Variant metabolic risk factor profile leading to premature coronary disease: time to define the syndrome of accelerated atherocoronary metabolic syndrome in Asian Indians

Jayasinghe S R, Jayasinghe S H

ABSTRACT
Coronary artery disease (CAD) is fast becoming a major morbidity and mortality burden in the developing world. The magnitude of the problem is predicted to exceed that of the developed world due to the sheer population numbers at risk. The Indian subcontinental ethnicity has been associated with a more severe form of CAD that has its onset at a younger age. This form of coronary disease and its risk factors seem quite different from what has been previously described in studies done among non-Asian Indian populations (mainly Caucasians living in the West). This fact has led to a situation where the current preventative and management protocols that have worked well in the non-Asian Indian populations, have failed to bring about the anticipated control over this disease condition, its progression and its incidence in this population. The time has come to identify the variant of CAD in the Asian Indian ethnic population and the associated metabolic factors, as a separate and distinct entity, and as a unique syndrome. This distinction may facilitate more focused and ethnicity-specific studies to be carried out to unravel the mysteries surrounding the clinical, pathological and molecular biological aspects of the CAD syndrome among Asian Indian ethnics. The outcomes and findings of such investigations may help gain a stranglehold on this rapidly-progressing disease condition among the populations in emerging and densely-populated economies of the South Asian region, as well as among millions of Asian-Indian ethnics living all over the world. Thus we may brace ourselves to better address or even prevent what has been dubbed “the next major clinical epidemic of our times”.

Keywords: atherosclerosis, coronary artery disease, cardiovascular prevention, metabolic syndrome

INTRODUCTION
It is predicted that more than half the worldwide cardiovascular disease burden will be borne by the Indian subcontinent in the next decade. The highest age-standardised cardiovascular disease death rates (per 100,000) in the world among the middle-aged population (30–69 years) are recorded in this region (> 400). Disease burden as well as the mortality from cardiovascular morbidities are projected to grow rapidly and relentlessly in this population, according to recent epidemiological studies. The control measures, proven effective in other populations, have clearly failed to address the cardiovascular disease-related morbidity and mortality, and its rise among Asian Indians worldwide. The lack of accurate recognition of the combination of risk factors, and clinical and epidemiological features of the disease has led to a misguided application of not-so-optimal therapeutics and management protocols in this setting. This is clearly due to the paucity of convincing evidence from ethnicity-specific and focused scientific studies.

Landmark studies focusing on the causation, prevention and treatment of coronary artery disease (CAD) in the past have mostly engaged Caucasian subjects. Therefore, the available evidence on clinical, investigational, preventative and therapeutic aspects of CAD is significantly skewed to this population. The achievement of a noteworthy control of CAD among the white males is testimony to this effect. However, these fundamental applications are not sufficiently effective to curb the epidemic of CAD in the Asian Indian ethnics. This is due to the clear and fundamental differences in the pathophysiology and clinical features of the cardiovascular disease syndrome in the Asian Indian that we have...
reviewed and discussed in this article. Therefore, it is important to recognise the disease among Asian Indians as a distinct entity different from that of the Caucasians. After a thorough review of the available information including published materials, we have identified the distinct features of the unique metabolic derangements leading to CAD in the Asian Indian, its clinical and angiographical manifestation and possible genetic associations, described and defined in this article as the accelerated atherocoronary metabolic syndrome of the Asian Indian (AAMSAI). We believe that the recognition of the distinctiveness of this condition is crucial to the efforts of studying and managing this syndrome, to meet tangible objectives at controlling its relentless spread today, as well as in the future.

**MAGNITUDE OF THE PROBLEM**

Multiple studies have demonstrated the alarmingly high prevalence of CAD in the Asian Indian population worldwide. (4) Cardiovascular disease was the cause of mortality in 40% of urban Indians and 30% of rural Indians, and this trend has shown an exponential increase over time. (5) Even the most liberal assessments of the magnitude of the cardiovascular disease burden in the Indian subcontinent are believed to be gross underestimates, due to the lack of accurate and sophisticated data. (6) The published data on the incidence and prevalence of CAD and the mortality rates associated with CAD, from the multiple geographical regions where Asian Indian populations are aggregated, paint an alarming picture. There is a growing body of evidence emerging from the countries in the subcontinental region (India, Bangladesh, Pakistan and Sri Lanka) that corroborates with the findings elsewhere. Despite the clinical and public health importance of this phenomenon, not enough work that is finely focussed and ethnicity specific, has been carried out thus far, to study and remedy this situation. CAD in the Asian Indian has some unique characteristics that warrant the recognition as a separate syndrome. Such recognition should lead to suitably political as well as scientific initiatives to address the issue of CAD in the Asian Indian.

**DISTINCTIVE FEATURES**

The clinical condition that culminates in coronary heart disease in the Asian Indian demonstrates a combination of well-described distinctive features. These include a unique cluster of risk factors clearly different from that of the traditional coronary risk factor profile, as described historically in relation to the Caucasian. The appearance of the diseased coronary anatomy is distinctive. Its onset at a younger age and the higher distribution in the upper socioeconomic demographics signify its epidemiological uniqueness. At the molecular biology level, there are distinct genetic features that further support our argument. The combination of the above peculiarities is a unique phenomenon, and the intimate interplay of these factors is responsible for the pathogenesis as well as the clinical outcomes related to the unique form of CAD in the Asian Indian. The unique features of this syndrome are elaborated in this article.

**PAUCITY OF TRADITIONAL RISK FACTOR PROFILE**

The traditional risk factors for atherosclerotic vascular disease were first described in studies such as the Framingham study in the mid-twentieth century. (7) The evidence indicates that apart from the high prevalence of diabetes mellitus, all the other risk factors described predominantly for the white populations, were comparatively rare among the Asian Indians, quite disproportionate to the high incidence of CAD. (6,7) However, their ethnicity itself has been identified as a possible specific coronary risk factor, alluding to an entirely different set of ethnicity-specific risk factors that is at play. In the comparative study done in Canada on the incidence of CAD and its risk factors, Anand et al showed that Asian Indians have a significantly higher prevalence of atherosclerotic CAD compared to the Europeans and the Chinese (11%, 5% and 2%, respectively; p = 0.0004), but apart from insulin resistance, the Asian Indians lack other conventional risk factors. (8)

The prevalences of smoking, hypercholesterolaemia and hypertension are generally lower in Asian Indians compared to the Europeans, implying that the traditional risk factors, including the metabolic syndrome in its classic definition, do not account for the high CAD mortality in this ethnic group. (9) Even the so-called novel risk factors identified as significant in the Caucasian have no direct relevance to the Asian Indian. One salient example is the apolipoprotein A-1/B ratio. There is emerging evidence to support the value of the apolipoprotein A-1/B ratio as a useful and accurate risk marker for CAD in the Caucasians. Prospective studies have demonstrated that these apolipoprotein levels are generally low among Asian

### Table I. Median lipoprotein (a) levels among Americans of different ethnic origins

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Median LP(a) level (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>6</td>
</tr>
<tr>
<td>American Indian</td>
<td>3</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5</td>
</tr>
<tr>
<td>Asian Indian</td>
<td>16</td>
</tr>
</tbody>
</table>

LP: lipoprotein
Based on the available evidence, it is clear that there is an entirely different collection of risk factors that is consistently observed, that predisposes the Asian Indian to a premature manifestation of clinical CAD, and this is discussed in this article as a variant metabolic syndrome.

**IS IT DIABETES MELLITUS?**

The relatively higher incidence of diabetes mellitus has been initially proposed as a possible explanation for this disproportionately high incidence of CAD in the Asian Indian. However, it was found that the incidence of diabetes mellitus is much less than the incidence of CAD in this population, and it is insulin resistance, rather than diabetes mellitus, that contributes to the higher prevalence of CAD in the Asian Indian.

**OBESITY PARADOX**

The majority of Asian Indians have a smaller body habitus. Obesity, by its classic definition, is rare among Asian Indians. However, the peculiar body habitus and in particular, the unique pattern of fat distribution, are critically significant risk factors described specifically for Asian Indians. They have a higher visceral fat mass than persons of other ethnicities with comparable body mass indices (BMI). The fat distribution is focussed in the abdominal visceral space, and this peculiarity is seen even in subjects of normal or even subnormal body weight. This factor has a direct relationship to an increased risk of CAD. Accordingly, and correctly so, the description of BMI is corrected for the Asian Indian race. Thus obesity, by its classic definition, is not a metabolic risk factor in the Asian Indian.

**NON-CONVENTIONAL RISK MARKERS: LIPOPROTEIN (a), HOMOCYSTEINE AND ADIPONECTIN**

Three non-conventional risk factors seem to play a very significant role in the pathogenesis of CAD in Asian Indians. Therefore, these can be considered the conventional risk factors for this population. Elevated homocysteine and lipoprotein (a) [LP(a)] levels have a direct association with accelerated CAD. Asian Indian populations living in various geographical locations in the world have been found to have disproportionately high circulating levels of both of these substances (Tables I & II). Some studies have shown a prevalence of more than 75% of hyperhomocysteinemia in India. Unlike in the Caucasians, the elevated homocysteine levels have a higher association with cobalamin deficiency than with folate deficiency in Asian Indians. LP(a) is ten times more atherogenic than low-density lipoprotein (LDL). Due to its homology to plasminogen, LP(a) is highly thrombogenic and antifibrinolytic. Many studies have reported the presence of high levels of LP(a) in many Asian Indians from different parts of the world. Thus, LP(a) may be one of the main factors responsible for accelerated atherosclerosis and early-onset myocardial infarctions in this population. The finding of very high LP(a) levels even in Asian Indian infants testifies to the strong genetic linkage associated with CAD. High LP(a) and low high-density lipoprotein (HDL) levels, with a normal or low LDL level are hallmark features of the abnormal cholesterol profile in the Asian Indian. In a prospective association study in an Indian population, LP(a) elevation had the highest correlation and predictive value with angiographically-defined CAD, compared to all other cholesterol parameters.

The third novel risk factor of importance is low-circulating adiponectin levels. Adiponectin is a cytokine with insulin-sensitising, antiatherogenic and anti-inflammatory properties. Asian Indian ethnics have low plasma adiponectin levels. There is a growing body of evidence to support the direct association between hypoadiponectinaemia (both total adiponectin levels and high-molecular-weight adiponectin levels) and aggressive CAD in the Asian Indians. This association has not been observed in the Caucasians in the head to head comparisons with Asian Indians. Based on the available evidence, it can be concluded that high LP(a) levels, high homocysteine levels and low adiponectin levels are real risk markers of AAMSAI.

**CLINICAL MANIFESTATIONS**

Clinical manifestations of CAD in the Asian Indian are different from that of the Caucasian. A unique feature of CAD in the Asian Indian is the significantly

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Table II. Comparison of biomarkers levels between white Caucasians and Asian Indians.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Caucasian</th>
<th>Asian Indian</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma homocysteine</td>
<td>8.0</td>
<td>12.6</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>70</td>
<td>49</td>
<td>0.05</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>320</td>
<td>204</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Adapted from Chandala et al.
younger age of clinical manifestation with myocardial infarction developing, on the average, at least five to ten years earlier. The heightened risk of CAD is most apparent among those below the age of 40 years in Asian Indians. Another unique feature is the higher cause-specific mortality in the relatively young Asian Indian with CAD. The picture is common to both native Asian Indians and those who have migrated elsewhere. The rates of CAD and related hospitalisation, mortality and case fatality are significantly higher among migrant Asian Indian populations than the average rates of their adopted countries. This disproportionately high prevalence of CAD in Asian Indians living in the West is further testimony that control measures that work in other populations do not work in the Asian Indian.

CORONARY ANATOMY
The significantly different coronary anatomy with more diffuse disease manifested at a younger age is a hallmark feature of CAD in the Asian Indian. The prevalence of triple-vessel disease and more severe diffuse coronary atherosclerosis is much higher. Compared to the Caucasians, the coronary arteries in the Asian Indian appear smaller, with severe and diffuse atherosclerosis (Fig. 1). The smaller appearance of the coronary artery on angiography is attributed to the luminal narrowing caused by widespread and contiguous atherosclerosis. It is believed that atherosclerotic plaque deposition happens quite early in life in the Asian Indian ethnicities.

SOCIOECONOMICS AND DEMOGRAPHICS
In the white Western population, CAD is mostly prevalent among the lower socioeconomic strata, while in the Asian Indian population, it is observed mostly among the well-educated and the affluent.

GENETIC DETERMINANTS
The genetic basis of a deranged metabolic risk factor profile in the Asian Indian shows distinct differences from those observed in the Caucasian, in that the MTHFR 677 C > T genetic mutation does not contribute to elevated homocysteine levels in the Asian Indian. However, distinct and unique mutations in two paraoxonase genes (PON1 & PON2) have been identified in Asian Indians with CAD. There is still significant paucity of information on the genetic mutations and their associations with severe and premature CAD in the Asian Indian, due to the lack of targeted and focussed genetic studies in this ethnic population.

METABOLIC SYNDROME AND THE ASIAN INDIAN PARADOX
There is much controversy and contention associated with the term, metabolic syndrome. Metabolic syndrome as a concept was first introduced in Sweden in 1923, to define the association of hyperglycaemia, hypertension and gout. Since then, this concept has been defined by different authorities, in several different ways, and the latest being the new worldwide consensus definition, as described by the International Diabetes Federation. According to the new definition, metabolic syndrome comprises abdominal obesity, raised triglyceride levels, low HDL levels, hypertension and impaired fasting hyperglycaemia or diabetes mellitus. However, this definition of metabolic syndrome denotes a constellation of cardiovascular risk factors as identified and described predominantly in the Caucasians. The new worldwide consensus definition attempted to compensate (to a very limited extent) for this flaw by recognising a different set of measurements to define abdominal obesity in different Asian ethnics from the different regions in the Asian continent. It is widely recognised that there are variations in the combinations of different metabolic derangements in different populations groups, that can lead to a wide array of disease outcomes, of which the majority are cardiovascular in nature. Thus, it is clear that the traditional definitions of metabolic syndrome still fail to be representative of Asian Indian ethnicity. It is interesting to note that the conventional descriptions of metabolic syndrome have no mention of genetic factors that serve as CAD risk markers.

In defining the metabolic syndrome unique to the Asian Indian, it is important to recognise the accelerated
progression of coronary atherosclerosis, leading to myocardial infarction at a younger age. The unique constellation of known metabolic risk factors that predisposes the Asian Indian to CAD and its manifestation early in life can be recognised by the summary definition of AAMSAI. The distinct features of this metabolic syndrome with accelerated atherosclerosis in the Asian Indian include visceral adiposity, insulin resistance/hyperinsulinaemia, high \( Lp(a) \) levels, low HDL levels, high homocysteine levels and low adiponectin levels. The new worldwide definition of metabolic syndrome and the definition by the National Cholesterol Education Program Adult Treatment Panel III, both include hypertension, diabetes mellitus, hypertriglyceridaemia and obesity as integral elements. However, these are not consistently observed in the syndrome, as defined by AAMSAI. It is important to stress that AAMSAI is not a new disease, but a practical and appropriate term to recognise an existing constellation of clinical features more unique to the Asian Indian ethnic group.

As discussed before, often the clinical and angiographic manifestations of CAD associated with AAMSAI is different from the more prevalent CAD associated with traditional risk factors in the non-Asian Indian populations. It is important to acknowledge that the traditional definition of metabolic syndrome also exists in some Asian Indians. The INTERHEART study reported there has been a gradual increase in the incidence of traditional risk factors for CAD in the Indian Subcontinent lately. Though this observational study failed to establish a causative effect, this development coupled with AAMSAI can create an explosive situation in the Asian Indian communities, posing the threat of an unbridled and unprecedented spread of CAD. This underlines the urgent need to act fast. The identification of AAMSAI as a separate and distinct entity is thus important for the purpose of carrying out targeted research work, to better study this phenomenon and to identify unique and specific solutions to this rapidly-growing health problem.

### Table III. Salient features of the accelerated athero-coronary metabolic syndrome of the Asian Indian.

- Elevated \( Lp(a) \) levels
- Elevated homocysteine levels
- Low adiponectin levels
- Hyperinsulinaemia
- Visceral adiposity
- Clinical manifestation of CAD at a younger age (< 60 years)
- Diffused coronary atherosclerosis
- Asian Indian ethnicity

### INVESTIGATIONS AND THERAPEUTICS

It has been observed that the mere absence or the control of the conventional risk factors of CAD does not afford significant protection to the wide majority of risk-prone Asian Indians. Risk stratification in this population requires a battery of additional tests. Tests for serum homocysteine, \( Lp(a) \) and adiponectin levels are essential. Body habitus measurement, particularly the abdominal adiposity and serum insulin levels, needs to be routinely performed. A more complete and optimal test profile that accurately reflects the true coronary risk of the Asian Indian should emerge with more research. A comprehensive battery of genomic tests is a definitive future possibility. Studies exploring the therapeutics of CAD have mostly been carried out among the non-Asian Indian populations. Therefore, how cutting-edge treatment modalities would impact the control of the disease in this population, is largely unknown. The prevention and treatment of CAD in Asian Indians require a more rigorous approach than that for their western counterparts. Optimal control of conventional risk factors alone is evidently inadequate. Due to the paucity of information based on ethnicity-specific randomised control studies, it is difficult to conclusively define the optimal therapeutic protocols for coronary risk reduction among Asian Indians. Agents such as extended-release niacin with the dual effects of reducing \( Lp(a) \) and elevating HDL levels, may prove significantly beneficial. In addition, agents that control homocysteine levels, such as folate and cobalamin, may also constitute this optimal regimen. The efficacy of standard means of revascularisation also needs to be evaluated in this population. The recognition of metabolic aberrancies that contribute to the rapid and early progression of CAD as a distinct disease entity will result in more targeted research. This will provide the conceptual framework for new and focussed work to be designed and implemented.

### FUTURE DIRECTIONS

Significant knowledge gaps still exist in relation to this disorder. Although alarm bells regarding the devastating effects of CAD among Asian Indians have been ringing for some time, clinicians and researchers have paid little attention to it. There is a need for long-term definitive and large-scale population-based prospective studies (akin to the Framingham study) to be carried out to ascertain the dynamics of the clinical and pathological behaviours, and epidemiological evolution of AAMSAI. Population-specific DNA bio-banks should be developed to perform targeted genomic and proteomic research into AAMSAI. Such studies may see the development of more sophisticated molecular diagnostics and therapeutics that
could be applied to mass populations with much cost efficacy. New therapeutics should be developed to address the risk factors and clinical eventualities of this syndrome, and these should be tested in ethnicity-specific randomised controlled studies. Given that the wider majority of the affected populations live in poorer economies, future advancements should be cost efficacious enough to be within the reach of the poor and the needy.

The description and definition of the conventional metabolic syndrome have seen a metamorphosis over time, with the emergence of new knowledge. A similar evolution may also take place in the definition of AAMSAI, with the emergence of new knowledge and discoveries. But history would acknowledge us for taking a decisive stand today to identify AAMSAI as a separate entity. This will serve to create a catalyst for focussed scientific enquiry and investigation, that unequivocally remains the need of the hour.

CONCLUSION

AAMSAI is an appropriate term to define the early onset of diffuse CAD in the Asian Indian and its unique combination of risk factors. Its recognition as a distinct disease entity would attract an increased attention from both clinicians and researchers. This would generate knowledge, leading to a better understanding of the condition and helping to devise effective means of control and treatment. The cardinal features of AAMSAI include an early onset of symptomatic CAD and often diffuse coronary atherosclerosis, visceral adiposity, high serum levels of LP (a) (often with a normal total cholesterol level and low HDL levels), high levels of homocysteine, low levels of adiponectin, insulin resistance/hyperinsulinaemia, other conventional coronary risk factors and Asian Indian ethnicity (Table III). With due recognition given to AAMSAI, we may be better able to handle this major clinical epidemic of our times, which is our "greatest challenge in healthcare". (33)

REFERENCES

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