs of early heart failure. LDL cholesterol was 135 mg/dL, HDL 32 mg/dL, triglycerides 20 mg/dL, and total cholesterol 206 mg/dL; his body mass index (BMI) was 24 kg/m^2. Cardiac catheterization demonstrated severe and diffuse triple-vessel disease, including occlusion of the proximal left anterior descending artery, as well as moderate left ventricular dysfunction. While in the hospital, he was diagnosed with new-onset type 2 diabetes mellitus and subsequently underwent uncomplicated coronary bypass surgery.

South Asians and Cardiovascular Disease

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. In North America, more than 2 million South Asians reside in the United States and almost 1 million in Canada. 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 and cardiovascular death as compared with other ethnic groups.[1–3]

In an analysis of age-standardized coronary heart disease (CHD) mortality in Canada over a 15-year period, South Asians had the highest CHD mortality compared with individuals of Chinese and European descent.[4] In addition, South Asians are prone to developing CHD at a younger age, often before the age of 40 years in men.[5] Case-control studies have shown that compared with whites, South Asians in Canada present to the hospital later in the course of acute myocardial infarction and are more likely to have an anterior location of infarction.[6] South Asians are younger at the time of cardiac catheterization than whites yet are more likely to have significant left main, multivessel, and distal coronary artery disease.[7] In addition, South Asians are significantly younger at the time of first hospitalization for heart failure.[8]

Traditional Cardiac Risk Factors

The INTERHEART study demonstrated that traditional cardiovascular disease risk factors play an important role in the prediction of myocardial infarction in populations around the world, including South Asians.[9] However, numerous case-control studies documenting premature CHD in South Asians demonstrate similar or lower prevalence of traditional risk factors than with other populations.[10,11] A review of cross-sectional data from the United Kingdom, including the 1999 Health Survey of England, reveals that the prevalence of hypertension is similar in South Asians and the white population.[12,13] Tobacco use is generally low among South Asian men and almost unheard of among South Asian women.[14] Tobacco consumption is rapidly increasing in South Asian countries in conjunction with economic expansion.

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Although South Asians have levels of LDL cholesterol comparable to other populations, LDL particle size tends to be smaller.[15] Small LDL particles, through increased susceptibility to oxidation, are more atherogenic than larger particles. HDL particle size, in addition to the actual level of HDL cholesterol, also appears to be an important predictor of CHD risk. South Asians not only have lower HDL levels but also have a higher concentration of small, less-protective HDL particles.[16] Asian Indian males have a higher prevalence of low HDL_{2b} than non-Asian Indians, which suggests impaired reverse cholesterol transport. This finding was also observed in Asian Indian men with apparently normal HDL values.[17]

Unlike other traditional risk factors, the prevalence of diabetes mellitus is uniformly higher in South Asians than in many other populations. In fact, India alone is projected to experience the greatest global increase in type 2 diabetes mellitus by 2025.[18] In rural settings within India, the prevalence of diabetes is quite low, at ≈2%. This prevalence, however, rises dramatically in urban communities throughout India, and even more so among South Asian immigrants to the Western world.[19] In the United Kingdom, the prevalence of diabetes in South Asians approaches 15% to 20%.[12] This large variation in diabetes prevalence among South Asians suggests an interaction between genetic predisposition and environmental influences, the so-called "thrifty gene" hypothesis. In a contemporary, community-based study of Asian Indian immigrants in the Atlanta, Ga, area, the prevalence of diabetes was 18.3%, a rate markedly higher than reported for other populations in the United States, including whites, blacks, and Hispanics.[19]

An analysis of the California Mortality Database between 1990 and 2000 showed that Asian Indian men and women had the highest proportional mortality ratios for CHD compared with 6 other racial groups.[20] Although CHD mortality declined in all groups between 1985 and 1990, Asian Indian women actually experienced a 5% increase in CHD mortality during this period. In the Study of Health Assessment and Risk in Ethnic groups (SHARE), individuals of South Asian, Chinese, and European origin were randomly selected from telephone directories in 3 Canadian cities to volunteer for laboratory and clinical testing. South Asians were found to have a higher prevalence of subclinical atherosclerosis, and South Asian ethnicity was an independent predictor of cardiovascular disease.[14]

Abdominal Obesity and the Metabolic Syndrome

The metabolic syndrome identifies individuals at increased risk of developing both type 2 diabetes mellitus and CHD. Although the diagnostic criteria for this syndrome continue to evolve, integral components include abdominal obesity, glucose intolerance, hypertension, reduced HDL cholesterol, and increased triglycerides. There has been considerable debate as to whether the underlying cause of the metabolic syndrome is genetically or environmentally determined (innate insulin resistance versus consequences of obesity). Subjects with the metabolic syndrome face a 2-fold greater risk of all-cause mortality and a 2- to 3-fold increased risk of cardiovascular mortality compared with those without the syndrome.[21]

Visceral or abdominal obesity has recently been recognized as an important player in the pathogenesis of both glucose intolerance and atherosclerosis. Historically, obesity has been characterized by calculation of BMI. However, large studies have suggested that waist circumference and/or waist-hip ratio may provide a better estimate of both the degree of abdominal obesity and the risk for cardiovascular disease.[22] Compared with European populations, South Asians have increased abdominal visceral fat and greater insulin resistance at similar levels of BMI, which suggests that reliance on BMI alone may underestimate true risk in South Asians.[23–25] In addition, insulin resistance is commonly noted in South Asians at BMI levels that are traditionally considered "ideal" ($<$25 kg/m^2).[26] This body type, often termed "thin-fat phenotype" (muscle thin but body fat) is associated with an increased risk of developing diabetes. A comparison of newborns in the United Kingdom and in Mysore, India revealed that the thin-fat phenotype was more common in Mysore newborns and persisted into childhood.[27] The World Health Organization has recognized the need for definitions of obesity that are specific to individual populations.[28] Consequently, it has revised the obesity cutoff in Asians from BMI $>$30 kg/m^2 to BMI $>$25 kg/m^2. A more appropriate estimate of visceral fat and insulin resistance in South Asians may be measurement of waist circumference, a concept furthered by population-specific cutoffs suggested by the International Diabetes Federation.[29] Population-specific definitions for abdominal obesity have been incorporated into the diagnostic criteria for the metabolic syndrome by the National Cholesterol Education Program Adult Treatment Panel III Panel in the United States (Figure 1).

In the SHARE study, one third of South Asian volunteers had either glucose intolerance or overt diabetes as diagnosed by fasting glucose and a 2-hour glucose tolerance test, a prevalence much higher than in other populations.[14] Similar findings have been observed among urban adults in India.[29] When Adult Treatment Panel III criteria and modified waist circumference cutoffs were used, the metabolic syndrome was present in 41.1% of urban Indian adults and in 27.9% of subjects with normal plasma glucose levels. In those with elevated fasting plasma glucose, the prevalence of metabolic syndrome was $>$70%.

Emerging Cardiac Risk Factors

Although conventional risk factors account for the majority of CHD risk in

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:

Central obesity *(defined as waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women, with ethnicity specific values for other groups)*

plus any two of the following four factors:

- ***raised TG level:*** ≥ 150 mg/dL (1.7 mmol/L), or ***specific treatment for this lipid abnormality***
- ***reduced HDL cholesterol:*** < 40 mg/dL (1.03 mmol/L*) in males and < 50 mg/dL (1.29 mmol/L*) in females, ***or specific treatment for this lipid abnormality***
- ***raised blood pressure:*** systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, ***or treatment of previously diagnosed hypertension***
- ***raised fasting plasma glucose*** (FPG) ≥ 100 mg/dL (5.6 mmol/L), ***or previously diagnosed type 2 diabetes***
  If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

Country/Ethnic group		Waist circumference† (as measure of central obesity)
Europids*	Male	≥ 94 cm
	Female	≥ 80 cm
South Asians**	Male	≥ 90 cm
	Female	≥ 80 cm
Chinese	Male	≥ 90 cm
	Female	≥ 80 cm
Japanese***	Male	≥ 85 cm
	Female	≥ 90 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available	

** In the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes.*

*** Based on a Chinese, Malay and Asian Indian population.*

**** Subsequent data analyses suggest that Asian values (male, 90 cm; female 80 cm) should be used for Japanese populations until more data are available.*

† In future epidemiological studies of populations of Europid origin, prevalence should be given using both European and North American cut-points to allow better comparisons.

Although a higher cut-point is currently used for all ethnic groups in the USA for clinical diagnosis, it is strongly recommended that for epidemiological studies and, wherever possible, for case detection, ethnic group specific cut-points should be used for people of the same ethnic group wherever they found. Thus the criteria recommended for Japan would also be used in expatriate Japanese communities, as would those for South Asian males and females regardless of place and country of residence.[11]

Figure 1. International Diabetes Federation ethnicity-based definition of metabolic syndrome (adapted from Reference 29).

large populations, the identification of newer methods of risk stratification has been an area of active research. Among the many candidates, lipoprotein(a), apolipoprotein B, homocysteine, plasminogen activator inhibitor-1, fibrinogen, and C-reactive protein (CRP) have generated considerable interest. Lipoprotein(a), homocysteine, and plasminogen activator inhibitor-1 levels tend to be higher in South Asians than in white populations, although fibrinogen levels appear to be similar.[14,30] These factors support a prothrombotic milieu. Microalbuminuria is recognized as an independent cardiovascular disease risk factor. In a contemporary study, urinary albumin excretion was higher and microalbuminuria more frequent in UK South Asians than in the overall population, even after adjustment for age, hypertension, and diabetes.[31]

Altered Inflammatory Biomarkers and Adipokines

Several lines of evidence suggest that inflammation plays a central role in the development and progression of atherosclerosis.[32–35] In addition to CRP, the prototypical biomarker of inflammation, adipose tissue–derived circulating hormones, namely, adipokines, have been proposed to link insulin resistance to atherosclerosis[36,37] (Figure 2). These proinflammatory adipokines include tumor necrosis factor-α, interleukin-6, leptin, plasminogen activator inhibitor-1, angiotensinogen, resistin, and CRP. Adipose tissue is also the source of antiinflammatory and antiatherosclerotic adipokines, of which adiponectin is the best studied.[37–39] Insulin-resistant states are associated with diminished adiponectin levels, and augmenting adiponectin production is viewed as a cardioprotective intervention.[40]

Numerous studies have suggested that altered adipokine production or action may play a role in the heightened vascular risk observed in South Asian patients. In one of the largest multiethnic studies, Anand et al[41] studied CRP levels in 1250 adults of South Asian, Chinese, European, and aboriginal ancestry randomly sampled from 4 communities in Canada. The age- and sex-adjusted mean CRP levels were higher in South Asians than in Chinese and Europeans, and this effect remained significant even after adjustment for metabolic factors. CRP was independently associated with cardiovascular disease after adjustment for Framingham risk factors, atherosclero-

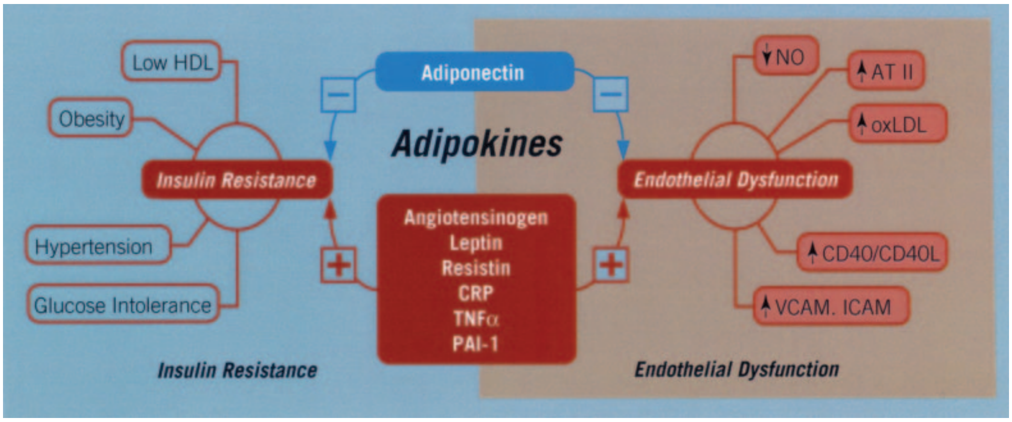

Figure 2. Adipokines link insulin resistance to vascular disease. Adapted from Lau et al.[37]

sis, anthropometric measurements, and ethnicity.

Studies have demonstrated abnormalities in the adiponectin-insulin sensitivity axis in nondiabetic South Asians, which may be an important biomarker linking visceral adiposity to atherogenesis in this population. In an elegant study by Raji et al,[42] adiponectin levels were found to be lower in Asian Indians than in whites, which corresponded to increased whole-body insulin resistance, impaired fibrinolysis, and altered endothelial function in this population. Low adiponectin levels in nondiabetic South Asians may not only confer increased vascular risk but also may be linked to the development of diabetes in Asian Indians.[43]

Altered adipokines may explain why lean nondiabetic Asian Indians have decreased insulin sensitivity compared with whites and Chinese subjects. In a study by Liew et al,[44] healthy, nondiabetic Asian Indians were compared with white and Chinese subjects living in Singapore with respect to insulin sensitivity and leptin levels. Indians had significantly higher fasting serum leptin and lower insulin sensitivities, and stepwise regression analysis showed that ethnicity was the only significant independent determinant variable for the differences in insulin sensitivity index. Similar observations were found by Abate and colleagues,[45] who reported that plasma concentrations of the adipose tissue metabolite leptin and nonesterified fatty acids were higher in Asian Indians than in whites.

Implications for Diagnosis and Treatment

Although it seems quite clear that South Asians are at increased risk for premature glucose intolerance and CHD, there is little evidence with regard to specific preventive and management strategies for South Asians. The INTERHEART case-control study of myocardial infarction in 52 countries concluded that in all ethnic groups, including South Asians, 9 risk factors account for >90% of the population's attributable risk of myocardial infarction.[9] These risk factors included smoking, raised apolipoprotein B/apolipoprotein A1 ratio, hypertension, diabetes mellitus, abdominal obesity, and psychosocial stress. Protective factors included daily consumption of fruits and vegetables, moderate alcohol consumption, and regular physical activity. Thus, these 9 factors warrant routine assessment and management in all subjects at risk for or with established CHD, including South Asians.

Clinicians should remain aware of the increased prevalence of metabolic syndrome and glucose intolerance in South Asians, and should screen subjects accordingly. Screening methods should include measurement of waist circumference and, ideally, waist-hip ratio, rather than BMI. Assessment of fasting glucose and a complete lipid profile are essential. In subjects with features of metabolic syndrome, a strong family history of diabetes, or impaired fasting glucose, an oral glucose tolerance test should be considered. In these same patients, who may otherwise be considered at intermediate Framingham risk, measurement of CRP may prove valuable for additional risk stratification. Although complete lipoprotein profiling cannot be advocated for all South Asians, measurement of lipoprotein(a), apolipoprotein B, and HDL subtypes may be useful in determining the need for combination lipid therapy in some individuals.

The therapeutic strategy likely to confer the greatest benefit to a South Asian individual is one of moderate weight loss through regular exercise and dietary restriction. Reduction of abdominal obesity through lifestyle measures can improve all components of the metabolic syndrome and likely delay the development of both diabetes and atherosclerosis. Beyond lifestyle intervention, optimal management of risk factors to evidence-based targets is essential. At present, there is no evidence to suggest that treatment targets should differ between ethnic groups. Importantly, evidence-based treatments should be optimized in South Asians at risk, including the use of aspirin, lipid-lowering agents, blood pressure control, and renin-angiotensin inhibition.

Disclosures

None.

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