Origin of atherosclerosis in childhood and adolescence[1–4]

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ABSTRACT Atherosclerosis begins in childhood as deposits of cholesterol and its esters, referred to as fatty streaks, in the intima of large muscular arteries. In some persons and at certain arterial sites, more lipid accumulates and is covered by a fibromuscular cap to form a fibrous plaque. Further changes in fibrous plaques render them vulnerable to rupture, an event that precipitates occlusive thrombosis and clinically manifest disease (sudden cardiac death, myocardial infarction, stroke, or peripheral arterial disease). In adults, elevated non-HDL-cholesterol concentrations, low HDL-cholesterol concentrations, hypertension, smoking, diabetes, and obesity are associated with advanced atherosclerotic lesions and increased risk of clinically manifest atherosclerotic disease. Control of these risk factors is the major strategy for preventing atherosclerotic disease. To determine whether these risk factors also are associated with early atherosclerosis in young persons, we examined arteries and tissue from ≈3000 autopsied persons aged 15–34 y who died of accidental injury, homicide, or suicide. The extent of both fatty streaks and raised lesions (fibrous plaques and other advanced lesions) in the right coronary artery and in the abdominal aorta was associated positively with non-HDL-cholesterol concentration, hypertension, impaired glucose tolerance, and obesity and associated negatively with HDL-cholesterol concentration. Atherosclerosis of the abdominal aorta also was associated positively with smoking. These observations indicate that long-range prevention of atherosclerosis and its sequelae by control of the risk factors for adult coronary artery disease should begin in adolescence and young adulthood. *Am J Clin Nutr* 2000;72(suppl):1307S–15S.

KEY WORDS Coronary arteries, aorta, atherosclerosis, risk factors, fatty streaks, adolescents, young adults

INTRODUCTION

The natural history of atherosclerosis, as described nearly 50 y ago (1), is depicted in **Figure 1** (2). This description of origin and progression is inferred predominantly from observations of the arteries of persons autopsied at various ages. It is based on the assumption that any type of lesion occurring in one age group (for example, fatty streaks in adolescents) may be transformed into another type of lesion occurring at the same anatomic site in an older age group (for example, fibrous plaques in young adults and middle-aged persons). There has been little or no doubt for many years that the raised lesions of atherosclerosis (a collective term for fibrous plaques and the associated complications) determine the risk of clinically manifest coronary artery disease (CAD), both for populations and for individuals. CAD events become frequent in a population when the average extent of coronary artery raised lesions in middle-aged persons approaches ≈30% of the coronary intimal surface (3); individuals with CAD have on average ≈60% of the coronary intimal surface involved with raised lesions (4–6). Recent studies by angiography, ultrasonography, and histochemistry show that the qualities of raised lesions also predict risk of an occlusive event (7).

Lowering serum lipid concentrations by diet and drugs reduces both first events of CAD (primary prevention) (8) and recurrent events (secondary prevention) (9) among adults. However, no trials have intervened in childhood, adolescence, or young adulthood and subsequently followed the subjects into middle age, and such a trial is not likely to be feasible. The age at which preventive regimens should begin depends on the extrapolation of results in adults to younger persons, on the significance of the juvenile fatty streak, and on the conditions affecting the transformation of fatty streaks into raised lesions.

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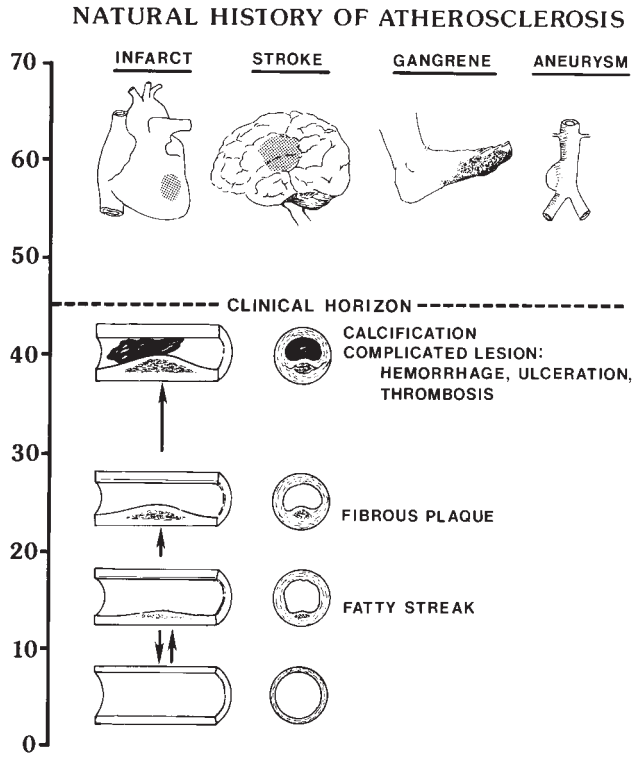

FIGURE 1. The development of the fatty streak in childhood is depicted as a reversible process. In adolescence, some fatty streaks accumulate more lipid and begin to develop a fibromuscular cap, forming the lesion termed a fibrous plaque. In subsequent years, fibrous plaques enlarge and undergo calcification, hemorrhage, ulceration or rupture, and thrombosis. Thrombotic occlusion precipitates clinical disease, depending on which artery is affected. Reproduced from reference 2.

In this article, we review the evidence that the fatty streak is the initial lesion of atherosclerosis and is the precursor of clinically important raised lesions, and relate this evidence to emerging knowledge of the molecular and cellular biology of atherosclerosis. We describe evidence regarding the associations of adult CAD risk factors with atherosclerosis in young persons and discuss the implications of these observations for the long-range prevention of CAD.

ORIGIN AND FATE OF THE FATTY STREAK

Aortic fatty streaks

Almost every North American child over the age of 3 y has some degree of aortic fatty streaks (10). Extensive aortic fatty streaks were present in children from post–World War I eastern Europe (11). Aortic fatty streaks were probably present in our hominid ancestors before they emerged as a separate species because fatty streaks occur frequently in both Old and New World nonhuman primates living in their natural habitat (12, 13) and in other mammalian species (14). Aortic fatty streaks differ only slightly in extent among children and adolescents of all populations, regardless of the frequency or severity of advanced atherosclerosis and CAD in adults in those populations (15). Women have more extensive aortic fatty streaks than do men in all populations (15), yet women develop an equal extent of aortic raised lesions (3). The thoracic aorta has about the same extent of fatty streaks as does the abdominal aorta, but raised lesions develop appreciably only in the abdominal aorta (3). The ecologic, epidemiologic, and topographic analyses that showed little or no relation between aortic fatty streaks and the clinically important lesions of atherosclerosis are largely responsible for the skepticism about the significance of the fatty streak (16–18).

Coronary artery fatty streaks

The relation of fatty streaks to more advanced lesions is different in the coronary arteries than in the aorta. Fatty streaks begin to appear in the coronary arteries 5–10 y later than in the aorta (15, 19). Comparisons of the localization of lesions in the coronary arteries show a close correspondence between the localization of fatty streaks in young persons and that of raised lesions in older persons (20). In nonblack populations, the extent of coronary artery fatty streaks in young persons predicts the extent of raised lesions in older persons (15). However, although women have about the same extent of or more coronary artery fatty streaks than do men, they have only half the extent of raised lesions at older ages (15).

Transitional lesions

The classification of atherosclerotic lesions in the coronary arteries as fatty streaks or fibrous plaques may not tell the whole story. The coronary arteries of white male children, adolescents, and young adults (who are at highest risk of advanced atherosclerosis and CAD) have more intimal cellular infiltration and connective tissue than do the coronary arteries of women or blacks. By the third decade, these differences are more pronounced and white male coronary arteries also show more vascularization (21). These observations were confirmed in a larger number of subjects from populations with a wide range of susceptibility to advanced atherosclerosis (22).

Chemical, physicochemical, histologic, and electron microscopic studies of fatty steaks and raised lesions of both the coronary arteries and the aorta (23–28) showed that both fatty streaks and raised lesions (as defined by gross criteria) contain free and esterified cholesterol, isotropic and anisotropic crystals, extracellular and intracellular lipid, collagen, and macrophages, and differ only in the proportions of each component. These observations suggest that there is a continuous spectrum of lesions ranging from those composed predominantly of lipid-filled macrophages (foam cells) in a relatively normal intima (the fatty streak) to those containing predominantly extracellular lipid and cholesterol ester crystals with a collagenous and muscular cap (the fibrous plaque). Between these 2 extremes of the fatty streak and the fibrous plaque, transitional stages of atherosclerosis exist that are not identifiable by gross examination alone.

These transitional stages were related to age by histologic examination of a standard site in the left coronary arteries of >500 persons from birth to 29 y of age (29). About one-third of children under 9 y of age had simple intimal fatty streaks composed exclusively of macrophage foam cells. By the age of puberty, more than one-half of the children had larger accumulations of macrophage foam cells, extracellular lipid, and lipid in smooth muscle cells. A small percentage of these children had large accumulations of extracellular lipid. By the late 20s, about one-third of the young adults had well-developed raised lesions with large extracellular lipid cores and thick fibromuscular caps.

These results correspond with the observation 36 y earlier of advanced coronary artery lesions in young (average age: 22 y) soldiers killed in the Korean War (30). Thus, there seems little doubt that in the coronary arteries the juvenile fatty streak—an apparently innocuous cluster of macrophage foam cells in the arterial intima—can, in some individuals, progress to advanced atherosclerotic lesions within a few decades.

The fatty streak as a byproduct of macrophage function

The origin of the ubiquitous juvenile fatty streak has long been an enigma, but now we have a plausible molecular and cellular mechanism for its origin and its transformation into a fibrous plaque. The discovery of oxidized LDL (31) and its uptake by the macrophage receptor for acetylated LDL (32) led to the identification of a family of macrophage receptors, commonly known as scavenger receptors (33–35), that bind a wide range of ligands (36) and probably are also involved in host defense mechanisms. One scavenger receptor that has a high affinity for oxidized LDL also recognizes apoptotic cells and facilitates their phagocytosis (37, 38). The common denominator of oxidized LDL and apoptotic cells is probably a modified phospholipid (39, 40).

These observations suggest that macrophages are stationed in all tissues, including the arterial wall. Each macrophage possesses a battery of versatile receptors that enable it to participate in host defenses and to remove apoptotic cell debris. Some of these receptors also have an affinity for the LDL that is oxidatively modified during or after passage through the endothelium. Any one of several conditions can accelerate the uptake of oxidized LDL: higher concentrations of LDL susceptible to oxidation, more rapid oxidation of LDL, less antioxidants, genetic variations in receptor structure and function (41), impairment of the macrophage's ability to discharge the phagocytosed sterols (42), or secretion of cytokines by macrophages loaded with cholesterol (43). A combination of a few of the factors favoring LDL oxidation and macrophage lipid accumulation and retention, even with a normal plasma LDL concentration, might explain the initial cluster of macrophage foam cells. If the process is accelerated by an elevated plasma LDL concentration, and overloaded foam cells die to form a pool of extracellular lipid, the transitional lesion forms. Macrophages stimulate adjacent smooth muscle cells to accumulate lipid (44). Inflammatory cytokines are generated, attract more macrophages, and autocatalyze the chronic inflammatory process. Thus, plausible molecular and cellular mechanisms can now explain the origin of the fatty streak as a physiologic process that can transform the fatty streak into a pathologic lesion under certain conditions. The risk factors for adult CAD augment the process of transforming the fatty streak into a lesion that causes arterial occlusion.

CORONARY ARTERY DISEASE RISK FACTORS AND ATHEROSCLEROSIS IN YOUTH

Association of risk factors for CAD with atherosclerosis

The longitudinal epidemiologic studies of the 1950s left little doubt that certain individual characteristics, which came to be known as risk factors, predict the probability that an individual will subsequently develop a clinical manifestation of atherosclerosis. Early attempts to relate these risk factors to atherosclerotic lesions yielded negative results (45–48), and these reports are frequently cited by skeptics of the hypothesis that serum cholesterol is an important intervening variable in the etiology of atherosclerosis (16). However, positive results began to emerge when better methods of quantifying atherosclerosis were developed, when antemortem risk factor measurements became available, and when investigators began to examine subjects dying as a result of accidents and other external causes rather than elderly persons dying of chronic diseases (49–60). The cumulative evidence is now overwhelming that the major risk factors for clinically manifest CAD (elevated serum cholesterol, hypertension, smoking, and diabetes) are strongly associated with atherosclerosis in the aorta and coronary arteries of adults older than ≈35 y of age. A few studies have extended the associations to 25 y of age (61, 62).

Risk factors and atherosclerosis in youth

In the 1980s, several epidemiologic studies measured serum total and lipoprotein cholesterol, blood pressure, adiposity, and other variables identified as risk factors for adult CAD in children and adolescents (63, 64). These studies showed that, although the average values were lower than those in adults, there were wide ranges of values for these variables beginning during the preschool period. These findings suggested that the predisposition to accelerated atherosclerosis might begin early in life and that control of these variables might be useful in long-range primary prevention.

Except for the rare cases of homozygous familial hypercholesterolemia in which accelerated atherosclerosis is common (65), and except for the studies of 25–44-y-old men cited above (61, 62), little evidence existed regarding the relation of the adult CAD risk factors to atherosclerosis in children, adolescents, or young adults under the age of 35 y. This issue is important in deciding at what age hygienic measures (eg, diet, physical activity, and weight control) should be advocated to control the risk factors and thereby retard the progression of atherosclerosis in youth and defer the onset of CAD years later.

In the Bogalusa Heart Study, atherosclerotic lesions were measured in arteries from 66 persons aged 6–30 y whose risk factors had been measured during life and who were autopsied after death due to accidents, homicide, or suicide (66). LDL-cholesterol concentrations were positively associated with the percentage of surface involved by fatty streaks in the coronary arteries and aorta. The number of subjects was not sufficient to detect associations with raised lesions nor to examine associations within age, sex, and race subgroups.

The Pathobiological Determinants of Atherosclerosis in Youth Study

In 1985 a group of investigators organized the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study to obtain more extensive information about the relation of risk factors to atherosclerotic lesions in youth (67). These investigators collected arteries, blood, and selected tissues from ≈3000 persons aged 15–34 y who had died within 72 h of accidental injury, homicide, or suicide, and were autopsied within 48 h of death in a medical examiner's laboratory. Seven collaborating centers collected this material following a standardized procedure and submitted specimens and information to central laboratories for analysis.

PDAY collection teams removed the aorta and coronary arteries from each body. They split the aorta in half longitudinally, fixed one half for gross examination, and preserved fixed and frozen samples from the other half for histochemical and chemical analyses. They opened the right coronary artery longitudinally and

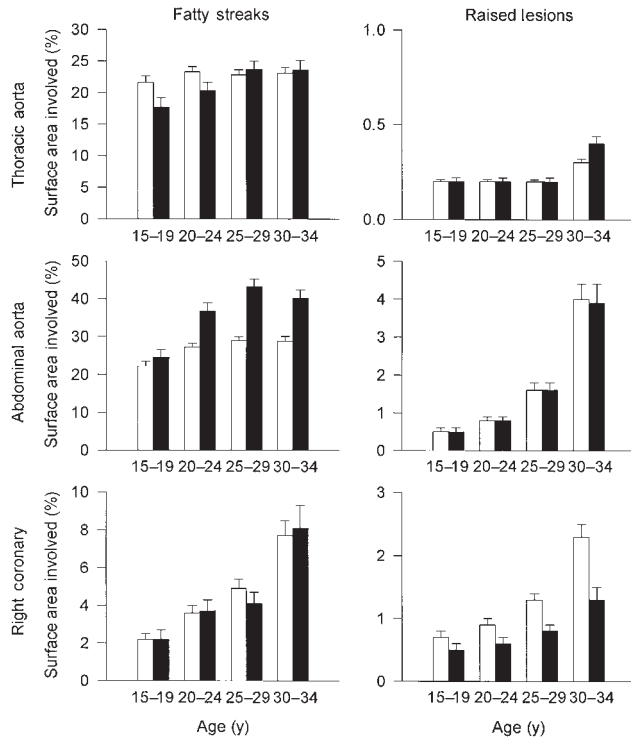

FIGURE 2. The mean (+SE) extent of fatty streaks and raised lesions by 5-y age groups of men (□) and women (■) in the thoracic aorta, abdominal aorta, and right coronary artery. The values are adjusted for race, non-HDL-cholesterol concentration, HDL-cholesterol concentration, and smoking. Drawn from data reported in reference 74.

fixed it in the flattened state for gross examination, fixed the left anterior descending coronary artery by pressure perfusion for histologic study, and froze the circumflex coronary artery for chemical analyses.

A central laboratory measured total and HDL cholesterol in postmortem serum and derived the non-HDL-cholesterol concentration by subtraction. The laboratory also measured thiocyanate in postmortem serum as an indicator of smoking status and measured glycosylated hemoglobin in red blood cells as a measure of blood glucose and incipient diabetes mellitus. Mean arterial blood pressure was estimated by an algorithm that used the thickness of the intima of small renal arteries. Adiposity was evaluated as the body mass index (BMI; in kg/m^2) computed from the weight and height of the body measured at autopsy.

The fixed aortas and right coronary arteries were stained with Sudan IV (Sigma-Aldrich, St Louis) to display fatty streaks. A team of pathologists in a central laboratory estimated the percentage of intimal surface of the left half of the aorta and the right coronary artery that was involved with fatty streaks and with raised lesions, a category that included fibrous plaques and plaques with calcification or ulceration. In this age group the raised lesions were predominantly uncomplicated fibrous plaques. Photographs of the stained arteries were digitized in another central laboratory and converted to standardized formats. Computerized algorithms produced composite images of specified groups that showed the prevalence of fatty streaks and raised lesions at each pixel location over the entire arterial surface (68, 69). Percentage of surface involvement was also computed for specified regions of each artery.

The collection phase of the project, which began in June 1987, was completed in August 1994. A total of 2876 subjects met the study criteria. Of these, serum for the measurement of lipoprotein cholesterol and thiocyanate was available for 1506 subjects and red blood cells for measurement of glycosylated hemoglobin were available for 2544 subjects. Kidney samples for assessment of hypertension were available for 2833 cases. About one-half of the subjects were white and the other one-half were black; about three-quarters were men and one-quarter were women. About one-third of the subjects died of accidents, one-half of homicide, and one-tenth of suicide. In preliminary analyses, the associations of risk factors with atherosclerosis were similar across all cause-of-death categories and these were pooled for the final analyses.

The major results describing the progression of atherosclerosis with age and the associations of serum lipids, smoking, hypertension, glycosylated hemoglobin, adiposity, and polymorphisms in candidate genes have been reported (70–77) and further analyses of the data are under way. In this review, we focus on effects of the risk factor variables most closely related to nutrition: serum lipoprotein cholesterol concentrations, glycosylated hemoglobin, and adiposity.

Risk factors among PDAY subjects

Non-HDL- and HDL-cholesterol concentrations were remarkably similar to those reported between 1980 and 1993 in surveys of living populations (74). The major limitations in use of these values are errors introduced by hemodilution as a result of the infusion of fluids or hemoconcentration due to hemorrhage after injury and before death. We excluded cases with serum cholesterol concentrations <2.59 mmol/L (100 mg/dL) to eliminate severely diluted sera. Errors due to hemodilution or hemoconcentration are likely to degrade associations but are not likely to produce spurious associations.

About one-half of the subjects aged >20 y were smokers as indicated by a serum thiocyanate concentration ≥90 μmol/L (74), a prevalence higher than in most surveys based on self-reported smoking habits. This higher prevalence was probably due to the association of smoking with accidents and suicides and use of an objective marker for smoking.

About 40% of the subjects had a BMI >25 and 10% had a BMI >30 (72). These results are consistent with surveys of adiposity in US adolescents and young adults (78). About 2% of the cases had glycosylated hemoglobin concentrations ≥0.08 (72). The prevalence of hypertension was similar to that seen in living populations (75).

Progression of atherosclerosis with age

Shown in **Figure 2** is the average extent of fatty streaks and raised lesions of the thoracic aorta, the abdominal aorta, and the right coronary artery by sex and 5-y age groups. The values are adjusted for race, non-HDL- and HDL-cholesterol concentrations, and smoking. By 15–19 y of age, fatty streaks occupied ≈25% of the aortic intima in both the thoracic and abdominal aortas. In subsequent age groups, fatty streaks remained constant in the thoracic aorta, but increased to occupy ≈40% of the abdominal aorta by the age of 30–34 y. By the age of 30–34 y, raised lesions occupied <0.5% of the thoracic aorta, but occupied ≈5% of the abdominal aortic surface. In the abdominal

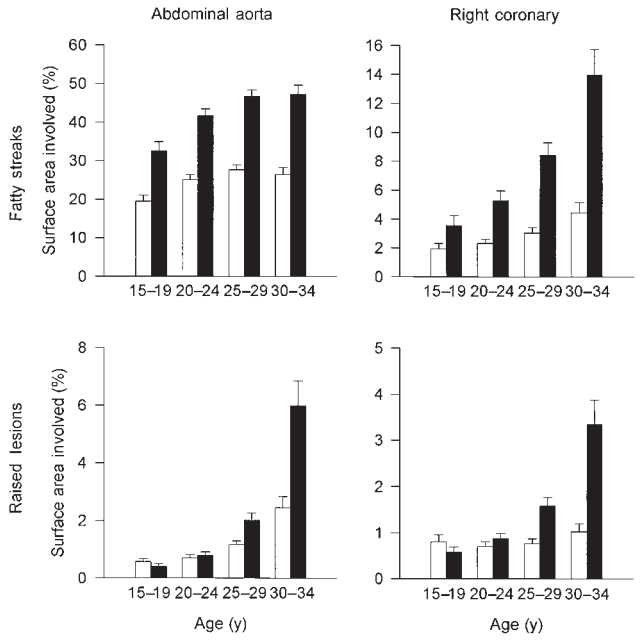

FIGURE 3. The mean (+SE) extent of fatty streaks and raised lesions in the abdominal aorta and right coronary artery by 5-y age groups in persons with a favorable lipoprotein profile [□; non-HDL cholesterol <2.89 mmol/L (108 mg/dL), HDL cholesterol >1.55 mmol/L (60 mg/dL)] compared with an unfavorable lipoprotein profile [■; non-HDL cholesterol >3.88 mmol/L (150 mg/dL), HDL cholesterol <1.11 mmol/L (43 mg/dL)]. Values are adjusted for race, sex, and smoking. Drawn from data reported in reference 74.

aorta, fatty streaks were more extensive in women than in men, but the extent of raised lesions did not differ significantly between men and women.

In the right coronary artery, fatty streaks increased in extent from ≈2% of the intimal surface at the age of 15–19 y to ≈8% at the age of 30–34 y and were equal in men and women. Raised lesions increased from ≈0.5% at the age of 15–19 y to >2% at the age of 30–34 y in men, but women had about one-half the extent of raised lesions at all ages. These results are consistent with results from many previous studies (3, 10, 15, 19) showing that the thoracic aorta is highly susceptible to fatty streaks, but not to raised lesions; that the abdominal aortas of women have more extensive fatty streaks than the abdominal aortas of men but an equal extent of raised lesions; and that the coronary arteries of women and men have an equal extent of fatty streaks, but that women have less extensive raised lesions.

Association of serum lipoprotein cholesterol concentrations with atherosclerosis

Non-HDL-cholesterol concentrations were positively associated with both fatty streaks and raised lesions in both the aorta and the right coronary artery; the opposite was true of HDL-cholesterol concentrations. Compared in **Figure 3** are fatty streaks and raised lesions in persons with favorable lipoprotein profiles (lowest third of non-HDL-cholesterol concentration, highest third of HDL-cholesterol concentration) and in those with unfavorable lipoprotein profiles (highest third of non-HDL cholesterol, lowest third of HDL cholesterol) (74). The values are adjusted for race, sex, and smoking. The unfavorable profile was associated with more extensive fatty streaks in both the abdominal aorta and the right coronary artery in all age groups. In the right coronary artery of 30–34-y-olds, the difference was nearly 3-fold. The lipoprotein profile began to affect raised lesions in the 20–24-y age group, and the difference in raised lesions was nearly 3-fold by 30–34 y. The unfavorable lipoprotein profile as defined here (combination of high non-HDL and low HDL cholesterol) is not rare: ≈10% of the PDAY cases fell into this category.

Association of BMI with atherosclerosis

The BMI was associated with more extensive fatty streaks and raised lesions in the right coronary arteries of men but not of women (**Figure 4**) (72).

Association of glycosylated hemoglobin with atherosclerosis

An elevated glycosylated hemoglobin concentration (≥0.08), which corresponds to an average blood glucose concentration of ≥8.3 mmol/L (150 mg/dL) for the previous 2 or 3 mo, was associated with increased fatty streaks and raised lesions of the right coronary artery (**Figure 5**) and with raised lesions of the abdominal aorta (72).

Association of smoking with atherosclerosis

In the abdominal aorta, smoking was associated with more extensive fatty streaks in the 15–24-y age group and with 3-fold more extensive raised lesions in the aorta in the 25–34-y age group (74). Smoking was also associated with a greater population of macrophage foam cells in atherosclerotic lesions (79).

Association of hypertension with atherosclerosis

Hypertension (mean arterial pressure ≥110 mm Hg) was associated with more extensive raised lesions in the right coronary artery and abdominal aorta, but did not affect fatty streaks (75).

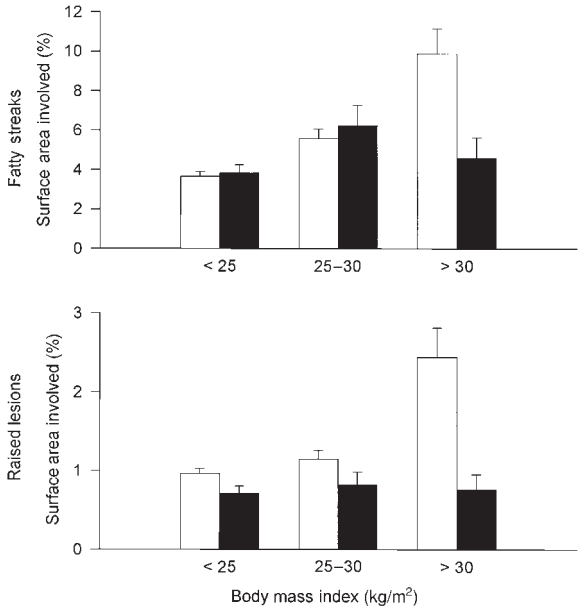

FIGURE 4. The mean (+SE) extent of fatty streaks and raised lesions in the right coronary artery by BMI in men (□) and (■). Values are adjusted for race and age. Drawn from data reported in reference 73.

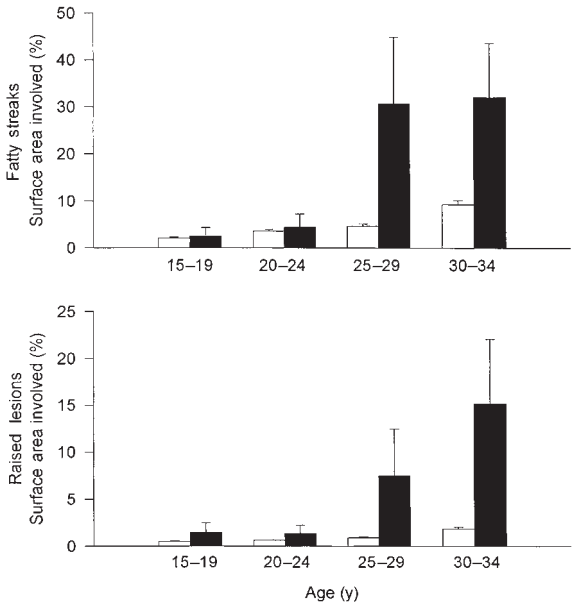

FIGURE 5. The mean (+SE) extent of fatty streaks and raised lesions in the right coronary artery by age and normal glycosylated hemoglobin concentration (□; <0.08) compared with elevated glycosylated hemoglobin concentration (■; ≥0.08). Values are adjusted for race and sex. Drawn from data reported in reference 73.

Topography of coronary fatty streaks and raised lesions

The topographic association of fatty streaks with raised lesions in the right coronary arteries of PDAY specimens is shown in **Figures 6** and **7**. In Figure 6, composite computerized images of right coronary artery intima stained with Sudan IV (fatty streaks) by 5-y age groups of white males are shown in the left panel and raised lesions are shown in the right panel. The extent of raised lesions followed that of fatty streaks by ≈5 y and the topographic distributions of fatty streaks and raised lesions were similar in all age groups. These results are consistent with those derived from a different population (20) and suggest that local factors in the artery wall affect fatty streaks and raised lesions similarly.

SUMMARY AND IMPLICATIONS FOR THE PREVENTION OF CORONARY ARTERY DISEASE

Fatty streaks as the initial lesions of atherosclerosis

Morphologic observations show a continuous progression from uncomplicated juvenile fatty streaks to raised lesions. The associations of risk factors with fatty streaks and raised lesions are similar and the topographic distributions of fatty streaks and raised lesions are similar in the coronary arteries and the abdominal aorta. The juvenile fatty streak, defined grossly, varies widely in characteristics. Under certain conditions and at certain anatomic sites, it is converted into a fibrous plaque and eventually undergoes other changes that directly cause arterial occlusion. Although harmless if it remains a fatty streak, the fatty streak nevertheless appears to be the initial lesion of atherosclerosis.

Mechanisms of transformation to raised lesions

The associations of CAD risk factors with fatty streaks and raised lesions in young adults are consistent with the cellular and molecular mechanisms derived from emerging knowledge of oxidized LDL, macrophages, and scavenger receptors. An elevated LDL concentration is the most common determinant of progression. HDL has antioxidant properties (80) and provides reverse cholesterol transport. Smoking has many effects, including increasing oxidative stress (81). Estrogen also has many effects, including antioxidant and antiinflammatory properties (82, 83). Hyperglycemia increases the formation of advanced

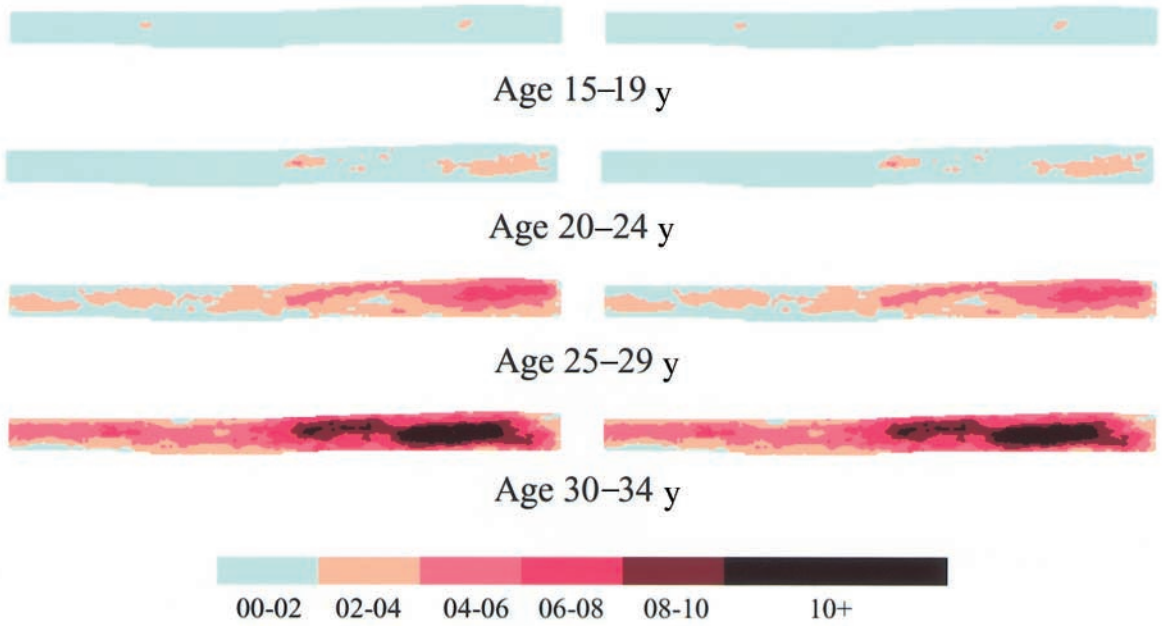

FIGURE 6. Composite digitized images of the right coronary artery of white males by 5-y age groups to depict the prevalence of fatty streaks stained with Sudan IV (Sigma-Aldrich, St Louis) (left panel) and the prevalence of raised lesions (right panel). *n* = 193 (15–19 y), 231 (20–24 y), 276 (25–29 y), and 234 (30–34 y). Color scale at bottom indicates prevalence.

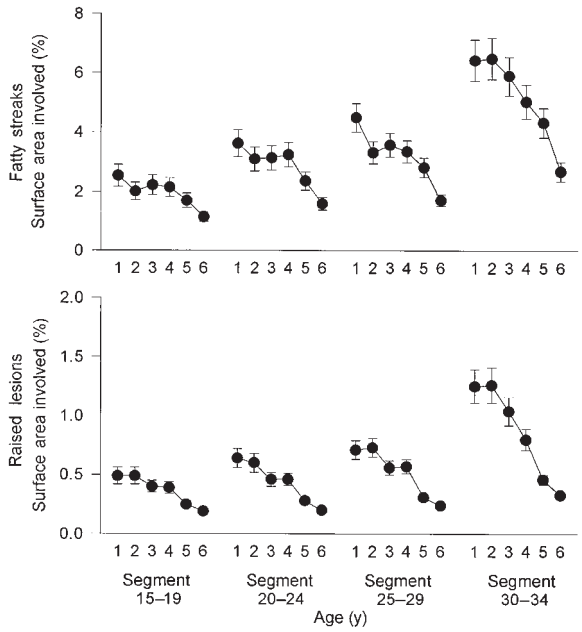

FIGURE 7. The mean (+SE) extent of fatty streaks and raised lesions in 1-cm segments of right coronary artery by 5-y age groups. Values were adjusted for race and sex and were generated by computerized digital image analysis.

glycosylation end products, which are ingested by scavenger receptors and further damage macrophages (84).

Mechanisms by which obesity augments raised lesions in men but not in women are not yet obvious. Despite many hypotheses involving the angiotensin system, it is not clear how hypertension accelerates the formation of raised lesions but not fatty streaks. It is still necessary to consider local anatomic and hemodynamic factors to account for the localization of fatty streaks, and for the tendency of fatty streaks in some locations to progress and in other sites to regress or remain static.

Implications for the prevention of CAD

We now have evidence that serum lipoprotein concentrations, smoking, obesity, and hyperglycemia are closely associated with fatty streaks in the second decade of life. The same risk factors, along with hypertension, are associated with raised lesions in the third decade of life. These results indicate that the long-range prevention of CAD should begin in childhood with control of the risk factors for CAD to limit the extent of juvenile fatty streaks and, more critically, to prevent or retard their progression to raised lesions.

NOTE ADDED IN PROOF

Subsequent to the submission of the manuscript, several articles that supplemented or modified statements in this article were published by the PDAY Research Group.

Transitional lesion

We state that "transitional stages of atherosclerosis. . . are not identifiable by gross examination alone." Wissler et al (85) compared the microscopic characteristics of several gross lesions in PDAY cases with microscopic counterparts and developed criteria for the identification of transitional lesions, known as fatty plaques or raised fatty streaks. These criteria were applied to ≈3000 aortas and coronary arteries, and the areas previously designated fatty streaks were divided into flat fatty streaks and raised fatty streaks. There were significant associations of raised fatty streaks with the risk factors for adult CAD (eg, non-HDL cholesterol- and HDL-cholesterol concentrations, hypertension, smoking, obesity, and impaired glucose tolerance), and these associations became evident in the late teenage years, earlier than the associations with grossly detected raised lesions (86). These results are consistent with the hypothesized progression of atherosclerosis from fatty streaks to fibrous plaques under the influence of the risk factors for adult CAD.

The microscopic qualities of atherosclerotic lesions at a standard site in the left anterior descending coronary artery were evaluated in 760 PDAY cases by using the American Heart Association (AHA) grading method (87) and computerized morphometry (88). Advanced (AHA grade 4–5) lesions were more frequent in men than in women and were positively associated with non-HDL-cholesterol concentrations, obesity, hypertension, and impaired glucose tolerance. AHA grade 2–3 lesions were associated with low HDL-cholesterol concentrations and smoking. Approximately 19% of 30–34-y-old men and 8% of 30–34-y-old women had stenosis ≥40%, and stenosis was associated with high non-HDL-cholesterol concentrations and obesity. The effects became evident in the 15–19-y age group. These results show that the risk factors affect the microscopic qualities related to the progression and the gross extent of atherosclerosis in youth.

Regional variations in the progression of atherosclerosis

PDAY investigators extended the analyses of computerized images of the right coronary artery and aorta shown in Figures 6 and 7 to >2000 cases (89). The results confirmed quantitatively the statements in this article about the topographic localization of aortic and coronary artery fatty streaks and their relationship to raised lesions that develop in the same areas in subsequent years. Estimates of the risk factor effects are ≈25% stronger in the vulnerable arterial segments than are estimates for the entire arterial intimal surface. The results also showed that there are some variations between arterial segments in their susceptibility to different risk factors, eg, smoking selectively augments atherosclerosis in the dorsolateral region of the distal third of the abdominal aorta.

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