Risk Factors For Coronary Artery Disease In Young South Asians: A Cross-Sectional Study Of Indians Living In India And Second-Generation Indian Immigrants To The United States of America.

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A. Study Purpose And Rationale

Approximately one-sixth of the world's population lives in India, and there are about 15 million Indian immigrants who live outside India, including about one million in the USA. South Asians have been found to have one of the highest rates of coronary artery disease (CAD) among all ethnic groups. Several studies have reported high rates of CAD in this population. For example, men in New Delhi were found to have four times the prevalence of CAD than in men in Framingham, MA. (1, 2) Not only are the rates higher, but the current trend in India reveals and increasing number of cases whereas the number seems to be decreasing in developed countries. For example, the hospitalization rate for CAD at Christian Medical college Vellore, South India, has increased from 4% of all cardiac admissions in 1960 to 33% in 1989. In a study in England between 1979 and 1983, the CAD mortality rate among American immigrants declined 23% in men and 36% in women, whereas among Asians Indian men the rate increased by 6% and in (4) Asian Indian women the rate increased by 13%.

This CAD risk appears to be conserved among Indians who have emigrated out of India. In a study of Asian Indian physicians and their family members, the age-adjusted prevalence of myocardial infarction was approximately three times more in Asian Indian men compared to the Framingham Offspring Study (7.2 % vs. 2.5%). (5) Such high rates of CAD have been noted in Indian immigrants in other areas as well such as Singapore, Uganda, South Africa, and UK. Data further suggests that not only is CAD more prevalent among Indians, but it also appears to be more malignant with diffuse three vessel disease being more common than among other ethnicities. In a British study, more Indians were found to be unsuitable of coronary artery bypass grafting than whites, and among those refused surgery, 25% died within a period of 19 months as compared with 6% of whites. The size of myocardial infarction as assessed by peak CK levels or by degree of ventricular dysfunction was also significantly greater in Asian Indians.

South Asians also seem to be predisposed to early and accelerated atherosclerotic disease as compared with other ethnic groups, resulting in a high rate of premature morbidity and mortality. Premature CAD is defined as CAD occurring below the age of 65 in women and 55 in men. CAD in the young is defined as CAD occurring in patients less than 40 years of age. About 70% of MI patients in Calcutta and 97% in Madras were less then 60 years old. Another report from Madras found that 10% of all patients undergoing catheterization for angina pectoris were 27-40 years old with a mean age of 38 years. In a recent study in Texas the prevalence of CAD in the young in the American population was found to be less then 2% ;(8) among Indians, this number is as high as 12%. (9) A British study found that among all patients admitted to a coronary care unit, the rate of a first myocardial infarction was five times higher among Indians than among native English when all age groups were examined. Yet, among the 30-39 age group, the rate among Indians was ten fold higher.(10) Similarly, in Malaysian study, the incidence of CAD in young Indians was fifteen fold higher as compared with Chinese, and ten fold higher as compared with Malays. In terms of mortality due to CAD, when rates among Asian Indians were compared with overall rates in England and Wales, mortality was 2.1 times higher in Asian Indian men between the ages of 30-39, and 3.1 times higher between the ages of 20-29.

The traditional risk factors of HTN, hypercholesterolemia with high LDL and low HDL, smoking, and diabetes do not completely explain the higher prevalence of severe CAD among South

Asians. Several studies have shown that hypertension does not explain a higher incidence of CAD in Indians; in fact, several subgroups of South Asians have a lower systolic and diastolic blood pressure than whites. In the Indian Physician study in the USA, hypertension was less prevalent in Asian Indian men then in whites. (13) Although several subgroups of South Asians do have high smoking rates, especially in urban areas, there are a larger number who do not smoke, and yet maintain a high incidence of CAD. In a study of Indian physicians in the USA, the prevalence of cigarette smoking in Indians was 1.3% as compared with 27% in whites. Thus although smoking can partially explain the high incidence of CAD in some groups, it does not appear to be a dominant factor among all South Asians High total cholesterol and LDL levels are known to be powerful risk factors for CAD among white males. Among South Asians, however, this does not seem to be the case. In a study in (14) Madras, 75% of people with MI had a plasma cholesterol level less than 200 mg/dL. In the UK, (15) cholesterol levels among Indians were found to be lower than the native population, while in the USA total cholesterol and LDL levels among Indians and whites were similar.

HDL levels, however, among Indians and Indian immigrants abroad seem to be higher, and data consistently show low levels significantly linked to higher CAD morbidity and mortality. in a study of migrant Indian physicians to the USA, Mean levels of HDL levels were significantly less in younger (30-39) Indian men (0.98 vs. 1.18 mmol/1) and women (1.24 vs. 1.45 mmol/1) than their (17) western counterparts. Similar trends have been found for triglycerides as well.

Lp(a) has also recently been identified in several studies as an independent risk factor for CAD, especially among South Asians who tend to have baseline higher levels than whites. Lp(a) is a subfraction of LDL, but is several times more atherogenic than LDL. It consists of an LDL-like molecule which contains apolipoprotein B-100 which is attached by a disulfide linkage to a polymorphic apolipoprotein(a) moiety which is very similar to plasminogen. Thus, the LDL portion of Lp(a) is pro-atherogenic, and the apo(a) moiety, which resembles plasminogen, is prothromogenic. (18) In a multi-ethnicity study in Singapore, Lp(a) was found to be significantly higher among Indians than Chinese and Malays.(19) In another study, Lp(a) was examined in patients with and without angiographically defined CAD, and was found to have a mean value of 26 mg/dL in CAD patients compared with 15 mg/dL for normal controls .(20) Further, Lp(a) levels in infants have (21) been found to be identical with those of the affected parent, suggesting that the pathologic processes associated with high levels of Lp(a) start much earlier than other risk factors, possibly accounting for premature CAD in South Asians.

Diabetes and insulin resistance have been found to be strong independent risk factors for CAD among South Asians. In a study of South Asian men in London, ischemic ECG abnormalities with major Q waves were strongly associated with glucose intolerance and (22) hyperinsulinemia. In Singapore, glucose intolerance was much higher among Indians than Chinese or Malays in both men and women, and correlated with a higher incidence of dyslipidemias. Indian diabetics also seem to have a pronounced tendency for abdominal obesity (23) as is evident by a higher waist to hip ratio. The combination of diabetes, hyperinsulinemia with the correlated dyslipidemias, and higher WHR suggest a possible higher incidence of Syndrome X among South Asians, and might account for higher CAD morbidity and mortality.

There is considerable variation in dietary patterns among South Asians, with some estimating that more than half are vegetarian. The high amount of diversity makes is hard to generalize about nutrient intake, but it has been suggested that even vegetarians often have diets that are rich in saturated fats, known as "contaminated vegetarianism." Alcohol consumption among Indians tends to be lower than among their western counterparts.

Recently, there has been considerable data on inflammation and CAD. It has also been suggested that infectious agents such as chlamydia and CMV might mediate some of this inflammation, although definitive studies still need to be done. It is possible that environmental factors in South Asia may play role in induction of inflammation and the pathogenesis of CAD among Indians living in India.

It is apparent that the traditional risk factors, which were used to identify at risk populations in the western world, are not entirely applicable to South Asians. It is possible that migration of South Asians to western countries compounds their risk factors to include aspects of both environments. For example, in a

recent study of Indians living in London and their siblings in India, both groups had higher Lp(a) levels than Europeans in the UK, yet the South Asians in London had higher body mass index, plasma cholesterol, fasting blood glucose, as well as lower HDL cholesterol with reduced insulin sensitivity in comparison with their siblings. Thus, South Asians in migrant environments may be at a higher risk of CAD due to (1) the confluence of genetic factors that predispose to high Lp(a) levels, central obesity/dyslipidemias/glucose intolerance complex with (2) environmental influences that lead to weight gain, rise in plasma cholesterol and blood pressure levels.

The purpose of this study is to quantify possible CAD risk factors among young Indians living in India, and among second generation South Asians born in the USA. Given the predisposition of Indians to premature CAD, it is important to examine risk factors from a very young age. The prevalence of risk factors among teenaged South Asians has not been studied. In order to separate the effect of environment from genetic predisposition, it is important to study populations that have not migrated from one place to the other, thus possibly having been influenced by both environments. All studies on migrant South Asians so far have examined populations that have lived part of their lives in India. This study will examine South Asians who have been born in the USA and lived here all of their lives. The data will help to evaluate which risk factors are prevalent in all South Asians independent of environment, and which ones are functions of the environment. It will also help to determine if the presence of risk factors from an early age is possibly responsible for premature CAD seen in South Asians. The data from the two populations of South Asians will then be compared with existing data on American whites.

B. Study Design

This study is a cross-sectional study of CAD risk factors among Indians living in an urban environment in Bombay, India, and of South Asians born and living in the USA. Subjects to be studied are men and women aged 15-45 in order to include a sample of post-pubertal teenagers.

C. Recruitment of Subjects

The sample will be taken from a non-medical environment so as to avoid any bias towards patients with CAD. In India the sample will be taken from a school and university population where a health fair will be conducted with qualified nurses drawing blood, doing physical exams, and administering a questionnaire. A similar health fair will be done in a temple in New York, which will serve as a center visited by a diverse South Asian population, although of only one religion.

a. Criteria of Selection

- Age: 15-45
- No lipid lowering therapy
- USA sample: Born in USA with no stay in India over 1 year

D. Sample Size

In order to have the power to significantly detect a difference in HDL levels of 5% between the two populations, the sample size will have to be 300 in each population. This sample size should be able to detect differences in prevalence of DM, insulin resistance, smoking, alcohol consumption, and also levels of Lp(a), HDL, LDL, total cholesterol, and trigy1cerides.

E. Study Procedures

Each of the following variables will be assessed for both groups and then compared to available data for Caucasians.

a. Questionnaire

- Age
- Sex
- Medications
- Past History
- Hx of CAD
- HxofCVA
- Hx of DM
- Hx of PVD
- Hx of HTN
- Family/Social Hx:
- Hx of Cigarette smoking and duration
- Hx of Alcohol consumption and duration
- Family Hx of CAD, HTN, CVA, PVD, DM
- Leisure time activity - to be assessed by the third National Health and Nutrition
- Examination Survey

b. Diet

By either 24 hr. recall, or food frequency questionnaire. A sample size of 300 should be adequate to assess differences in dietary pattern between the two groups. The diet will then be broken down into levels of carbohydrates, protein, fat, saturated fat, and monounsaturated fats via existing data on recipe composition of Indian food.

c. Physical Exam

- SBP, DPB
- Height/Weight
- Waist-Hip Ratio
- Body Mass Index
- Skin Fold Measurement

d. Labs Values

- Lipids:
  - Total Cholesterol
  - HDL
  - LDL
  - Triglycerides
  - Apo A-1
  - Apo B
  - LP (a)
- Inflammatory markers:
  - PAW
  - TPA
  - Fibrinogen
  - CRP
  - VCAM
  - Homocysteine
- Glucose metabolism markers:
  - Fasting Insulin
  - Fasting Glucose

A qualified nurse will perform all physical tests and administer all questionnaires. Laboratory measurements of lipid markers, glucose metabolism markers, Fibrinogen, CRP, and Homocysteine are done routinely in both India and in the USA. In order to measure consistency, 5% of the samples will be sent to the corresponding labs in the other country. Blood samples for measurement of PAW, tPA, and

VCAM from India will be frozen and sent to the USA and ELISA tests will be done on all samples together by the same operator and from the same kits.

e. Statistical Methods

Statistical significance for difference in the continuous variables (TC, HDL, LDL, TG, Lp(a), tPA, Fibrinogen, VCAM, CRP, Apo B, Apo A-1, PAI-1, Glucose, Insulin) will be compared using a one way analysis of variance and a two tailed t-test.

F. Study Drugs

N/A

G. Study Devices

N/A

H. Confidentiality Of Study Data

All data will be dept strictly confidential. All study material will be identified with a study code and no person identifiers will be used on these documents.

I. Potential Conflict Of Interest

There are no potential conflicts of interest for the investigators regarding this study.

J. Location Of Study

The study will take place at the site of patient recruitment. In India it will be at the site of the school/university where the patients are present. A health fair will be set up to attract the right number of people. In the USA the study will take place at the site of the temple or community center where a health fair will be set up.

K. Potential Risk

The only potential risk of participating in the study is due to venipuncture. Patients will be informed of this and any coagulation disorder of use of anticoagulation medicine will be assessed prior to venipuncture.

L. Potential Benefits

Potential benefits include being told of their Blood Pressure and other vital signs. If patients wish, the results of their laboratory tests can be forwarded to them.

M. Compensation To Subjects

None

N. Costs To Subjects

None

O. Minors As Research Subjects

Parent or Guardian Consent will be obtained prior to getting information/blood from minors.

P. Radiation Or Radioactive Substances

N/A

Q. References

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