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ISSN: 0975-3583

Journal of Cardiovascular Disease Research

An Official Publication of SciBiolMed.Org (A publishing division of Phcog.Net)

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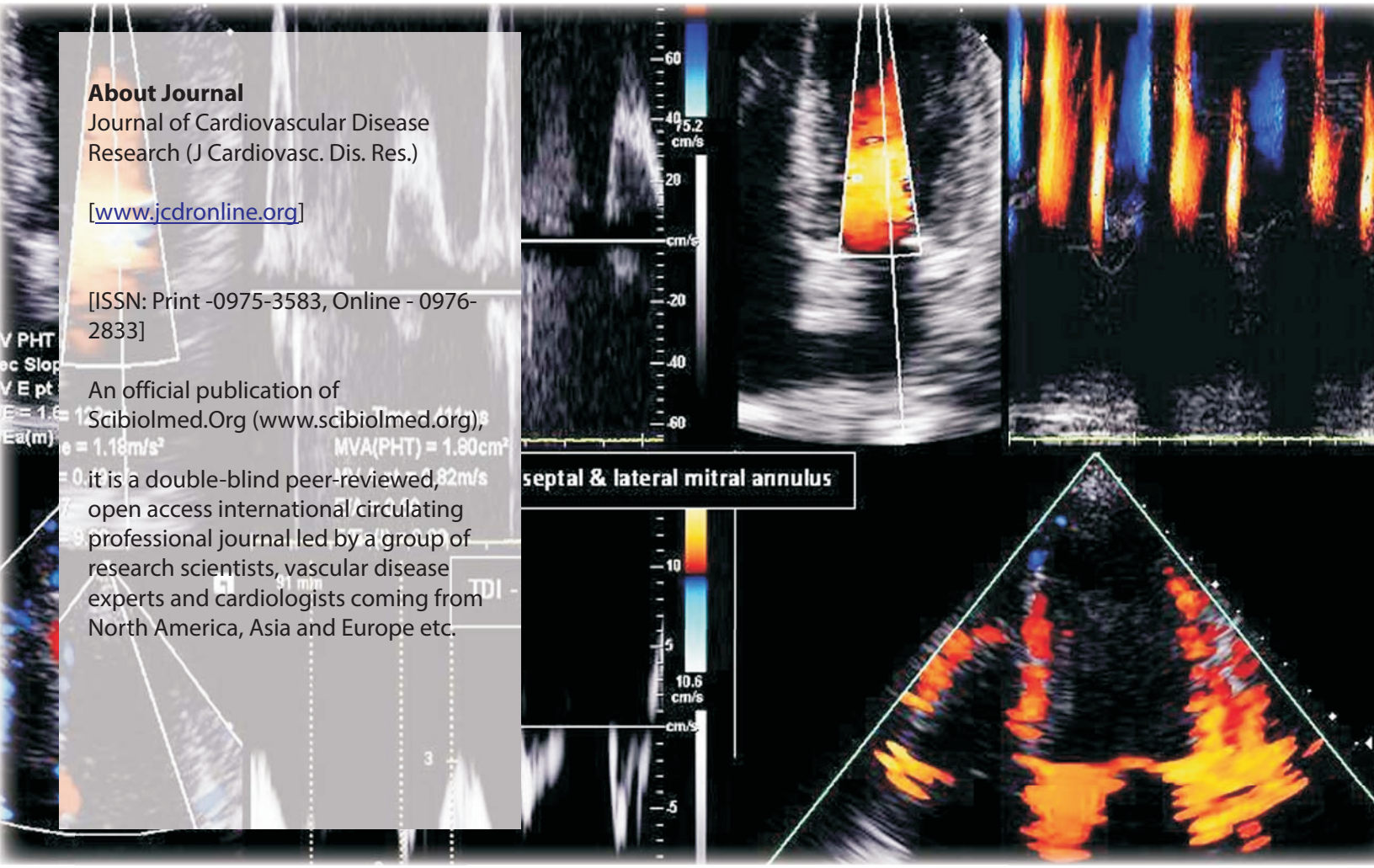
Volume 7, Issue 1, Jan-Mar, 2016



About Journal

Journal of Cardiovascular Disease Research (J Cardiovasc. Dis. Res.)

[www.jcdronline.org]

[ISSN: Print -0975-3583, Online - 0976-2833]

An official publication of Scibiolmed.Org (www.scibiolmed.org),

it is a double-blind peer-reviewed, open access international circulating professional journal led by a group of research scientists, vascular disease experts and cardiologists coming from North America, Asia and Europe etc.

Indexed and Abstracted in : The journal is indexed with Caspur, Chemical Abstracts, CNKI (China National Knowledge Infrastructure), DOAJ, EBSCO Publishing's Electronic Databases, Expanded Academic ASAP, Genamics JournalSeek, Google Scholar, Health & Wellness Research Center, Health Reference Center Academic, Hinari, Index Copernicus, MANTIS, OpenJGate, PrimoCentral, ProQuest, Scimago Journal Ranking, SCOLOAR, SCOPUS, SIIC databases, Summon by Serial Solutions and Ulrich's International Periodical Directory

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J Cardiovasc Disease Res., 2016; 7(1): 16-22
A Multifaceted Peer Reviewed Journal in the field of Cardiology
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Original Article

Atherosclerosis in the age group of less than 30 years in relation to panniculous fat thickness: An autopsy analysis

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ABSTRACT

Introduction: Non-communicable diseases (NCD) are a clear threat not only to human health, but also to development and economy. Fatalities due to chronic non-communicable diseases occur in prime of productive life. Coronary heart disease such as angina pectoris, myocardial infarction or sudden death due to coronary thrombosis is well known NCD which is mainly due to atherosclerosis. Information about the start of an atherosclerotic process in arterial wall, as well as various stages of atherosclerosis and the relationship of risk factors is evident from autopsy studies, as living subjects can provide information about lesions when they are quite advanced. Thus, the information gathered from autopsies in this study will assess the earliest age at which atherosclerotic process starts to occur and age by age progression of the process. **Methodology**: A cross-sectional pathobiology study of atherosclerosis was conducted among 40 apparently normal individuals within the age group of 30 years who died accidentally were included in the study (28 males and 12 females; mean age, 22.42 years) The histopathological report was tabulated and analyzed with respect to age and life style. Age related progress in atherosclerosis was assessed in correlation of panniculus fat thickness. **Results**: The results were based on macroscopic and microscopic appearance of atherosclerotic changes. The earliest age at which microscopic atherosclerotic change was seen at 7 years of age and the earliest macroscopic changes was seen at 17 years of age. Most of the subjects under 30 years of age showed fatty streaks, the precursors to develop advanced plaques. Among the risk factors smoking, obesity, and alcohol consumption surpass the others. **Conclusion**: In stratification of risk, and in monitoring the effects of intervention in obese children with non manifesting clinical atherosclerotic cardiovascular disease, assessment of the subclinical markers of atherosclerosis may help in the evaluation of the progression of atherosclerosis. The assignment of a "vascular age," may be a useful method to quantify the "end organ" effects of exposure to these various risks. Broad social, cultural, legislative and policy changes that support healthy lifestyles within families and communities need to be implemented to decrease the prevalence of childhood obesity and its cardiovascular consequences in communities.

Key words: Atherosclerosis, Panniculous fat, Dyslipidemias, Non-communicable diseases, Smoking, Tobacco chewing, Alcohol, Junk food.

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Submission Date: 11-06-2015; Revised date: 31-08-2015;

Accepted Date: 12-09-2015

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DOI : 10.5530/jcdr.2016.1.2

INTRODUCTION

The global battle of non-communicable diseases (NCD) is becoming more and more furious with continuous rise in the prevalence of NCD, habits and life style. NCDs are clear threat not only to human health, but also to development and economy. Over the next 20 years, NCDs will cost more than US$ 30 trillion, representing 48% of global GDP in 2010, and pushing millions of people below the poverty line.[1] The rise in the prevalence of NCDs is strongly associated with universal trends such as ageing, rapid unplanned urbanization and the globalization of unhealthy lifestyles which has a dramatic impact on productivity and quality of life. Atherosclerosis is one such NCD whose prevalence is alarmingly increasing. Atherosclerosis or hardening of the arteries, occurs when fat, cholesterol, and other lipoid substances accumulate in the walls of arteries and form hard structure called plaques. With aging, these plaques escalate, narrow the arteries and make them stiffer. Blockage of blood flow starves the tissues from oxygen and nutrients and results in tissue damage, eventually leading to clinical endpoints of coronary heart disease, renal and cerebral ischemia, and peripheral ischemia.

Atherosclerosis starts earlier than one may think and hardening of the arteries starts earlier than one can estimate. The process of narrowing and hardening starts early and progresses over decades before complications arise at a later age. Developing atherosclerosis is often inevitable owing to its genetic preponderance. However, behavior and lifestyle choices are of paramount importance in initiation and progression of atherosclerosis throughout life. Atherosclerotic process in arteries occurs as a result of interaction between known and unknown genetic and environmental factors, the effect on the arterial wall of a particular individual is dependent not only on the genetically determined response to the risk factor but also the level of risk varies with type, intensity, nature and the duration of exposure, even among the most homogenous subgroups with the same age, sex, race, disease, and cause of death.[2]

Among the risk factors obesity, smoking, and alcohol consumption surpass the others. Obesity is a positive risk factor for atherosclerotic lesions and smoking has the greatest effect on the development of advanced plaques in young adults, approximately 6-fold increased incidence.[3] Conclusive evidence has been provided in autopsy studies such as the Oslo study where in elevated serum cholesterol and increased blood pressure have been associated with increased atherosclerosis. Thus, it can be inferred that factors that lead to increased serum cholesterol and elevated blood pressure accelerate the development of atherosclerosis. Also, HDL cholesterol is inversely related to coronary atherosclerosis and probably also to cerebral atherosclerosis. Therefore, factors that lead to decreased HDL cholesterol can also be implicated in accelerat-

ing atherosclerosis. Owing to the definitive evidence provided by this study we can conclude that elevated serum cholesterol, elevated blood pressure, and lowered HDL cholesterol are factors which accentuate the atherosclerotic process, and the total risk for an individual varying depending on the duration of exposure and intensity of each risk factor. [4] Visceral obesity plays a key role in the development of an unfavorable metabolic and cardiovascular risk profile.[5] Fat depot is recognized as a rich source of free fatty acids and a number of bioactive molecules, such as adiponectin, resistin, and inflammatory cytokines, which might significantly affect cardiac pathology.[6,7]

Obesity is usually centripetal in nature. It is not uncommon for centripetal fat to correlate with the intra-abdominal visceral fat and several metabolic parameters. Therefore, assessment of centripetal fat could be a simple and reliable indicator of the amount of adipose tissue and cardiovascular risk. There is a vast variation in the age of initiation of habits like smoking and alcoholism among individuals of different environments and generally tends to be during early adulthood and beyond, however other modifiable risk factors for atherosclerosis such as obesity, unhealthy eating habits and a sedentary lifestyle are practices which take root at a ripe young age.

Active smoking, as well as exposure to environmental tobacco smoke has an impact on the initiation and progression of atherosclerosis. The fact that pack-years of smoking but not current v/s past smoking was associated with progression of atherosclerosis suggests that some adverse effects of smoking may be cumulative and irreversible.[8]

The relation between alcohol consumption and incident hypertension is still unclear, and most observational studies have not accounted for socio-economic factors. The consumption of low to moderate amounts of alcohol also appears to be associated with a higher risk of hypertension as explained due to atherosclerosis.[9]

Normally clinicians follow a specific recognition pattern for diagnosing the disease. As most of the illness has distinctive signs and symptoms and based on these, further confirmation is done through constellation of specific laboratory investigation. However, this knowledge or understanding of a disease becomes difficult when the clinical features are either few, subtle or insufficient to characterize. Information about the start of an atherosclerotic process in an arterial wall, as well as various stages of atherosclerosis and the relationship of risk factors to atherosclerotic process is evidence that can only be conclusively derived from autopsy studies, as living subjects can provide information about lesions when they are quite advanced. Thus, we have used autopsies to derive our data. The information gathered from autopsies in this study will assess the earliest age at which atherosclerotic process starts to occur and age by age progression of the process.

RESEARCH METHODS AND PROCEDURES

After ethical clearence and written consent from the kith and kin of the deseased, a cross-sectional study was conducted among 40 apparently normal individuals, over a period of 1 year who died due to RTA within the age group of 30 years without any cardiac pathology or other chronic disease; deaths occurred as a consequence of trauma were included in the study (28 males and 12 females; mean age, 22.42 years) at Department of Forensic Medicine and Toxicology, Jawaharlal Nehru Medical College, Belgaum, Karnataka, India. The intervals between death and refrigeration of the body, as well as performance of the autopsy, were generally short of 6-8 hours. The autopsy for studies of the Pathobiology of atherosclerosis was done among the individuals. The inclusion criteria being medico-legal cases of less-than 30 year of age and both sexes, and exclusion criteria being known cases of cardiac disorders, dyslipidemias and metabolic errors, family history of cardiac disorders, dyslipidemias and metabolic errors.

The information about personal data, date and time of admission, marital status, domicile, literacy level, occupation, socio-economic status and nature of morbidity for which the person was admitted were collected by the attendants (parents, relatives, and friends). Personal history like eating habits, smoking, alcoholism and any other addictions were enquired for and noted. A note on the duration of smoking and alcoholism was done. The medico-legal records and case sheets were referred for necessary information about the cause of death.

During the autopsy coronaries, whole of aorta and renal arteries were dissected out and histopathologically analyzed for presence of atherosclerosis. The pathologist, blinded to clinical or pathological observations or demographic data, independently evaluated the arteries by studying the formalin fixed paraffin embedded sections stained with hematoxylin and eosin stain. Using procedures developed in the International Atherosclerosis Project (lAP).[10] the extent of intimal surface coated by fatty streaks, fibrous plaques, and complicated and calcified lesions was estimated by inspection of the arteries. The sum of the percentages of surface involved with fibrous plaques, complicated lesions, and calcified lesions was designated "raised lesions." Thus the spectrum of atherosclerotic changes in the population was classified macroscopically into dots, streaks and plaques, and microscopically into Type I to Type VI as designated by the American Heart Association descriptive morphological classification. For centripetal or panniculus fat mass determination, the area subtended was midway between the xiphisternum and pubic symphysis. The thickness was noted by measuring panniculus adipesus in terms of millimeters between skin and the outer layer of rectus abdominis muscle with a metallic scale. The histopathological report was tabulated and analyzed respect to age and life style. Age related progress in atherosclerosis was assessed in correlation of panniculus fat thickness.

RESULTS

Data collected is allocated into two sets of information

- One set of data entails the information based on macroscopic appearance of atherosclerotic changes (Table 1), the purpose of this enquiry being to determine how many autopsies in individuals below 30 years of age have yielded the appearance of fatty streaks which are a prelude to atherosclerotic plaques and the amount of panniculous fat deposition of each individual.
- Another set of data provides information regarding the microscopic appearance of atherosclerotic changes in various arteries, from which we can determine:
  - > the blood vessel in which atherosclerotic changes are more common.
  - > type or severity of atherosclerosis as per the morphological classification, American Heart Association
  - > from the enquiry regarding lifestyle changes we can postulate which unhealthy habit may have been associated with atherosclerotic process.

According to the data provided (Figure 1),

- the earliest age at which macroscopic changes were seen was in the autopsy conducted in a 17 year old. Fatty streaks are the predominant macroscopic lesions that were present in most of the subjects under 30 years of age, which are nothing but the precursors to developing advanced plaques, and the rate of development of advanced plaques being dependant on the subject's genetic constitution as well as environmental factors. Presence of fatty streaks in majority of the subjects' maybe even suggests that their appearance is inevitable but their progression is dependent on an amalgamation of factors.

Table 1: Macroscopic appearance of atherosclerotic process and its age wise progression

Age (years)	Lesion				
	Normal	Thickening	Streaks	Dots	Plaques
5	+				
6	+				
6	+				
7	+				
16	+				
17	+				
17			+		
17			+		
20			+		
20			+	+	
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30			+	+	
30			+	+	
30			+		
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30			+	+	
30		+		+	
30			+	+	

Sample size=40.

- atherosclerotic changes that typify under advanced changes as per the histological evaluation are Types IV, V, VI according to a definition of advanced atherosclerotic lesion provided by American Heart association. Types I, II, III are the initial fatty streaks and intermediate lesions which are classified as three different types based on their distinguishing histological features.

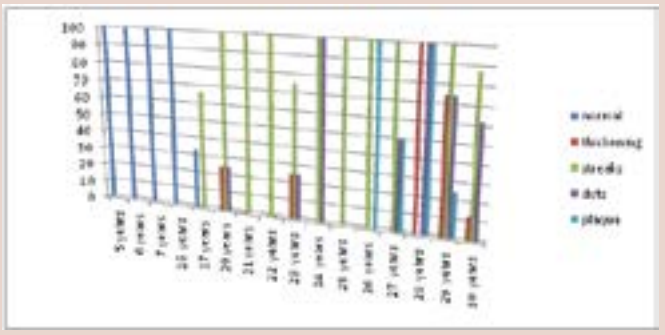

Figure 1: Macroscopic changes in atherosclerotic process

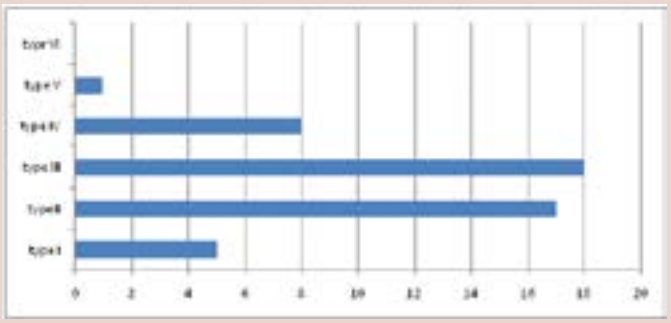

Figure 2: Microscopic changes in atherosclerotic process

According to the data provided (Figure 2),

- Among the 40 autopsies done, type III and Type II atherosclerotic lesions were the most prevalent, advanced lesions of type IV and V were seen in a few individuals. Type VI was absent in these sample of individuals below thirty years of age, and no changes at all were found in two autopsies of a five and six year old. The earliest age at which a histological change was found was in a seven year old (Figure 2).

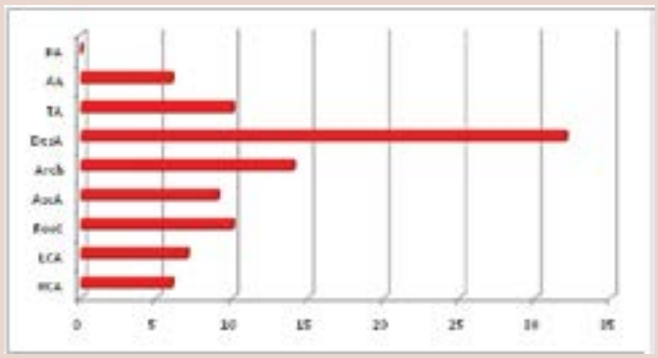

Figure 3: Arterial segments involved in coronary and aortic atherosclerosis

According to the data provided (Figure 3),

- Sample-40 autopsies
- RCA-Right coronary Artery
- Root-Root of Aorta
- Arch-Arch of Aorta
- TA-Thoracic Aorta
- RA-Renal Artery
- LCA-Left coronary Artery
- AscA-Ascending Aorta
- DesA-Descending Aorta
- AA-Abdominal Aorta

- According to the figure shown above, descending aorta was the most common site for atherosclerotic changes among the 40 autopsies followed by the arch of aorta.
- Among the 40 deaths that occurred, almost every autopsy with the exception of 3 cases (all below the age seven), had both macroscopic as well as microscopic atherosclerotic changes. Addictions and unhealthy eating habits were enquired for from the family members of these 40 individuals, and we found that unhealthy eating habits was a common operating factor among the majority, possibly contributing to the early initiation of atherosclerotic process. The earliest microscopic changes in the wall of the arteries were found in a seven year old, and the earliest macroscopic changes in a seventeen year old, also suggesting that microscopic deterioration starts occurring much before it even presents as a significant macroscopic lesion and even more earlier before it presents as a clinical condition.

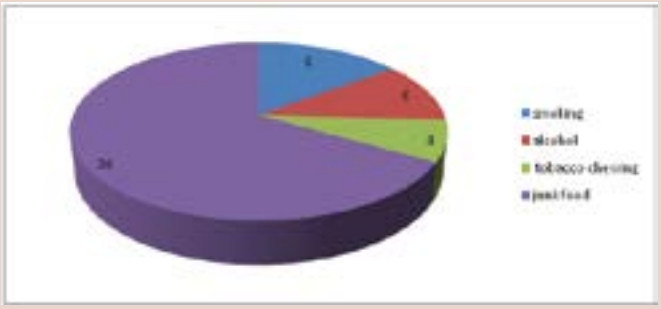

Figure 4: Distribution of subjects in relation to habits

As per the Figure 4 the habits and life style of the cases were noted.

- Junk food and unhealthy eating habits-36 individuals (90%)
- Smoking-8 individuals (20%)
- Alcohol consumption-6 individuals (15%)
- Tobacco chewing-4 individuals (10%)
- Including those individuals who practice more than one of these habits.

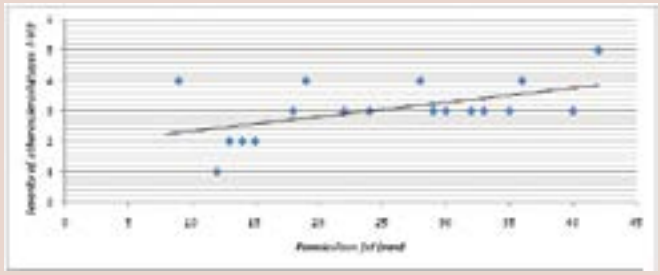

Figure 5: Relation between severity of atherosclerosis and panniculous fat

- The above graph (Figure 5) shows that there is in fact a positive correlation between the panniculous fat and severity of atherosclerosis. With the increase in panniculous fat, there is an increase in the type or severity of atherosclerosis. There are however a few exceptions, as in subjects who even with a small amount of panniculous fat have type IV or V atherosclerosis, probably due to their genetic constitution or unhealthy lifestyle causing the progression of atherosclerotic process to be augmented.

Figure 6: Dots and streaks in descending aorta

Figure 7: Plaques in descending aorta

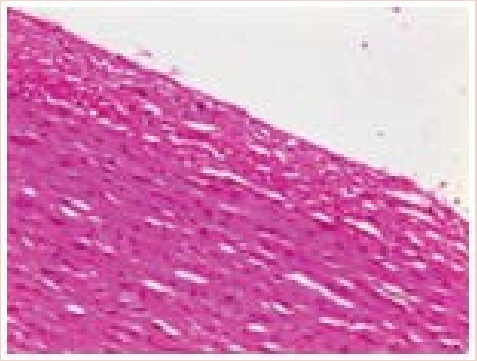

Figure 8: Type 2 atherosclerosis (100x, H and E stain)

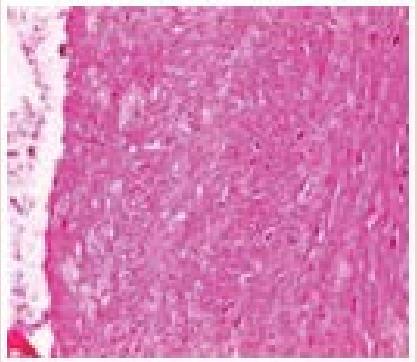

Figure 9: Type 3 atherosclerosis (100x, H and E stain)

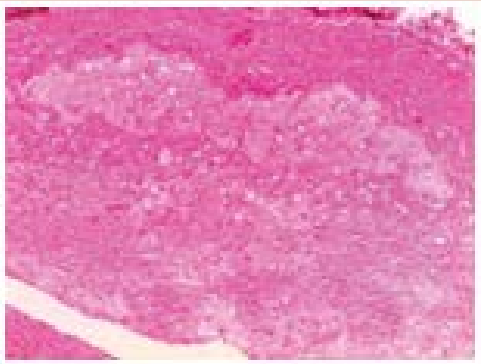

Figure 10: Type 5 atherosclerosis, Fibroatheroma (100x, H and E stain)

DISCUSSION

Atherosclerosis of the aorta has become a universal phenomenon due to a conglomeration of numerous risk factors operating from ones childhood. The common risk factors attributed to this disease process are tobacco smoking, diabetes mellitus, hypertension, hypercholesterolemia, obesity, and sedentary lifestyle.[11] Age of onset of atherosclerosis and its progression correlates positively with the duration of exposure and age of initiation of habits, contributing to an unhealthy life style. Global burden of this non-communicable disease is 63% of all deaths worldwide currently.[1] Atherosclerosis remains the major cause of death and premature disability in developed societies and moreover, current predictions estimate that by the year 2020 cardiovascular diseases, notably atherosclerosis, will become the leading global cause of total disease burden. Although many generalized or systemic risk factors predispose to its development, atherosclerosis affects various regions of the circulation preferentially and yields distinct clinical manifestations depending on the particular circulatory bed affected. Atherosclerosis of the coronary arteries commonly leads to myocardial infarction and angina pectoris. Atherosclerosis of the arteries supplying the central nervous system frequently provokes strokes and transient cerebral ischemia. In the peripheral circulation, atherosclerosis causes intermittent claudication and gangrene and can jeopardize the viability of the limb itself. Involvement of the splanchnic circulation can lead to mesenteric ischemia. Atherosclerosis can affect the kidneys either directly by involving the renal vessels (e.g., renal artery stenosis) or as a frequent site of atheroembolic disease.[12]

Childhood obesity has got lifetime cardiovascular risk. An increase in the incidence of coronary artery disease, as well as an earlier age of onset is expected in these children at a later age. Consequences of obesity, such as dyslipidemia, insulin resistance syndrome, hypertension, associated nutritional deficiencies, and a sedentary lifestyle or associated lifestyle factors such as tobacco smoke exposure, are likely to account for this increase because these are all independent risk factors for accelerated atherosclerosis.[13] Risk factors like high cholesterol or blood pressure, smoking, and diabetes are the fundamental causes prevailing in causing damage to the endothelium, and damage, which cannot be detected with routinely used tests. Endothelial disruption causes endothelial dysfunction. The endothelium actively works to keep arteries free from plaques or clots. Healthy endothelium means healthy arteries. Impaired endothelium is a "canary in the coal mine," signaling that atherosclerosis is likely to develop. The fatty streaks (Figure 6) are the earliest form of atherosclerosis; these are cholesterol deposits in the walls of arteries. Virtually, in every individual fatty streak starts developing in early life. In our autopsy based analysis, among the 40 autopsies conducted the earliest age at which microscopic changes of atherosclerotic process were seen at 7 years of age and the earliest macroscopic changes were seen at 17 years of age. The severity of atherosclerosis was designated based upon the microscopic changes (Figure 8, 9, and 10) that were seen in the arterial wall and was typified as per American Heart Association morphological classification for atherosclerosis, which includes type I-VI and type I being the least severe and type VI being the most severe. Type III (Figure 9) was the predominant type found among the autopsies and ascending aorta was the most common site of lesion in majority. We were also able to determine that among the subject's unhealthy eating habits were the premiere and most common practice that could possibly be attributed to the initiation and progression of the atherosclerotic process. Risk factors, lifestyle choices, and genetic factors are amalgamation of factors which cause fatty streaks to grow further, becoming atherosclerotic plaques. The plaques are continued cholesterol deposits in artery walls, thus fatty streaks are quintessentially nothing but predecessors of atherosclerotic plaques, whose rate of growth is dependent on numerous factors stated above. Plaques represent "true" atherosclerosis. Fatty streaks turn into fibroatheromas and advanced plaques are sometimes complicated by hemorrhage, calcification, ulceration and thrombosis resulting in myocardial ischemia and even cerebrovascular accidents. The present study describes the risk involved by assessing centripetal fat and correlation with the atherosclerotic changes in aorta within the age group of 30 years. In terms of age by age analysis of atherosclerosis, the process of atherosclerosis may begin as early as infancy. Studies of premature babies show that fatty streaks develop even before birth. Babies whose mothers had high cholesterol had more prominent fatty streaks. Similar features were found in other studies involving children younger than 13. Fatty streaks began to look more like atherosclerosis in older children, especially kids with obesity or higher cholesterol. For many of us, these fatty streaks have progressed to mild atherosclerosis even before we turn 20. In a study that looked inside young people's arteries with ultrasound, the arteries of 17% of teenagers had small plaques of atherosclerosis.[12] As stated by Wissler *et al*[14] "the results of the (PDAY) study reflect the state of atherosclerosis development in young people living in the U.S.A. late in the 20th century." Among the many important findings reported, the following were the significant observations.

1. All U.S. teenagers sampled had fatty streaks in some segment of their arterial system.
2. Intermediate lesions (fatty plaques) developed from fatty streaks in the aorta and coronary with wide age variation but the extent of the lesions increased steadily from 15 to 34 years, as measured in 5-year age-group intervals.
3. Raised lesions were detected earlier in the aorta than in coronary arteries; lesions containing lipids were present in the aorta of 15-to 20-year-old individuals.
4. The presence of coronary artery lesions having concentric microarchitecture and a large number of inflammatory cells was correlated with the presence of circulating immune complexes.
5. Obesity was a positive risk factor for the development of vascular lesions.
6. Raised lesions in the abdominal aorta were greatly increased in smokers in the 25–34 age group.
7. Smoking and hypertension had the greatest effect on the development of advanced plaques in young adults (approximately 6-fold and 4-fold increased incidence, respectively).
8. Ten percent of the individuals in this study had advanced atherosclerosis consisting of plaques with necrotic fat-filled centers and fibrous caps. Approximately 80% of these individuals were smokers.

It is debatable whether the presence of fatty streaks in individuals 15 to 34 years of age has pathogenetic importance for the development of atherosclerosis. However, it is truly alarming that 10% of individuals in this age group had advanced atherosclerosis. There is no reason to believe there was a bias in the selection of cases for study. Indeed, I agree with Wissler *et al* that the PDAY cases represent a random sample of U.S. youth. Do all individuals with advanced lesions have gene mutations known to predispose one to atherosclerosis? Answers to this question and many others still remain uncertain and undetermined. The material used in the PDAY project is available to the scientific community through the administrative center at Louisiana State University. I hope that publication of the paper by Wissler *et al* will further increase the use of this material for scientific investigation of the causes and progression of atherosclerosis. Although not completely explained, the remarkable differences in the development of lower abdominal aortic atherosclerosis compared to the thoracic involvement are strikingly demonstrated by the results of the recently published study of Miller *et al.*[15] They revealed that young women had more extensive fatty streaks in the abdominal aorta and the young men had more fatty streaks in the thoracic aorta. Also, Male subjects had more extensive lesion distribution and a higher prevalence of raised lesions in the right coronary artery than did female subjects.[16,17,18]

The unique sampling strategy resulted from the demonstration by Cornhill, Herderick, and Stary, that there is a disctinctive pattern in human descending aortic lesion development. This explains the remarkable contrasts which are evident between the extent of lesion development in the lower abdominal aorta and the thoracic aorta where lesions rarely progress substantially in this 20-year period. Similarly, this study led to a sampling strategy in which the lesions of the ventral and dorsal areas of the aorta could be quantified separately because their study confirmed that progression of lesions and the development of raised fatty plaques are more or less limited to the dorsal parts of the aorta.[19]

Important Prevention Procedures for the Pediatrician and the Primary Care Physician Derived from PDAY Observations; This research program is far from complete and is likely to yield many more publishable contributions to our understanding of the development of atherosclerosis during youth. Nevertheless, the results thus far have produced a number of important guidelines that can support national and international efforts to prevent the development of coronary heart disease starting with young people in their mid-to late teens. These efforts include:

1. Increased organized efforts to prevent smoking among children and adolescents and to prevent and overcome addiction to tobacco;
2. speeded-up development of programs to systematically check for serum hypercholesterolemia and low HDL cholesterol levels in people as young as their late teens;
3. expanded efforts to prevent and treat obesity and to encourage and support organized exercise for young people;
4. increased support for research on atherogenic genetic traits to develop practical ways to identify and to reveal the mechanisms by which these factors influence atherogenesis, including the special augmenting effects of Lp(a) and homocysteine on the artery walls;
5. intensified efforts to identify and control hypertension in youth;
6. encouragement of effective testing for a tendency toward hyperglycemia and glucose intolerance in young people; and
7. greater vigilance and sensitivity to the evidence indicating that disorders with sustained circulating immune complexes or with frequent hyperstimulation of the release of vasoactive amines may constitute important accelerating influences on atherogenesis.

It is also the responsibility of the entire biomedical scientific community to encourage and support the development of new noninvasive methods to identify, measure, and evaluate the developing plaque components in the coronary artery wall and abdominal aorta of young people even when lesions are at the intermediate plaque stage.

Value of the PDAY Study for the Anatomical Pathologist and Forensic Pathologist; The PDAY Research Program demonstrates the value of the autopsy as a powerful research tool and establishes forensic centers as valuable generators of research data and the forensic pathologist as an important medical research scientist. This is particularly true if one wishes to obtain accurate and much needed information about the development of our most important and most serious disease processes, such as cardiovascular disease.

In our society, these external forces often represent the most frequent causes of death among our young people. Studying the arteries of 3000 of these individuals can give us a reflection of the risk factors at work in the development of our country's number one killer, atherosclerosis, which is responsible for most fatal heart attacks and strokes: two clinical events which, combined, cause more fatalities in our population than any other serious disease.

CONCLUSION

Because clinical atherosclerotic cardiovascular disease does not manifest in obese children, assessment of the subclinical markers of atherosclerosis may help in the evaluation of the progression of atherosclerosis, in further stratification of risk, and in monitoring the effects of intervention. Furthermore, because multiple risk factors with poorly understood interplay might be present in obese children and younger age group, assessment of the vasculature directly, and perhaps the assignment of a "vascular age," may be a useful method to quantify the "end organ" effects of exposure to these various risks. Broad social, cultural, legislative and policy changes that support healthy lifestyles within families and communities need to be implemented to decrease the prevalence of childhood obesity and its cardiovascular consequences in communities. The effect of risk factor modification on the vasculature will continue to be a resource for the direction of evidence-based therapy in obese children.

ACKNOWLEDGEMENT

The author acknowledges the deceased relatives for giving consent for the study and Department of Forensic Medicine and Toxicology, and Department of Pathology of Jawaharlal Nehru Medical College, Belgaum, Karnataka for providing the facilities for the research

CONFLICT OF INTERST

The author declare no conflict of interest.

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