

## ATHEROSCLEROTIC PLAQUES IN HUMAN CORONARY ARTERIES

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**Abstract:** Atherosclerosis or coronary artery disease (CAD) is the most common form of cardiovascular disease (CVD) where the main component is lipid accumulation and inflammation of the large arteries, which eventually may lead to its clinical complications, myocardial infarction (MI) and stroke. As a disease of slow progression, clinically significant atherosclerosis occurs primarily in older individuals and, despite declining incidence in some countries, remains the leading cause of mortality worldwide. Atherosclerotic lesions are characterized by a lifetime long accumulation and transformation of lipids, inflammatory cells, smooth muscle cells, and necrotic cell debris in the intimal space underneath a monolayer of endothelial cells (ECs) that line the interior vessel wall. Typically, lesion growth can reduce blood flow in the lumen by >50% and may cause angina particularly during exercise or stress. Lesions can become unstable and rupture, particularly if they have fatty and inflammatory composition. If this occurs in the coronary arteries, it can result in a local clot that may completely obstruct the blood flow to cause an MI. Alternatively, the clot can escape the heart and travel to the brain where it may cause a stroke.

**Key words:** Atherosclerosis, lipids, stroke, inflammatory cells, plaque.

**Aim.** This article summarizes the natural history of aortic and coronary atherosclerosis among adolescents from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study, which was a multi-institutional study of atherosclerosis in 15- to 34-year-old, The PDAY Study focused on 25- to 45-year-old subjects because fatty streaks are prevalent and fibrous plaques begin to appear in this age group.

**Methods.** Study subjects were persons aged 25 through 45 years who had died due to external causes. Of the 3210 cases collected, 334 were excluded because they did not meet the study criteria. Of the 2876 cases included in this report, thoracic aortas were obtained from 2856, abdominal aortas from 2823, and right coronary arteries from 2788. Blood, liver, kidney tissue, and standardized arterial wall samples, including samples from the perfusion-fixed left anterior descending coronary artery, were also collected in this study. These samples were used to investigate the associations of atherosclerosis with the risk factors for adult CHD, which are reported elsewhere, and for studies of the microscopic features of aortic and coronary lesions including cellular, fibrous, and lipid-containing components.

**Results.** Intimal lesions appeared in all the aortas and more than half of the right coronary arteries of the youngest age group (25-35 years) and increased in prevalence and extent with age through the oldest age group (35-45 years). Fatty streaks were more extensive in black subjects than in white subjects, but raised lesions did not differ between blacks and whites. Raised lesions in the aortas of women and men were similar, but raised lesions in the right coronary arteries of women were less than those of men. The prevalence of total lesions was lower in the right coronary artery than in the aorta, but the proportion of raised lesions among total lesions was higher in the right coronary artery than in the aorta.

Due to continued lipid deposition and proliferation of smooth muscle and connective tissue, fatty streaks and fibrous plaques increase in size and extent and some undergo qualitative changes. The most serious change is rupture, which exposes the blood to lipid-rich thrombogenic material and precipitates an occlusive thrombus, which in turn leads to myocardial infarction or sudden cardiac death. The PDAY Study encompassed the transition from innocuous fatty streaks to clinically significant fibrous plaques and attempted to determine the conditions associated with this process.

Previous PDAY reports have described selected aspects of the effects of age, sex, race, serum lipoprotein levels, smoking, hypertension, glycohemoglobin levels, and obesity on the gross extent and microscopic characteristics of atherosclerotic lesions in these subjects.<sup>9-16</sup> In brief, the conditions that predict risk of clinically manifest coronary heart disease (CHD) are also associated with the extent and severity of atherosclerosis in youth. This article summarizes the natural history of the grossly detectable lesions of atherosclerosis in American youth and confirms the rapid progression of atherosclerosis in some young adults examined at autopsy between 1987 and 1994. Collection centers shipped the left half of each aorta and the right coronary artery in a plastic bag to the central laboratory. The central laboratory stained the arteries with Sudan IV<sup>17</sup> and then x-ray films were made. Three pathologists, blinded to specimen source or other information, independently evaluated the stained right coronary arteries and left halves of the aortas. They visually estimated the extent of intimal surface involved with fatty streaks, fibrous plaques, complicated lesions, and calcified lesions by procedures developed in the International Atherosclerosis Project.<sup>17</sup> The sum of the percentages of surface involved with fibrous plaques, complicated lesions, and calcified lesions by gross visual grading was designated raised lesions. Consensus grading of lesions was the average of the 3 independent gradings. The prevalence of cases with lesions was based on the recording by any of the pathologists of any nonzero value of percentage surface area involved from all lesion types except calcification. Prevalence also was computed based on 5% or greater surface area involved. Prevalence of calcified lesions was based on evaluation of the x-ray films.

In the thoracic aorta, the highest prevalence of fatty streaks occurred in the dorsal surface (>50%) while the ventral surface had few fatty streaks (<10%). The region of highest prevalence for fatty streaks was midway between successive pairs of intercostal ostia. The thoracic aorta was virtually spared of raised lesions even in the oldest age group (30-34 years: <4% raised lesions). In the abdominal aorta, the frequency of fatty streaks was greater in the dorsal than in the ventral area, but lesion-prone and lesion-resistant regions were not as sharply defined as in the thoracic aorta. Regions of high prevalence occurred between pairs of lumbar ostia and in flow tracts to the celiac, superior mesenteric, renal, and inferior mesenteric arteries, while regions distal to the flow dividers of these ostia were spared. A region on the left dorsal surface of the abdominal aorta, originating at the level of the inferior mesenteric ostium and extending distally to the bifurcation, was the most prone to raised lesions.

**Conclusion.** In the right coronary artery, fatty streaks formed a pattern with the highest prevalence of lesions in the proximal region. The highest prevalence of raised lesions was in the first 2 cm of the vessel. This distribution confirms that there are also lesion-prone and lesion-resistant regions of the coronary artery. Catheterization is the gold standard for diagnosis of atherosclerosis, but it is expensive and carries significant risk. Reliable noninvasive methods of diagnosis are urgently needed. Certain biochemical markers for the disease, such as C-reactive protein, and some noninvasive procedures, such as extravascular ultrasound and ultrafast computerized tomography, should prove useful but have limitations. As our understanding of the genetics of atherosclerosis increases, genetic diagnosis will become increasingly important. The anticipated 'biallelic map' of the genome is likely

to drive the evolution of new technologies for gene screening, from high-throughput, genome-wide methods to testing for particular gene variants in individuals. One application of screening will be to distinguish different forms of the disease so that pharmacological intervention can be better targeted. Atherosclerosis is heterogeneous, and the most appropriate therapy will depend on the particular variety of disease. Classification is already used clinically, as patients are grouped according to the variety of risk factors they display, but genetic testing should greatly expand the subdivisions of the disease.

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