Is South Asian ethnicity an independent cardiovascular risk factor?

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People of South Asian origin constitute a large, visible minority in Canada and are known to be at heightened risk for premature coronary artery disease. Conventional risk factors clearly confer risk in South Asians but do not adequately explain their excess risk compared with other populations. Rates of smoking, hypertension and levels of low density lipoprotein-cholesterol tend to be similar or lower in South Asians, although diabetes is more prevalent. Recent studies have suggested that the metabolic syndrome and abdominal obesity may play a causative role in both the prevalence of diabetes and the premature atherosclerosis noted in South Asians. It is possible that genetically susceptible individuals develop abdominal obesity and insulin resistance when exposed to a toxic environment of reduced energy expenditure and increased caloric consumption. This pattern is increasingly noted in parallel with urbanization, suggesting that the increased cardiovascular risk in South Asians may be preventable through lifestyle interventions and the judicious use of medicines to attain optimal levels of blood pressure, lipids and glucose.

Key Words: Coronary artery disease; Ethnicity; Insulin resistance; Metabolic syndrome; Population health

Cardiovascular mortality has declined considerably in the Western world over the past few decades. However, differential cardiovascular outcomes have been noted in certain patient subgroups based on sex, race, ethnicity and socioeconomic status. In recent years, ethnicity-based research has assumed prominence, particularly in Canada and the United States. In fact, an entire issue of the cardiovascular journal *Circulation* was recently devoted to disparities in cardiovascular care and outcomes (1). People of South Asian origin are known to be at increased risk for premature cardiovascular disease, and constitute a large, visible minority in Canada. Although conventional risk factors for cardiovascular disease clearly confer risk in South Asians, they do not adequately explain the excess risk noted in this population.

CORONARY ARTERY DISEASE RISK IN SOUTH ASIANS

The South Asian subcontinent represents more than one-quarter of the developing world, and refers to a group of countries that includes India, Pakistan, Sri Lanka, Nepal and Bangladesh. People of South Asian origin represent one of the

Le fait d'être originaire de l'Asie du Sud serait-il un facteur de risque indépendant de maladie cardiovasculaire?

Les personnes originaires de l'Asie du Sud forment une minorité visible, importante au Canada et elles connaissent un risque accru de coronaropathie précoce. Les facteurs de risque habituels prédisposent nettement les populations sud-asiatiques à ce type de maladie, mais ils n'expliquent pas à eux seuls leur risque excédentaire par rapport aux autres populations. Les taux de tabagisme, d'hypertension artérielle et de cholestérolémie à lipoprotéines de basse densité ont tendance à être comparables, voire inférieurs, chez les personnes d'origine sud-asiatique, mais la prévalence du diabète y est supérieure. Selon des études récentes, le syndrome métabolique et l'obésité abdominale joueraient un rôle causal dans la prévalence et du diabète et de l'athérosclérose précoce. Il se peut que des personnes soient génétiquement prédisposées à l'obésité abdominale et à la résistance à l'insuline lorsqu'elles sont exposées à un environnement défavorable, associé à une diminution de la dépense énergétique et à une augmentation de l'apport calorique. Le phénomène suit de plus en plus une évolution parallèle à l'urbanisation, ce qui donne à penser que le risque excédentaire de maladie cardiovasculaire chez les habitants de l'Asie du Sud pourrait se corriger par des modifications du mode de vie et une utilisation judicieuse des médicaments afin de permettre une normalisation de la pression artérielle, de la lipidémie et de la glycémie.

largest ethnic groups in the world, with India's population alone exceeding one billion. Migration has resulted in significant numbers of South Asians settling in western countries, including Canada, the United States and the United Kingdom. In Canada, South Asians represent the second largest visible minority and, in a 2001 census, numbered 917,070 (3.1% of the Canadian population) (2). By 2017, South Asians are expected to be the most populous visible minority in Canada, numbering almost 1.7 million. Importantly, South Asians represent the fastest growing visible minority in Canada, with a 36.8% increase in population between 1996 and 2001. Although there are approximately 1.7 million South Asians in the United States, they represent a much smaller proportion of the American population in comparison with the South Asian population in Canada.

In 2000, more than one-half of the world's almost 17 million cardiovascular deaths occurred in developing countries. It is well established that South Asians face an increased risk of premature coronary artery disease (CAD), a pattern that has been recorded among Indians in urban India, and among South Asian migrants in other countries (3-6). Reports of

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increased CAD risk and mortality among South Asians first appeared in Singapore in the 1950s (7), and subsequently in Fiji (8,9). In parallel, studies from the United Kingdom have shown that CAD mortality in South Asians is up to 50% higher than in the general population (10,11). This difference is particularly exaggerated when comparing CAD mortality in South Asian and British men in their 20s and 30s (12). An analysis of the Canadian Mortality Database between 1979 and 1993 revealed that South Asians in Canada experienced higher age-standardized mortality from CAD than did Chinese Canadians or those of European origin (13). South Asians are generally younger at the time of first myocardial infarction or development of heart failure, have larger myocardial infarctions, and have more severe coronary disease at angiography (14-16). A recent retrospective analysis of a large cardiac surgical database in Canada demonstrated that South Asians undergoing coronary artery bypass graft surgery (CABG) have significantly poorer outcomes and survival than do non-South Asians (17). When compared with other Canadian populations, South Asians are more likely to have evidence of CAD even in the absence of symptoms or clinical findings (18). Given the consistent findings of increased prevalence, premature onset and increased mortality from CAD in South Asians, there has been much interest in determining the underlying causes in an effort to develop effective prevention and treatment strategies.

CONVENTIONAL CAD RISK FACTORS

A recent, large, case-control study including subjects in India confirmed that conventional risk factors are clearly associated with CAD in South Asians (19). These risk factors include hypertension, hypercholesterolemia, diabetes mellitus and tobacco use. However, comparative studies from other countries have consistently shown that differences in these risk factors do not fully account for the excess incidence of CAD noted in South Asian immigrants (10). As well, other immigrant populations do not demonstrate the same degree of heightened CAD risk compared with indigent populations, suggesting that there may be unique mechanisms at play in South Asians. When comparing risk factors among populations, it is important to recognize that South Asians represent an extremely heterogeneous group of people, with wide variations in the use of tobacco and meat products, as well as differing cultural approaches to health, diet and exercise.

Conventional risk factors

Tobacco use among South Asian men varies widely according to place of origin and religion, with higher smoking rates in South India and extremely low rates in North Indian Sikh men. Overall, tobacco use in South Asian men is similar to or lower than that in other groups, and is almost nonexistent among South Asian women (4,10,20). Total and low density lipoprotein (LDL) cholesterol levels are similar between South Asians and other populations, including Caucasian populations in the United States and United Kingdom. South Asian high density lipoprotein (HDL) cholesterol levels tend to be lower, and triglyceride levels higher. Rates of hypertension seem to be similar or lower in South Asians compared with other populations (4,10). Obesity, an increasingly important CAD risk factor, is also less prevalent in South Asians, as defined by a body mass index (BMI) of 30 kg/m² or more (21,22).

Diet

Diet is a particularly difficult risk factor to compare among populations, particularly because there is considerable variation in diets within and between South Asian countries. The average Indian diet tends to be high in carbohydrates, polyunsaturated fats and vegetable fibres, and low in cholesterol and saturated fats. In general, South Asians are more likely to be vegetarians and use high-fat dairy products and fried foods. Vegetarianism often results in reduced consumption of omega-3 fatty acids, which are found in fish products and are thought to be cardioprotective. However, CAD rates are similarly increased in people from Bangladesh and South India, areas where fish consumption is typically high (21). Common to certain parts of North India, ghee (clarified butter) has been implicated as a dietary risk factor for CAD. Boiling butter, which results in water evaporation, produces ghee. Some have suggested that this process results in high levels of atherogenic cholesterol oxides compared with standard butter, but this remains controversial (23,24). Although ghee may be atherogenic, all South Asian populations do not uniformly use it, yet most South Asians experience high rates of CAD morbidity and mortality. Therefore, although there are clear dietary differences within and between South Asians and other ethnic groups, these differences do not seem to translate into significantly higher rates of hyperlipidemia or obesity in South Asians. An inverse correlation has been noted between birth weight and lifetime cardiovascular risk, suggesting that in first-generation South Asians, poor maternal nutrition and low birth weight may contribute to increased CAD risk (25). However, the mechanisms underlying this association remain unclear.

Glucose intolerance

In a study comparing South Asian-, European- and Chinese-born Canadians without overt CAD (18), South Asians had similar or lower rates of tobacco use, treated hypertension and treated hyperlipidemia. However, South Asians had an almost threefold increased prevalence of treated diabetes, as well as reduced HDL cholesterol and raised triglyceride levels. Upon completing a 2 h glucose tolerance test, almost one-third of all South Asian participants were identified as having either impaired glucose tolerance or overt type 2 diabetes. These findings were noted despite a lower BMI in the South Asian group. This pattern of type 2 diabetes or glucose intolerance, often associated with reduced HDL cholesterol concentration and increased plasma triglyceride levels, has been consistently noted in many studies of South Asians (10,12,22), suggesting that insulin resistance and the metabolic syndrome may partly explain their excess CAD risk. In the Study of Health Assessment and Risk in Ethnic groups (SHARE) (18), South Asian ethnicity was noted to be an independent risk factor in multivariate logistic regression for cardiovascular disease.

EMERGING CAD RISK FACTORS

Contemporary knowledge implicates a complex interaction between genes and environment in the pathogenesis of CAD. A genetic basis for an increased CAD risk among South Asians is supported by the finding that South Asians tend to have higher lipoprotein(a) levels than other ethnic groups (26). Apolipoprotein A, the constitutive protein of lipoprotein(a), shares homology with plasminogen and may adversely affect fibrinolysis (27-29). Indeed, South Asians have been reported

to have reduced fibrinolytic activity compared with Africans and Europeans. In subjects without manifest CAD, South Asians have also been found to have increased levels of homocysteine and plasminogen activator inhibitor-1 compared with Chinese- and European-born Canadians (18); however, fibrinogen levels were similar among the three groups.

LDL/HDL particle size

When compared with mostly Caucasian subjects from the Framingham Offspring Study (30,31), South Asian men in the United States had similar concentrations of HDL cholesterol and LDL cholesterol. However, the South Asian men had higher concentrations of small HDL particles and had smaller overall HDL particle size. The cardioprotective benefits of HDL are likely restricted to the larger particles, suggesting that those individuals with smaller HDL particles may be at increased risk for CAD. In the same study, LDL particle size also trended lower in South Asians, but the difference was not statistically significant. Other studies, however, have demonstrated an increased prevalence of small, dense LDL particles in South Asians, as well as impaired cholesterol transport (32,33). Additionally, vascular endothelial function has been shown to be altered in South Asians compared with Caucasians (34).

Vascular inflammation

The role of inflammation in the initiation, progression and clinical sequelae of both atherosclerosis and diabetes is an area of intense investigation. Because South Asians are at increased risk for both of these diseases, it is reasonable to consider that heightened inflammatory processes may be operative in this patient population. High-sensitivity C-reactive protein (hs-CRP) is known to be a powerful marker of cardiovascular risk and inflammation, and has been implicated in the pathogenesis of atherosclerosis (35). As well, hs-CRP levels are predictive of the development of diabetes and correlate with the number of abnormalities in the metabolic syndrome (36). Several studies have demonstrated higher hs-CRP levels in South Asians populations than in Caucasian populations (37-39). This difference persists even when adjusting for differences in total body fat and waist circumference, suggesting that South Asians may have an underlying proinflammatory state contributing to their excess CAD risk (40).

Abdominal obesity and the metabolic syndrome

The thrifty gene hypothesis has been particularly popular as an explanation for the excess CAD noted in South Asians. Simply put, this hypothesis proposes that genetically susceptible individuals, when exposed to a lifestyle involving a high-energy diet and reduced energy expenditure, as is common with urbanization, will develop insulin resistance and its attendant complications, including CAD. In the case of South Asians, certain genetic traits that were once protective during times of famine presumably turn harmful in settings of excess energy consumption. Indeed, rates of CAD in urban centres in India are far greater than in rural settings (10).

Numerous studies have shown a consistent pattern of increased abdominal obesity, type 2 diabetes and insulin resistance in South Asians compared with other populations (22,41). This pattern has been noted in South Asians in urban centres within the South Asian subcontinent, and in South Asian migrants to other countries. The prevalence of type 2

diabetes in South Asians ranges from 2% in rural areas up to 16% in those residing in North America or the United Kingdom (42). Recent investigations have revealed that South Asians are likely to have more abdominal visceral fat for any degree of BMI compared with European populations. Accompanying the greater amount of abdominal fat is a higher degree of insulin resistance for the same BMI, a pattern that has been noted in nonobese South Asians as well (43). The resultant hyperinsulinemia that accompanies insulin resistance has been implicated in the pathogenesis of premature CAD. In a study of subjects with established CAD (44), South Asians were found to have a significantly higher prevalence of the metabolic syndrome, despite having a lower BMI. Therefore, it appears that South Asians face increased CAD risk at lower BMI than do European populations. As a result of these observations, the World Health Organization has recommended different BMI cutoff points for overweight (23 kg/m²) and obesity (25 kg/m²) in all subjects of Asian origin (45). Accordingly, the cutoff for abnormal waist circumference in Asian subjects has also been lowered, to 80 cm in Asian women and 90 cm in Asian men. This should be taken into account when determining whether a South Asian patient has the metabolic syndrome because waist circumference is one of the five possible components of the syndrome. Very recently, the International Diabetes Federation has also endorsed differential waist circumference cutoffs in South Asians in its new classification of the metabolic syndrome (46). The International Diabetes Federation has taken this one step forward in recommending specific and different waist circumference cutoffs for people of South Asian, Chinese and Japanese origin. Although it is likely that not all Asians share the same degree of insulin resistance, whether there should be specific BMI cutoff values for obesity between different Asian populations remains unknown.

Adipokines

Adipokines are increasingly implicated in the pathogenesis of insulin resistance, its associated metabolic abnormalities, and eventual atherosclerosis (47). Adiponectin, produced by visceral adipocytes, seems to have a protective effect against insulin resistance, whereas resistin and leptin are considered causative (48). Given that South Asians have proportionately more visceral fat for any given BMI than do others, altered adipokine levels have been implicated in the pathogenesis of insulin resistance in South Asians (49-51). However, limited data are available regarding levels of adiponectin, resistin and leptin in the South Asian population.

IMPLICATIONS

The excess cardiovascular risk faced by people of South Asian origin cannot be explained by conventional risk factors alone. Among emerging cardiovascular risk factors, the complex interplay between abdominal obesity and insulin resistance appears to be a prime candidate in explaining this excess risk. If so, it appears likely that South Asians' enhanced susceptibility to cardiovascular disease results from both genetic and environmental influences. The recognition and adoption of ethnic-specific BMI and waist circumference cutoffs represent a major step forward in refining risk stratification in different ethnic groups, including South Asians.

The metabolic syndrome likely contributes significantly to the excess CAD risk faced by South Asians, and can be easily

suspected at the bedside and confirmed by simple clinical and laboratory tests. Reduction of abdominal obesity in South Asians, primarily through intensive lifestyle changes, can improve all components of the metabolic syndrome. In particular, this approach has been shown to significantly reduce the risk of developing diabetes (52). For those South Asians in whom lifestyle intervention fails, early and aggressive treatment of hypertension, dyslipidemia and diabetes is mandatory. Agents that modify the renin-angiotensin-aldosterone system, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, are known to reduce the incidence of diabetes, and may prove especially useful in South Asian patients. The combination of statins with drugs that can

raise HDL cholesterol levels seems particularly attractive in dyslipidemic South Asians, as do insulin sensitizers in those with diabetes. Future studies may support the earlier use of these drugs in South Asians with milder derangements of lipids and glucose.

An integral component of any strategy aimed at reducing the incidence and impact of CAD in South Asians is the education of both patients and health care professionals. Early recognition of risk factors, adoption of healthy lifestyle behaviours, and appropriate and targeted use of pharmacological therapy are all warranted in this high-risk population. South Asian ethnicity indeed appears to be an independent cardiovascular risk factor, one that clearly deserves our attention.

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