Third Meeting of the International Working Group on
Coronary Artery Disease in South Asians
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Introduction

The Third Meeting of the International Working Group (IWG) on Coronary Artery Disease (CAD) in South Asians (SAs) was held at Atlanta, Georgia, USA on 29 March 1998. Several scientists from India, United States, Canada and Nepal participated in the discussions. The first two meetings of the IWG had concluded that CAD is a major problem among SAs and special efforts may be required to control the epidemic'2. It called for the beginning of preventive strategies at an earlier age in SAs than in other populations due to the aggressive nature of premature CAD in the former. The goals of this meeting were similar to the previous two, that is:

1. To reassess the burden of CAD in SAs in various countries;
2. To provide a forum for scientists working in this field to present their ideas, data and future plans;
3. To prioritise and coordinate future research;
4. To plan future international conferences on this topic; and
5. To compile a list of ongoing major scientific studies in SAs in various countries.

Terminology. 'South Asian' is the preferred term in the UK and Canada, whereas 'Asian Indian' (AI) is preferred in the US. The term 'Indian' is used in India and Singapore. Therefore, the terms Indian, Asian Indian and South Asian are used interchangeably in this report and signify people originating from the Indian subcontinent. This meeting focused on some of the emerging risk factors that may be of greater relevance in SAs.

Triglycerides

Dr. Michael Miller presented data highlighting the growing importance of triglycerides in CAD, which has since been published'. He pointed out that although serum triglycerides levels below 200 mg/dL are generally considered desirable, the median level of triglycerides in the US population is about 100 mg/dL. This is in contrast to serum total cholesterol (TC) levels, for which both the mean and median levels are about 200 mg/dL. He used triglycerides more than 100 mg/dL as the cut-point in assessing the CAD risk associated with triglycerides levels. During a follow-up of 18 years, he found an odds ratio (OR) for CAD of 1.5 for serum fasting triglycerides levels above 100 mg/dL (compared to those with triglycerides level <100 mg/dL). In this study, the OR for CAD for triglycerides more than 200 mg/dL was similar to that of diabetes.

Dr. Miller reviewed several recent studies which showed a significant risk of CAD at triglycerides levels generally considered desirable (<200 mg/dL) or borderline (200-400 mg/dL). In a recent meta-analysis of 17 population-based prospective studies involving 46,413 men and 10,864 women, a 90 mg/dL (one mmol/L) increase in triglycerides level was associated with a 30 percent increase in cardiovascular risk in men and a 75 percent increase in risk in women1. In the Copenhagen Male Study, the eight-year incidence of CAD in subjects with serum triglycerides levels between 142 and 221 mg/dL was 14 percent versus 9.5 percent in those with TC above 310 mg/dL5. An increase of triglycerides from 90 mg/dL to 180 mg/dL was associated with a doubling of the incidence of CAD6. Whereas the previous studies focused on fasting triglycerides, the Physician's Health Study7 has reported an OR for CAD of 1.4 per 100 mg/dL increase in non-fasting triglycerides levels. Drexel et al8 reported that an increase in triglycerides by 90 mg/dL had the same effect on the extent of coronary atherosclerosis as an increase in age by 10 years. In the Quebec Cardiovascular Study9 the OR for CAD was higher for triglycerides than other lipoproteins.
(triglycerides level > 135 mg/dL, OR 3.5; LDL > 143 mg/dL, OR 2.4; small dense low-density lipoprotein (LDL), OR 2.5; apolipoprotein B > 110 mg/dL, OR 2.7). In addition, elevated triglycerides had a higher prevalence (77%) than elevated LDL (68%), elevated apolipoprotein B (69%) and small dense LDL (69%).

Triglycerides levels have an effect on LDL particle size, density, distribution and composition leading to smaller, denser and more atherogenic particles. However, triglycerides levels are inadequate surrogates for atherogenic lipoproteins because chylomicrons and large very low-density lipoprotein (VLDL) particles are not atherogenic. This explains why the CAD risk is not increased in Frederickson Type I and Type V dyslipidemia. Serum triglycerides levels provide an indirect measurement of LDL particle size, whereas the apolipoprotein B levels provide a reasonable estimate of the number of atherogenic particles. Therefore measurement of apolipoprotein B levels may help identify those with "atherogenic hypertriglyceridemia". Whereas "Statins" are highly effective in lowering the LDL and apolipoprotein B levels, these drugs have little impact on LDL particle size. Conversely, fibrates and niacin, which lower triglycerides and raise the high-density lipoprotein (HDL), have greater effects on LDL particle size, with less impact on particle number. Gemfibrozil and bezafibrate have been found to reduce cardiac mortality. In addition, bezafibrate has also been shown to reduce the angiographic progression of CAD.

These data suggest that current guidelines in the management of dyslipidemia may be underestimating the significance of triglycerides as an important risk factor. Furthermore, the levels well within the range currently considered desirable or borderline may be associated with significant risk of CAD. High triglycerides with low HDL levels has been a universal finding among Asian Indians worldwide. Currently a study (by University of Maryland, Baltimore) is underway to ascertain the role of triglycerides and HDL in premature CAD. The study has enrolled a substantial number of Asian Indians.

Antioxidants

Dr. Sampath Parthasarathy discussed the role of lipid oxidation and antioxidants in CAD. Recent research indicates that modification of LDL is an important step before it can be taken up by the macrophages to produce foam cells — the earliest precursor of atherosclerosis. Oxidation of LDL is a free radical-mediated process involving peroxidative modification of the polyunsaturated fatty acids (PUFA). In general, PUFA are highly susceptible to oxidation and yet associated with a lower risk of CAD. Monounsaturated fatty acids (MUFA) are generally resistant to oxidation and populations consuming large amounts of MUFA for centuries such as the Mediterranean countries have very low rate of CAD. Saturated fatty acids (SAFA) are also resistant to oxidation, but are highly atherogenic by virtue of their profound LDL-raising properties. Currently, there are no simple standardised assays for LDL oxidation that can be used in clinical practice.

The initial step in the oxidation of LDL is the formation of minimally modified LDL (MM-LDL) in the subendothelial space. MM-LDL induces several chemotactic proteins including macrophage colony stimulating factor by the endothelium. It promotes the differentiation of monocytes into macrophages, which in turn further oxidise MM-LDL to oxidised LDL. MM-LDL is still recognised by the LDL receptor, since it has undergone only mild lipid peroxidation. Oxidised LDL is not recognised by the LDL receptor but is taken up by the scavenger receptor system on the macrophages, which are not regulated by the intracellular cholesterol content. The resulting accumulation of cholesterol in macrophage leads to foam cell formation. Oxidised LDL is cytotoxic, promotes endothelial dysfunction and stimulates tissue factor and plasminogen activator inhibitor-1 synthesis.

Whether the LDL is modified in the serum or in the arterial wall is the subject of intense research but Dr. Parthasarathy believes that it occurs in both places. The clinical significance varies depending upon the site of oxidation. Exercise is a powerful oxidant but it has several beneficial effects on the cardiovascular system. Short bursts of exercise will increase the oxidisability of the LDL but exercise training and regular sustained exercise will make the LDL more resistant to oxidation. Oxidation of LDL in plasma may be beneficial since the liver rapidly clears oxidised LDL. This may explain how exercise lowers serum LDL levels.

The oxidative susceptibility of LDL correlates with the severity of coronary atherosclerosis and antioxidants such as α-tocopherol reduces the progression of coronary atherosclerosis. In one study, supplementation of the diet with α-tocopherol (the most prevalent and active form of vitamin E) reduced the rate of recurrent myocardial infarction (MI) by 77 percent although it has no LDL lowering effect. There is little correlation between serum levels and daily intakes of vitamin E. HDL is believed to be an antioxidant and those with low levels of HDL might require a higher dose of antioxidants. The information on antioxidant status of Indians is limited.
One study has reported lower levels of vitamin C among Indians than among Chinese in Singapore.

HOPE, SHARE and INTERHEART

Dr. Salim Yusuf noted that several studies are underway testing the role of vitamin E in preventing cardiovascular events. The results of one such study (HOPE) involving 9,000 patients will be available by the end of 1999. If these studies demonstrate significant beneficial effects, dietary factors such as antioxidants could become an additional cost-effective member of the antiatherosclerotic repertoire.

A recent study reported a new methodology in determining the ethnicity more accurately by combining last name and country of birth rather than relying on the country of birth alone. This study highlighted the difference in the cause of death among Chinese, Whites and South Asians in Canada. South Asians have significantly lower rates of cancer of all organ systems than Whites but higher rates of CAD and diabetes. Chinese have very low rates of CAD and diabetes but a high rate of cancer, a pattern seen also in China and the US. Low CAD mortality in Chinese has been observed in other countries and is attributed to lower levels of serum cholesterol and a diet low in SAFA. Dr. Yusuf, one of the authors of the study also briefly reviewed the preliminary results of the Strategies for Health Assessment and Risk in Ethnic Groups (SHARE) study showing significant differences in the prevalence of risk factors and subclinical atherosclerosis as assessed by intimal medial thickness of carotid arteries by B-mode ultrasound. This study involved a carefully randomised sample of 1,200 individuals, consisting of about 300 each of South Asians, Chinese, Whites and native Canadians (First Nation). The results will be available by early 1999 and may be presented at the Fourth Meeting of the IWG. Dr. Yusuf also briefly discussed a multinational case control study (INTERHEART) involving 20,000 patients with MI and as many controls in more than 50 countries in four continents. This study is expected to involve at least 2,000 subjects in India and could provide new insight into determinants of CAD in the Indian subcontinent.

CADI Study Update on Lipoprotein(a) [Lp(a)]

Dr. Enas presented an update on the Coronary Artery Disease in Asian Indians (CADI) study focusing on the Lp(a) levels in Asian Indians in North America. The final result of the study has since been published. The high rate of CAD in Indians despite low rates of risk factors suggests the possible role of a genetic risk factor, uninfluenced by even maximum modification of lifestyle. Lp(a) is such a risk factor, since its levels are genetically determined and minimally by diet and exercise. It has significant thrombogenic and antifibrinolytic properties due to its structural homology with plasminogen. Lp(a) is not normally distributed and because it is markedly skewed to the lower end of the range, the use of mean Lp(a) concentration may be potentially misleading. Lp(a) level is an important predictor of the risk of CAD in patients with hypercholesterolemia and hypertension. Lp(a) appears to be a stronger risk factor than diabetes for CAD in young women.

The CADI study was the first to report elevated serum levels of Lp(a) in Asian Indians. Lp(a) levels above 30 mg/dL (generally considered the threshold for high risk of CAD) was the most common risk factor and was found in 25 percent Asian Indians. For comparison, 17 percent of Whites and 8 percent of Hispanics have Lp(a) levels above 30 mg/dL. Subsequent studies from North America by our own group and others have repeatedly confirmed high Lp(a) levels in Asian Indians in the US, India, UK and Singapore. In Canada 50 percent of the South Asians had elevated levels of Lp(a).

Lp(a) levels in the cord blood were higher among Indian newborns than in the Chinese newborns in Singapore and the difference in Lp(a) levels parallels the 4-fold difference in CAD mortality among adults between these two ethnic groups in that country. The Lp(a) levels as well as the CAD mortality rates were intermediate in the Malays. Since stable adult levels are reached in infancy, its pathological effects start about 15 to 20 years earlier than other risk factors. This explains the crucial role of Lp(a) in premature CAD. Lp(a) levels are highly correlated with the severity of CAD in Indians, similar to that found in Whites. More recently, Lp(a) was found to be an independent predictor of CAD in diabetic patients in India.

Lp(a) levels above 30 mg/dL are associated with a 3-fold higher risk of CAD, which increases markedly when TC levels are also elevated. Recent research indicates that Lp(a) over 40 mg/dL increases the risk associated with cigarette smoking by a factor of 1.9, diabetes by a factor of 3.4, elevated TC levels by a factor of 4.2, hypertension by a factor of 4.6, high TC/HDL ratio by a factor of 6.9, and high homocysteine levels by a factor of 9.3. The risk of CAD with elevated Lp(a) appears to be greater with low HDL (<40 mg/dL) or high TC/HDL ratio than with elevated LDL (>200 mg/dL). For example, in subjects with Lp(a) above 40 mg/dL, the OR for premature CAD is 26 when TC/HDL...
ratio is more than 5.85 compared to 14 when TC level is above 260 mg/dL. In addition, among those with an Lp(a) level over 40 mg/dL, the OR for CAD increased to 122 when a TC/HDL ratio of more than 5.85 is accompanied by two other risk factors. Thus, Lp(a) appears to be an important risk factor, especially in individuals with high TC/HDL ratio, elevated homocysteine or other risk factors.

Substantially lowering LDL by statins has been the mainstay of management of elevated Lp(a). Lp(a) levels can be lowered by large doses of niacin in both sexes and by estrogen in post-menopausal women. Inexpensive vitamins such as folic acid, B6, and B12 can lower elevated homocysteine levels. However, randomised clinical trials supporting the benefit of such treatment are yet to be reported.

Concluding Remarks

There was agreement among the participants that CAD is a major problem for Indians both in India and abroad. The participants stressed the importance of a coordinated effort in addressing the high rate of CAD in Indians. At present, there is very little coordinated and concerted effort directed to prevention of CAD in India. Assessing and accepting the magnitude of the problem and developing national guidelines for Indians incorporating relevant information from the National Cholesterol Education Programme and the 4th Report of the Joint National Committee on Detection and Treatment of High Blood Pressure were emphasised. The success in reducing CAD mortality by more than 50 percent in Finland and the US by aggressive public health campaigns and the desirability of adopting such measures in India were highlighted. The potential role of cooking oils and cooking habits in excess CAD in Indians has not been studied adequately. The need for studies assessing the role of emerging risk factors such as homocysteine, Lp(a), triglycerides and low HDL and development of strategies for reducing the risk from both emerging and conventional risk factors deserves urgent consideration by the government as well as the physicians of the country.

References

Lipoprotein (a) levels in Indian physicians. Comparison with Black and White physicians in the USA [abstract]. Indian Heart J 1994; 46 (Suppl): 185


32. Solyomos BC, Marcil M, Wesolowska E, Gilfix B, Lesperance J, Campeau L. Relation of coronary artery disease in women, 60 years of age to the combined elevation of serum lipoprotein (a) and total cholesterol to HDL cholesterol ratio. Am J Cardiol 1993; 72: 1215–1219


