National Journal of Basic Medical Sciences ORIGINAL ARTICLE Volume - IV, Issue-3

# STUDY OF ATHEROSCLEROSIS IN RURAL INDIA USING MODIFIED AMERICAN HEART ASSOCIATION CLASSIFICATION WITH SPECIFIC REFERENCE TO YOUNG ADULTS

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**ABSTRACT**

**Objective:** Atherosclerosis begins in childhood and progresses through young adulthood to form the lesions that cause coronary artery disease. Currently Indians experience cardiovascular deaths at least a decade earlier than their counterparts in developed countries. **Materials and Methods:** The study was conducted on 113 hearts and aorta of patients who had died of nonvascular causes of which 52 were between the age group of 15-34 years. Microscopic examination of atherosclerosis in the coronary arteries and aorta was done using the modified American Heart Association classification. Proportions were analyzed using Chi-square test. **Results:** Thirty three (63.5%) were males and 19 (36.5%) were females. In males, 16.51% of the coronaries showed advanced lesions, 44.54% showed raised lesions and in Aorta 23.01% showed advanced lesions and 62.54% showed raised lesions. Among females, 9.73% of the coronaries showed advanced lesions and 28.91% showed raised lesions. In Aorta 16.37% showed advanced lesions and 66.66% showed raised lesions. Three arteries showed erosion and small thrombus in the background of pathological intimal thickening. Moderate and severe inflammation was noted in thick and thin fibrous cap atheroma respectively. **Conclusion:** Hence the incidence of atherosclerosis in young individuals is high in present study which suggests requirement of preventive measures.

**Key words:** Atherosclerosis, Autopsy, Young adults

## INTRODUCTION

Cardiovascular disease (CVD) has emerged as a major health burden worldwide.[1] Ischemic heart disease (IHD) following atherosclerosis forms the major chunk of CVD burden in India.[1,2] Atherosclerosis and especially coronary atherosclerosis is the leading cause of mortality and morbidity in the industrial world and fast catching up with other causes of death in the developing world. Coronary artery disease (CAD) typically presents with symptoms after 40 years of age but autopsy studies have demonstrated that atherosclerotic changes in the vessel wall begins in childhood and progresses during adolescence and young adulthood.[3,4] Young individual without extensive atherosclerotic disease but with single lesions can experience sudden death when a thrombus forms over the lesion.[5] The modified American Heart Association (AHA) classification describes thick fibrous cap atheroma (FCA) and thin fibrous cap atheromas (TFCA) with the thin cap atheroma carrying higher chances of rupture and thrombosis with consequent obstruction of blood flow in the coronaries causing IHD.[6]

With CVD attaining epidemic proportions and Indians experiencing cardiovascular deaths at least a decade earlier than their counterparts in developed countries, the study of subclinical atherosclerosis is the need of the hour to estimate the disease burden in the asymptomatic population. As the method to assess atherosclerosis *in vivo* by angiography is invasive and expensive, we are highly dependent on autopsy material for describing atherosclerotic patterns.[6] Studying the disease burden in young individuals is useful not only for estimating the magnitude of the problem but also to guide the health administrators to set up national programmes for prevention and if possible, the reversal of atherosclerotic lesions. Data on the prevalence of coronary atherosclerosis or clinical CAD are extremely diverse; hence each population needs to be specifically studied due to the ethnic, racial, dietary and genetic differences between various populations. In this study we specifically studied the prevalence of atherosclerosis in the population aged between 15 and 34 years which gives an estimate of the future CVD burden.

## MATERIALS AND METHODS

The study was conducted on 113 hearts and aortas obtained from medicolegal autopsies conducted by the

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Department of Forensic Medicine in Kolar, a district with mostly rural population located in the South-Eastern part of Karnataka. Among the 113 hearts and aorta, 52 were between the age group of 15-34 years (defined as young individuals in the Pathobiological Determinants of Atherosclerosis in Youth [PDAY] Study). Nineteen (36.5%) were females and 33 (63.5%) were males and all the subjects had died of non-vascular and non-cardiac causes. 22 had died due to road traffic accidents, 29 due to suicide and one death due to ruptured uterus. 13 cases were between 15 and 19 years, 10 cases between 20 and 24 years, 20 cases between 25 and 29 years and 9 cases between 30 and 34 years. The male group had 33 cases whose mean age was 24.24 years. The female group had 19 cases whose mean age was 20.73 years.

The hearts and aortas were fixed in 10% buffered formalin. Left anterior descending (LAD) left circumflex and right coronary arteries (LCA and RCA) were dissected longitudinally until they entered the musculature. The coronaries were examined for the presence of thrombus, narrowing and atherosclerosis. Aorta was cut along its posterior surface and examined for atherosclerosis. Bits were taken from the LAD artery, LCAand RCA, ascending aorta (AA), thoracic aorta (TA) and abdominal aorta (AbA) from gross atherosclerotic lesions as well as suspicious lesions for microscopic assessment of the atherosclerosis. If no lesions were found, random bits were taken from above mentioned 6 sites. Microscopic grading of atherosclerosis was done using the modified AHAConsensus Classification of atherosclerosis based on morphological descriptions [Table 1].[6] According to this classification the non-atherosclerotic intimal lesions are intimal thickening and intimal Xanthoma which differs based on the amount of foam cells in the intima. The progressive atherosclerotic lesions are pathological intimal thickening (PIT)± erosion, FCA± erosion [Figure 1], TFCA [Figure 2], calcified nodule and fibro calcific plaque. The lesions were designated as PIT [Figure 3] which had extracellular lipid and their predominance is an indicator of progression to advanced atherosclerotic lesions.[7] These intermediate lesions are comparable to the raised fatty streak described in the AHA classification.[8]

Proportions were analyzed using Chi-square test. Ethical clearance for the study was obtained from Institutional Ethical Clearance Committee.

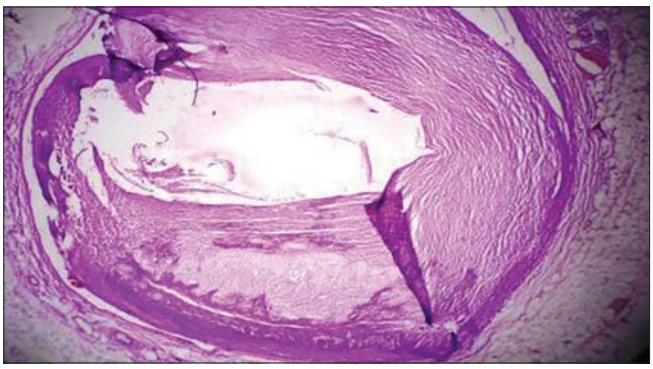

**Figure 1:** Microphotograph showing coronary thick fibrous cap atheroma (Hematoxylin and eosin X 100)

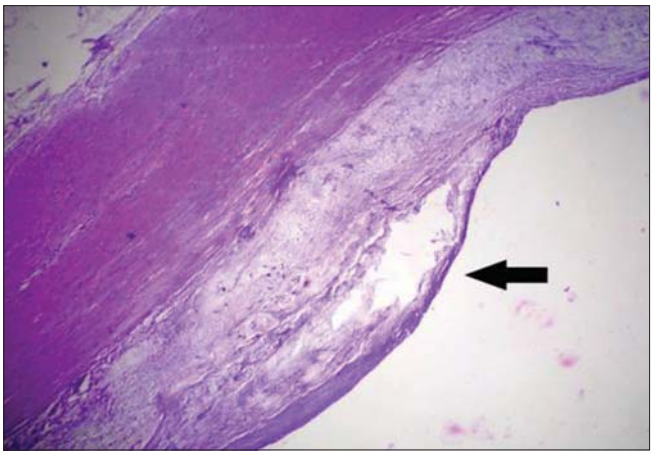

**Figure 2:** Microphotograph showing aortic thin fibrous cap atheroma (Hematoxylin and eosin ×100)

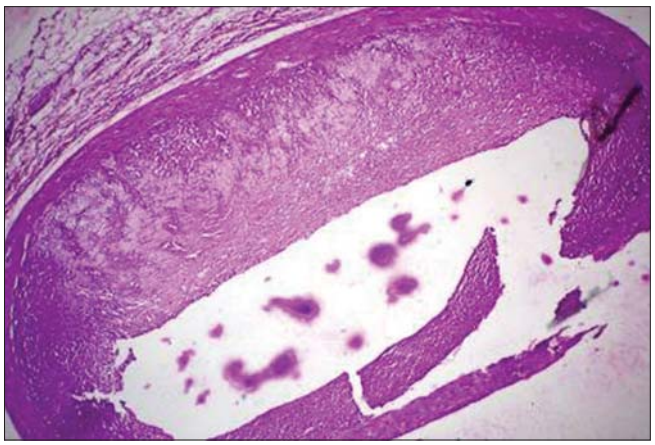

**Figure 3:** Microphotograph showing coronary pathological intimal thickening (Hematoxylin and eosin ×100)

## RESULTS

All the cases sampled had fatty streaks in some segment of their arterial tree. Most segments of the aorta showed fatty streaks. Raised lesions were more in number in the aorta compared to coronary arteries. All grades of atherosclerosis were more common in

the aorta compared to coronary arteries. Intermediate lesions developed from fatty streaks in the aorta and coronary arteries with wide age variation but the extent of the lesions increased steadily from 15 to 34 years, as measured in 5 years age group intervals.

Among the male group, 16.51% of the coronaries showed advanced lesions (FCAs), 44.54% showed raised lesions (PIT) which are known to progress to overt atherosclerosis. 23.01% of aortas showed advanced lesions and 62.54% showed raised lesions. Among males, in the left anterior descending artery, 40.71% showed PIT and 16.81% showed thick FCA; in the LCA 44.25% showed PIT, 13.27% showed thick FCA and 3.54% showed TFCA; in the RCA 48.67% showed PIT and 15.93% showed thick FCA [Table 2]. AA of males showed 66.37% PIT, 10.63% showed thick FCA and 3.54% showed TFCA; TA showed 61.06% PIT, 12.39% showed thick FCA and 12.39% showed TFCA; AbA showed 60.18% PIT, 20.36% showed thick FCA and 9.73% showed TFCA [Table 3].

Among females, 9.73% of the coronaries showed advanced lesions and 28.91% showed raised lesions. 16.37% of aortas showed advanced lesions and 66.66% showed raised lesions. Among females, in the left anterior descending artery, 24.78% showed PIT and 11.5% showed thick FCA; in the LCA 30.09% showed PIT, 7.96% showed thick FCA; in the RCA 31.86% showed PIT and 9.73% showed thick FCA [Table 4]. AA of females showed 65.49% PIT, 9.73% showed thick FCA; TA showed 64.6% PIT, 14.16% showed thick FCA and 5.31% showed TFCA; AbA showed 69.91% PIT, 14.16% showed thick FCA and 5.31% showed TFCA [Table 5]. Males showed higher incidence and severity of atherosclerosis in both coronaries and aorta when compared to females.

Left circumflex artery in one case and RCA in 2 cases showed erosion and small thrombus formation occurring in the background of PIT. Left anterior descending artery did not show erosion in any of the cases studied. Moderate to severe inflammation was noted in 14 of the 52 cases and were seen in intermediate lesions or FCA. One case had severe inflammation which was associated with TFCA and was seen in the RCA. AA in 2 cases, thoracic in 4 cases and abdominal artery in 5 cases showed erosion. Inflammation in the different parts of aorta was significantly more than that seen in

**Table 1: Modified American Heart Association classification of atherosclerosis**

| |
|---|
| Nonatherosclerotic lesions |
| Intimal thickening |
| Intimal xanthoma |
| Progressive atherosclerotic lesions |
| Pathological intimal thickening + erosion |
| Fibrous cap atheroma + erosion |
| Thin fibrous cap atheroma |
| Calcified nodule |
| Fibrocalcific plaque |

**Table 2: Atherosclerotic lesions in coronary arteries in males**

| Male - coronaries | | | |
|---|---|---|---|
| | LAD % | LCA % | RCA % |
| Nonatherosclerotic intimal lesions | 42.48 | 38.94 | 35.40 |
| PIT | 40.71 | 44.25 | 48.67 |
| FCA | 16.81 | 13.27 | 15.93 |
| TFCA | 0 | 03.54 | 0 |

LAD: Left anterior descending artery, LCA: Left circumflex artery, RCA: Right coronary artery, PIT: Pathological intimal thickening, FCA: Fibrous cap atheroma (thick), TFCA: Thin fibrous cap atheroma

**Table 3: Atherosclerotic lesions in aorta in males**

| Male - aorta | | | |
|---|---|---|---|
| | Ascending aorta % | Thoracic aorta % | Abdominal aorta % |
| Nonatherosclerotic intimal lesions | 19.46 | 14.16 | 09.73 |
| PIT | 66.37 | 61.06 | 60.18 |
| FCA | 10.63 | 12.39 | 20.36 |
| TFCA | 03.54 | 12.39 | 09.73 |

PIT: Pathological intimal thickening, FCA: Fibrous cap atheroma (thick), TFCA: Thin fibrous cap atheroma

**Table 4: Atherosclerotic lesions in coronary arteries in females**

| Female - coronaries | | | |
|---|---|---|---|
| | LAD % | LCA % | RCA % |
| Nonatherosclerotic intimal lesions | 63.72 | 61.95 | 58.41 |
| PIT | 24.78 | 30.09 | 31.86 |
| FCA | 11.50 | 07.96 | 09.73 |
| TFCA | 0 | 0 | 0 |

LAD: Left anterior descending artery, LCA: Left circumflex artery, RCA: Right coronary artery, PIT: Pathological intimal thickening, FCA: Fibrous cap atheroma (thick), TFCA: Thin fibrous cap atheroma

**Table 5: Atherosclerotic lesions in aorta in females**

| Female - aorta | | | |
|---|---|---|---|
| | Ascending aorta % | Thoracic aorta % | Abdominal aorta % |
| Nonatherosclerotic intimal lesions | 24.78 | 15.93 | 10.62 |
| PIT | 65.49 | 64.60 | 69.91 |
| FCA | 09.73 | 14.16 | 14.16 |
| TFCA | 0 | 05.31 | 05.31 |

PIT: Pathological intimal thickening, FCA: Fibrous cap atheroma (thick), TFCA: Thin fibrous cap atheroma

the coronary arteries. Aorta in 7 cases showed TFCA and all of them were associated with moderate amount of inflammation.

**DISCUSSION**

In 1953, Enos *et al*. published a landmark article that described a high frequency of advanced coronary atherosclerosis in young Korean War causalities.[9] Since then two major autopsy studies, the PDAYstudy and the Bogulosa Heart study, have demonstrated a high prevalence of atherosclerotic lesions in young individuals (15-34 years).[10] Studies from Japan have shown that the atherosclerotic lesions are increasing in young Japanese males as a result of the westernized lifestyle.[11] CADmanifests a decade earlier with an increased prevalence in South Asians as compared to other ethnic groups.[12] CAD in the young is being recognized with increasing frequency and is as high as 12% in India.[13]

The modified AHAConsensus Classification of atherosclerosis based on morphological descriptions was used in this study since it offers better categorization of atherosclerotic lesions based on morphological descriptions compared to the earlier AHA classification which was too rigid with its descriptions of lesions using Roman numerical and was not useful in subdividing the intermediate lesions of atherosclerosis.[6] Defining these intermediate lesions is of great importance as they are the precursor lesions of future advanced atherosclerosis. A noteworthy addition to the modified classification is the description of occurrence of erosion and thrombus formation even with intermediate lesions like PIT which explains the thrombus formation in a few cases of sudden cardiac death occurring in young individuals where there is absence of advanced atherosclerotic lesions.[6]

In the present study, among male group, 16.51% of the coronaries showed advanced lesions (FCAs), 44.54% showed raised lesions (PIT) which are known to progress to overt atherosclerosis. 23.01% of aortas showed advanced lesions and 62.54% showed raised lesions. Fausto N who studied the atherosclerosis in young individuals found 10% of the individuals to be having advanced atherosclerosis consisting of plaques with necrotic fat-filled centers and fibrous caps in the coronaries.[14]

Risk factors measured in adolescence predict adult lesions better than the risk factors measured at the time of disease presentation, further stressing the importance of studying CVD risk factors at young ages.[9] Tobacco smoking is an important and modifiable cardiovascular risk factor.[15] Both smoking and smokeless tobacco is equally prevalent amongst the youth of developing countries.[12] A recent Indian study reported more than 25% of 13-15 years age group adolescence is tobacco users, contributing to 17% of current total tobacco users which is an alarming and dangerous sign.[16] More than 80% of established adult smokers initiate smoking before the age of 18 years which indicates the high incidence of this dangerous risk factor in the Indian youth.[17,18] Smoking has an additive effect along with other cardiovascular risk factors in speeding up the atherosclerotic process. This trend of smoking at an early age partly could explain the increased incidence of atherosclerosis in young individuals in our study but since CVD risk data was not available, such a deduction could not be proved.

Obesity in childhood and early adulthood is attaining an epidemic proportion at about 15-20% in India due to lack of proper knowledge of correct diet, lack of physical exercise and westernization of the diet.[19] Overweight and obesity in childhood are associated with many cardiovascular risk factors which are causally associated with premature atherosclerotic lesions.[12] India is facing the double burden of over and under-nutrition along with other South Asian countries.[20] The South Asian new-born children and adults have higher body fat compared to the Caucasians of similar body weight and cardiovascular risk manifests at a lower level of adiposity in South Asians.[21] Obesity in South Asian children is also reported to be related with adverse lipid profile.[12] Dyslipidemia is a proven cardiovascular risk factor.[15] Non-traditional lipid risk factors like alterations in serum levels of lipoprotein (a), apolipoprotein (Apo) A-I and Apo B-100 in children of premature CVD patients need to be studied since tradition risk factors do not completely explain the increased susceptibility of Indians to CVD.[12]

Early screening for hypertension in children and young individuals is necessary as it is a recognized predisposing factor as reported in the Bogalusa Heart Study.[22,23] In a study conducted in Pakistan, hypertension was detected in 51.4% of CAD cases under the age of 40 years.[24] The current guidelines suggest that children >3 years of age have to get their blood pressure measured during their routine health assessment.[25]

Inflammatory and infectious risk factors along with the role of immune mechanisms as the cause for atherosclerosis have been the major area of atherosclerosis research in recent times.[10] These risk factors need to be evaluated in the Indian context and their possible causative relationship to the increased degree of atherosclerosis in Indian youth. Research on the atherogenic genetic traits and polymorphisms need to be identified specially in the Indian population to discern the cause and mechanisms behind the increased incidence of CVD.[7]

South Asia has high rates of poverty, gender inequalities, illiteracy, ignorance and religious beliefs towards pregnant mothers that contribute to fetal early infant under nutrition and possible long standing effects on the adult chronic diseases.[26] Evidence from birth cohort studies has linked maternal glucose intolerance, diabetes, hypercholesterolemia, vitamin D, vitamin B12 status, placental morphology and birth weight with childhood onset of adult disease.[27,28] The hypothesis proposed and pioneered by Dr. David Barker stated that the 20th century epidemic of coronary heart disease in Western countries might have originated in fetal life.[29] He reported that the deaths from IHD were more common in men who had been small at birth and at 1 year of age. The highest risk of CVD and type 2 diabetes was more common in those who were small at birth but became overweight adults. This has been attributed to permanent metabolic and endocrine changes caused by impaired nutrition in fetal life which would have been beneficial if nutrition remained scarce after birth. If nutrition becomes plentiful, however, these changes predispose to obesity and impaired glucose tolerance, which are a few of the major causes of atherosclerosis. Indian babies are small, with a mean birth weight of only 2700 g and 30% have a birth weight 2650 g or less.[29] These findings of low birth weight in Indians can be a cause for the increased atherosclerosis at a young age. As atherosclerosis is multifactorial, such a deduction needs to be proved by future, larger, prospective studies.

The higher incidence of atherosclerosis in the young individuals in the present study might be due to the higher incidence of cardiovascular risk factors in the population, environmental factors and genetic influences which predispose Indians to a higher risk of CVD. In 29 of the 52 cases studied, the cause of death was suicide. Suicide is an indicator of depression and stress in the individual.[30] In humans, psychological stress, hopelessness and depression can be risk factors for disastrous cardiovascular events such as stroke, coronary ischemia and myocardial infarction, which occur secondary to increased atherosclerosis.[31,32] The potential physiological links between stress, depression and CVD are multiple and extremely complex.

No information regarding the cardiovascular risk factors was available in the patients autopsied, which is the major limitation of the study. The strength of the study is that, as far as our knowledge goes in English literature, this is the first Indian study where the modified AHA classification has been used. This classification defines intermediate lesions which are indicators of future burden of disease better than the earlier AHA classification. The findings of this study should alert the health care providers regarding the increased incidence of atherosclerosis in Indian young population. Further studies correlating the risk factor incidence and atherosclerosis are needed and this study would provide the baseline data.

## CONCLUSION

Atherosclerotic lesions tend to increase with age. In-depth quantitative and qualitative analysis of atherosclerosis found in each of the cases in the 15-34 age group may give new insights into why in some young people plaques seem to progress rapidly with age while others remain almost stationary. Risk factors for adult CAD are present in young people decades before the occurrence of CHD. The atherosclerotic rate in Indian youth has reached alarming proportions leading to higher rates of premature IHD. With a major chunk of the Indian population being young individuals, preventive measures need to be implemented through national health programs at the earliest so that the epidemic of CHD is controlled.

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