

Atherosclerosis

EPIDEMIOLOGY AND RISK FACTORS

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INCIDENCE AND PREVALENCE OF ATHEROSCLEROSIS

The clinical consequences of atherosclerosis are devastating to the health of the U.S. population. Atherosclerosis-related cardiovascular diseases are the most common cause of mortality and morbidity in the United States. The extent to which atherosclerosis impinges on American health can be gauged by the large number of annual deaths from coronary artery disease (approximately 550,000 people) and the approximately 5 million people with overt coronary disease. The American Heart Association estimates that approximately 63 million people in the United States have atherosclerotic cardiovascular disease. In addition, approximately 500,000 people suffer strokes each year and approximately 1.9 million people are stroke patients.

Age-adjusted mortality from atherosclerotic disease has decreased in the U.S. population since the late 1960s, as shown in Figure 5-1. This decreased mortality may be related to effects on the atherogenic process by such changes as diet modification, smoking cessation, and treatment of hypertension. Surgical and medical management improvements have also contributed to this declining mortality, but may not be as directly related to the atherogenic process. These improvements include the introduction of coronary artery bypass surgery, angioplasty, and improved therapy for patients suffering from acute myocardial infarction. Thus, the contribution of improved recovery after an acute manifestation of an atherosclerotic event to the decline in mortality, and to the reduced frequency of the disease is unknown. Although the reduction in the incidence of atherosclerotic disease in the United States has been encouraging, it is still

the leading cause of death in Western industrialized nations.

DEFINITION OF RISK FACTORS

Epidemiological studies are designed to define risk factors or predictors for a disease process. A mechanistic link between atherosclerotic cardiovascular disease and a risk factor is not always readily apparent because epidemiological studies are only observational and are not controlled experimental studies. An additional problem is the lack of noninvasive techniques for directly quantifying the dimensions of atherosclerotic lesions. The indirect endpoints used in epidemiological studies, such as cardiovascular morbidity and mortality, reflect both atherosclerosis and its associated thrombotic events.

The concept of the cardiovascular risk factor arose from early reports of the Framingham Heart Study. Since its initial use, the term *risk factor* now has a number of meanings, including

1. A statistical correlation with atherosclerotic diseases, usually one that emerges from a multivariate analysis of longitudinal epidemiological studies
2. A factor that has been identified as a cause of atherosclerotic diseases
3. A characteristic that predisposes a person to atherosclerotic diseases

Kannel and Schatzin¹ have proposed that several criteria should be met for a risk factor to be considered a causal factor in the genesis of atherosclerotic diseases. These criteria include

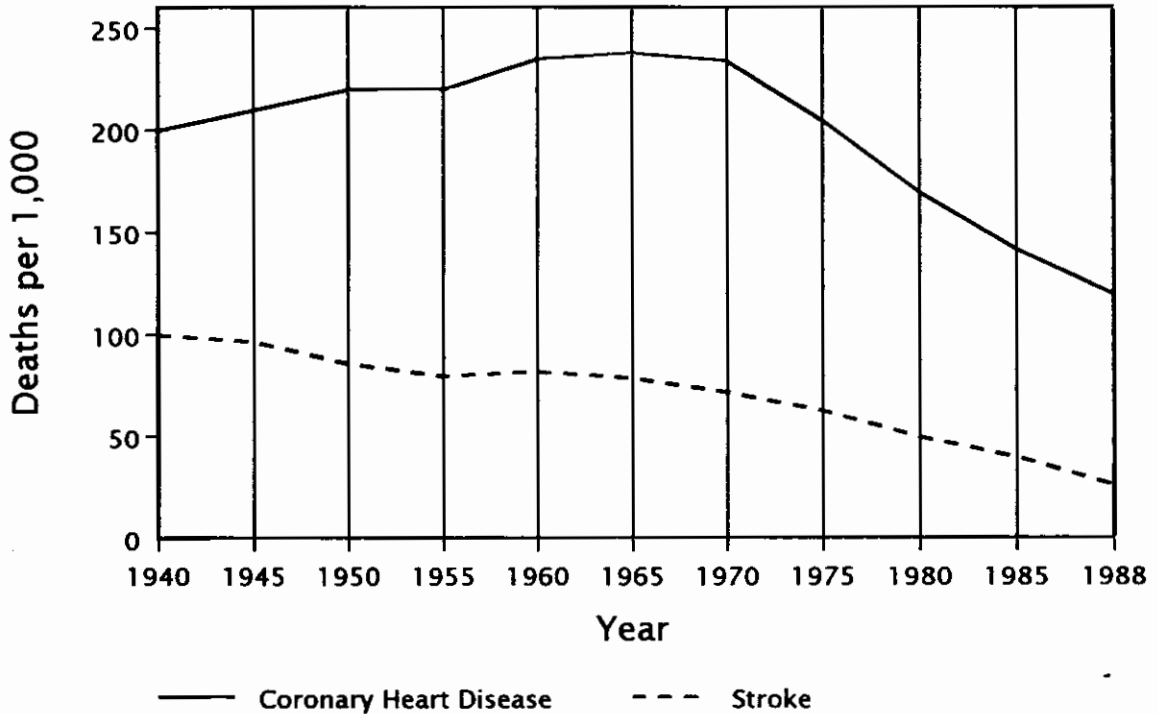


Figure 5-1. Percentage changes in age-adjusted mortality for atherosclerotic disease. The incidence of deaths from coronary heart disease is depicted in the solid line, and deaths due to strokes are represented as the dashed line. (From Research Update 1992. American Heart Association. With permission.)

- 1. Consistency of association.** The association of the disease should be consistent in different studies that use various measurement systems in diverse populations.
- 2. Strength of association.** People exposed to the risk factor should have a substantial increase in the incidence of the disease.
- 3. Biological plausibility.** The risk factor should be compatible with some underlying scientific cause for the disease.
- 4. Time sequence.** The presence of the risk factor must precede the appearance of the disease.
- 5. Dose response gradient.** The duration and intensity of the risk factor should be related to the severity of the disease.
- 6. Potential for intervention.** An intervention that influences the risk factor should appropriately modify the disease process.

Given the chronicity and complexity of atherosclerosis, it is not surprising that a multitude of risk factors have been associated with the disease process. One of the more extensive reviews of this topic is by Hopkins and Williams,² who surveyed 246 suggested coronary risk factors. It is important to note that risk factor analysis demonstrates correlations between the severity or frequency of the disease and specific param-

eters, but any such correlations do not prove causal involvement in the disease process. The credibility of a risk factor is increased when modulation of this risk factor causes a proportionate change in the extent of atherosclerosis either in animal experiments or human studies.

The etiology of atherosclerotic cardiovascular disease is now considered multifactorial. Consequently, no single risk factor has an absolute predictive power for the appearance of the disease. Rather, the relative risk associated with any single factor depends on the number and severity of other risk factors.

Unmodifiable Risk Factors

Increased age and male gender are major unmodifiable risk factors for atherosclerotic diseases. The pathological determinants of atherosclerosis in youth (PDAY) study firmly established that atherosclerosis begins in childhood³ and progresses with age. Prior to the age of 60, males are more prone than females to atherosclerotic diseases. The incidence and severity of atherosclerotic cardiovascular diseases in women, however, increases dramatically after menopause. A family history of premature atherosclerotic diseases is also strongly associated with an increased risk of coronary artery disease.⁴

POTENTIALLY MODIFIABLE RISK FACTORS

Hypercholesterolemia

Genetic and population studies, clinical trials, and animal experiments have indicated that plasma cholesterol concentrations are a major risk factor in the initiation and progression of atherosclerotic diseases. The strongest genetic evidence for a role of cholesterol in atherosclerosis in humans comes from familial hypercholesterolemic subjects. Patients suffering from the homozygous form of familial hypercholesterolemia have extremely high plasma cholesterol concentrations, generally greater than 600 mg/dL (15.52 mmol/L). Homozygous familial hypercholesterolemia, which affects about one in every one million people, is associated with a marked increase in the incidence and severity of atherosclerosis, and with coronary artery disease common in the first decade of life. Heterozygous familial hypercholesterolemic patients have plasma cholesterol concentrations in the range of 300 to 400 mg/dL (7.76 mmol/L) and often present with overt coronary artery disease in the fourth or fifth decade of life. Familial hypercholesterolemia is attributable to a genetic defect leading to a lack of functional receptors that recognize low-density lipoproteins (LDLs), the major cholesterol-carrying particle in the plasma. Although all familial hypercholesterolemic patients have a functional defect in LDL receptor activity, a multitude of genetic defects produce this physiological imbalance.⁵

Only a small percentage of the U.S. population has hypercholesterolemia that is attributable to a monogenic defect. Approximately 50% of all patients with premature coronary artery disease, however, suffer from a genetic form of hyperlipidemia. In the majority of people, modest hypercholesterolemia is probably the net result of multiple genetic factors that cause an imbalance between the mechanisms of synthesis, catabolism, and transport of cholesterol and its associated lipoproteins. Such defects confer a modest increased risk for atherosclerosis.

Numerous epidemiological studies have also shown a strong relationship between plasma concentrations of cholesterol and the risk for coronary artery disease. A major question regarding the role of hypercholesterolemia in coronary artery disease that has evolved from these epidemiological studies is whether there is a "safe" concentration of plasma cholesterol below which few atherosclerotic diseases will be present. This question has been studied further to determine whether the protection of hypocholesterolemia is a linear function (i.e., the lower the concentration, the lower the incidence of coronary heart disease). The data from the multiple risk factor intervention trial (MRFIT), which are shown in Figure 5-2, indicate

that the risk for coronary heart disease is not a linear function of plasma cholesterol concentration, but rather an accelerated risk occurs at concentrations above 200 mg/dL (5.17 mmol/L). In this trial, the risk doubled over 220 mg/dL (5.69 mmol/L) and tripled over 240 mg/dL (6.21 mmol/L).⁶

Although the concentration of plasma cholesterol as a predictor of coronary artery disease has been well documented, much of this evidence is based on trials studying middle-aged males. The pooled epidemiological data suggest, however, that these values may not be applicable to all ages and both sexes. Indeed, plasma cholesterol concentrations are typically above 240 mg/dL (6.21 mmol/L) in the population over 65 years old. These issues have been addressed in a combined analysis of studies performed by a National Heart, Lung, and Blood Institute (NHLBI) workshop.⁷ The relative and absolute risks of fatal coronary artery disease were determined for individual studies, and then pooled in a meta-analysis to determine risk estimates for the entire population. Due to the enormous body of available data, significant trends were observable by sex and age. In middle-aged men (<65 years old), the relative risk of hypercholesterolemia for coronary artery disease was greater in 23 out of 24 studies; the only study failing to show significance was the coronary artery surgery study (CASS).⁸ The pooled risk estimated for these studies demonstrated a 73% increase in coronary artery disease in individuals with cholesterol concentrations of 240 mg/dL (6.21 mmol/L) or higher.

Less data are available currently for women, though this is changing rapidly. An increased relative risk was found in 11 of 13 studies, with 9 observing significance at the 95% level.⁷ The aggregate risk was 2.4-fold increased risk of developing coronary artery disease for middle-aged women with cholesterol concentrations exceeding 240 mg/dL (6.21 mmol/L). Fourteen studies allowed comparisons between men and women; in all but one study the confidence intervals overlapped, implying that relative risk did not differ by sex. Absolute excess risks were lower in middle-aged women. Older women demonstrated an association between coronary heart disease and high cholesterol levels in 10 of 16 studies; however, only 1 was significant. The pooled relative risk was 1.12, suggesting a weak positive relationship between cholesterol concentrations and coronary artery disease in women over the age of 65. Older women displayed lower relative risks compared with men of the same age. Although more rigorous analyses are needed, the relative risks determined from this meta-analysis define a strong relationship between plasma cholesterol concentrations and coronary artery disease in middle-aged men and women and in older men, with a weaker relationship in older women.

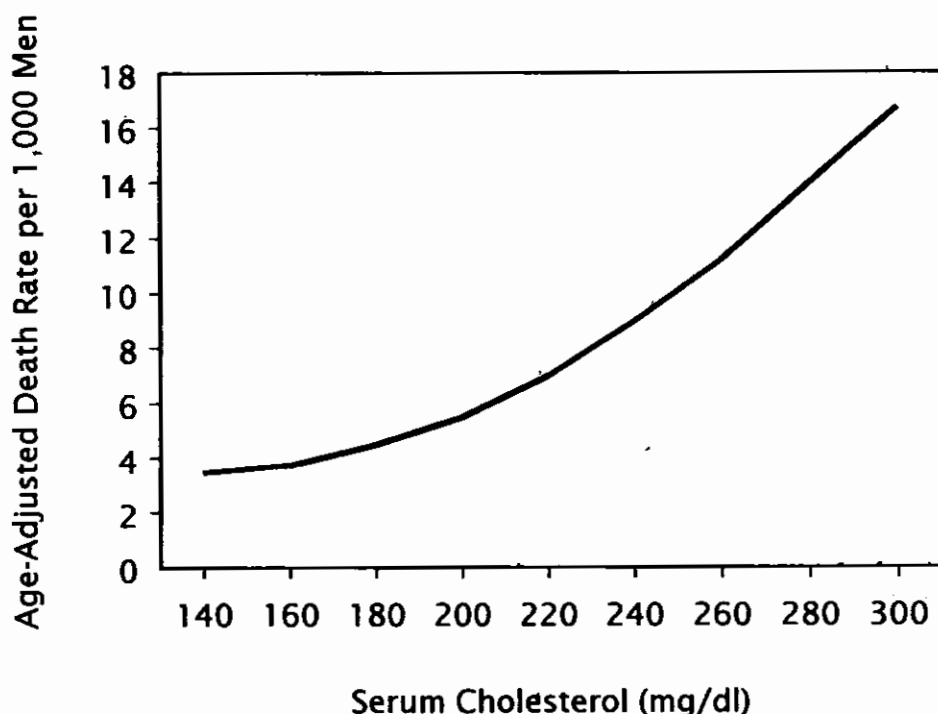


Figure 5-2. Data from the multiple risk factor intervention trial demonstrating the incidence of age-adjusted coronary heart disease against plasma cholesterol concentrations. The plot is the serum cholesterol concentration related to coronary artery disease mortality in a 6-year follow-up of men aged 35 to 57 years.

On the basis of the accumulated evidence, a national cholesterol education program has been established. This group has presented simple guidelines (Table 5-1) for the general population on the level of risk for coronary heart disease associated with plasma cholesterol concentrations. Note that these guidelines are simplifications and do not take into account such well known factors as the increase in plasma cholesterol concentrations that occurs with age and the lower concentrations in premenopausal females. It was considered that uncluttering the definitions would assist in the public recognition of high plasma cholesterol concentrations. Recent clinical trials further support the notion that hypercholesterolemia plays an important role in atherogenesis.⁹⁻¹³ Because cholesterol is amenable to both dietary and pharmacological intervention, great emphasis has been placed on treating this important risk factor.

TABLE 5-1. GUIDELINES OF THE NATIONAL CHOLESTEROL EDUCATION PROGRAM

Plasma Cholesterol Concentration (mg/dL)	Category
<200	Desirable
>220	Borderline high
>240	High

Further information on the role of cholesterol in the pathogenesis of atherosclerosis and in hyperlipidemia can be found in Chapter 8.

Hypertriglyceridemia

There is considerable controversy as to whether elevations in plasma triglyceride concentrations are associated with an altered risk for the development of cardiovascular diseases. Certainly syndromes exist in which plasma triglycerides are grossly elevated, such as in chylomicronemia and familial hypertriglyceridemia, which are not associated with an increased risk for cardiovascular disease. In other genetically determined syndromes, such as familial combined hyperlipidemia and remnant removal disease, hypertriglyceridemia is clearly a cause of atherosclerotic vascular disease.

Recent epidemiological results suggest that elevated triglycerides may predict coronary artery disease.⁷ Triglyceride concentrations were predictive of coronary heart disease in six studies each of middle-aged men and women, with significance being reached in three and five studies, respectively. The fact that pooled data demonstrated a significant relationship suggests that the sample sizes from the individual populations may have been too small to detect elevated risk.

The value of plasma triglyceride concentrations in predicting the development of atherosclerosis is more hotly contended than the predictive value of serum cholesterol. High or modest elevations of triglycerides are common findings in patients with coronary artery disease. The question has arisen, however, as to whether elevated triglycerides are an independent risk factor, since high plasma triglyceride concentrations are commonly associated with other potentially detrimental factors such as decreased plasma concentrations of high-density lipoprotein cholesterol.¹⁴ Another difficulty in equating alterations in plasma triglyceride concentrations with the risk for atherosclerosis diseases is the fluctuating nature of the measurement. Unlike cholesterol, which is little affected by fasting or an acute feeding stint, triglycerides are elevated in the postprandial phase. The magnitude of the hypertriglyceridemia following feeding varies widely among individuals. As a consequence of this variation, plasma concentrations of triglycerides are usually measured after an overnight fast. The average human subject, however, is in a postprandial phase for a major part of the day. A persistent postprandial state occurs because 6 to 10 h are required before triglyceride-carrying lipoproteins are completely cleared from plasma after ingesting food. Triglyceride-rich lipoproteins generated in the postprandial phase are present in small concentrations in plasma because these particles are cleared rapidly from plasma. Consequently, although postprandial triglyceride-rich lipoproteins do not contribute much to lipid concentrations measured at any single time interval, this system has an extremely high flux of lipids (i.e., the mass of lipid removed from the plasma over a specific period). The most important measurements may not therefore have been performed: that of total flux of triglyceride in the postprandial phase. Thus, the atherogenicity of triglycerides, either as a function of static concentrations or as total flux, is an open question that is likely to receive considerable attention in the coming years.

Further discussion on the role of triglycerides in the production of atherosclerosis can be found in Chapter 7.

Diabetes

Approximately 6 million Americans are afflicted by diabetes, a chronic disease of impaired glucose utilization that results from either a deficiency of or a resistance to insulin. Insulin-dependent diabetes mellitus (IDDM) often develops before the age of 20 and represents about 10% of all diabetes. The more common noninsulin-dependent form of diabetes mellitus (NIDDM) generally occurs in older people.

Diabetes is associated with the accelerated development of atherosclerotic lesions in all of the muscular

TABLE 5-2. POTENTIAL FACTORS THAT ENHANCE ATHEROGENESIS IN DIABETICS

Abnormalities of lipoprotein metabolism
Glucose modification of proteins
Enhanced susceptibility to oxidation
Procoagulant state
Insulin resistance

arteries, including coronaries, aorta, cerebral circulation, and kidneys.¹⁵ As a result of this increased propensity to atherosclerosis, patients with diabetes have at least a twofold greater incidence of myocardial infarction than nondiabetics. Certainly diabetics have a very high incidence of cardiovascular deaths, with coronary artery disease being the cause of death in 60% and stroke occurring in 25% of patients. Indeed, approximately one third of IDDM subjects of both sexes have died from coronary artery disease by the age of 50. The incidence of peripheral vascular disease in diabetics is also greatly increased, with gangrene of the lower extremities being relatively common. Many factors potentially contribute to the enhanced atherosclerosis in diabetics as summarized in Table 5-2. In addition to defects in the control of plasma glucose concentrations, diabetics are often afflicted by abnormalities in lipid metabolism. The most common defect is hypertriglyceridemia. Triglyceride concentrations may be elevated due to increases in very low-density lipoproteins (VLDL), VLDL remnants, and chylomicron remnants, all of which have been implicated in the atherogenic process. Hypertriglyceridemia is also associated with a procoagulant state, which is characterized by increased plasma concentrations of factor VII, factor X, and tissue-type plasminogen activator inhibitor. This procoagulant state may contribute to the atherogenic process or may enhance the likelihood of a thrombotic event, precipitating acute arterial occlusion.

The increased atherosclerosis in diabetics is not readily explained by known risk factors, suggesting that unidentified factors are involved.¹⁶ It has been proposed that a chronic imbalance of glucose may alter the function of specific proteins, particularly apolipoproteins. These alterations include the formation of glucose-protein adducts and subsequent oxidation that occurs after adduct formation. Although such changes in proteins have been documented, these alterations have yet to be definitely linked to the disease process.

Hypertension

Hypertension is commonly defined as a blood pressure of greater than 140/90 mm Hg, by which criterion 58

TABLE 5-3. CATEGORIZATION OF ARTERIAL BLOOD PRESSURE

Range (mm Hg)	Category
<i>Diastolic Blood Pressure</i>	
<85	Normal
85-89	High Normal
90-104	Mild
105-114	Moderate
>114	Severe
<i>Systolic Blood Pressure (when diastolic is below 90 mm Hg)</i>	
<140	Normal
140-159	Borderline
>159	Systolic hypertension

(From 1988 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.)

million people in the United States are considered above normal. The 1988 Report of the Joint Committee of Detection, Evaluation, and Treatment of High Blood Pressure provided guidelines for the interpretation of high blood pressure as described in Table 5-3. The Framingham study¹⁷ demonstrated that a progressive increase occurs in the risk for coronary artery disease with increases in blood pressure. In this study, the incidence of coronary artery disease was five times higher in males with pressures greater than 160/95 mm Hg compared with normotensive males that had blood pressures of 140/90 mm Hg or less. Hypertension appears to be equally detrimental in both males and females, with the diastolic component generally considered the most important factor.

The mechanism for increased atherosclerosis in hypertensive subjects has not been defined. Potential mechanisms include a possible increase in the functional "injury" to the endothelium that promotes flux of proteins, lipoproteins, and cells into the intima. Hypertension may also increase intraarterial pressure variations with attendant increases in shear and turbulent stresses. If the increase in hydrodynamic forces exceeds the mechanical strength of a lesion, plaque rupture might promote acute thrombosis and arterial obstruction.

In the case of hypertension, pharmacological intervention has been shown to reduce the incidence of both coronary artery disease and stroke. This reduction may be a consequence of a reduction in the atherosclerotic process, although this has yet to be directly demonstrated.

Fibrinolytic Mechanisms

Atherosclerotic lesions commonly cause acute thromboembolisms. Evidence also exists that the coagulation

system may participate in the formation of atherosclerotic lesions. A prominent component of a thrombus is fibrin, which is derived from circulating fibrinogen. Meade and colleagues¹⁸ reported that plasma concentrations of fibrinogen were a better predictor than cholesterol concentrations for the subsequent development of coronary artery disease in middle-aged men. This finding has been confirmed in a number of other studies.¹⁹ The effects of the fibrinolytic system may be interrelated to the lipoprotein system because increased plasma concentrations of fibrinogen are a common occurrence in patients with either hypercholesterolemia or hypertriglyceridemia.

Lipoprotein A may be a specific link between the fibrinolytic and lipoprotein systems, given the structural similarity between plasminogen and the apolipoprotein A component of lipoprotein A. Plasminogen is the precursor of plasmin, the enzyme responsible for the degradation of fibrin. Lipoprotein A may block the fibrinolytic process by preventing the activation of plasminogen.²⁰ Elevated plasma concentrations of lipoprotein A are generally considered a strong and independent risk factor for the development of atherosclerotic diseases, although a recent prospective study found no evidence for such a relationship.²¹

Overall, the evidence for the involvement of the fibrinolytic system in the development of atherosclerotic disease is relatively weak, although this is more related to the lack of evidence rather than conflicting data. Given the high level of interest in fibrinolysis for treatment of acute occlusive diseases, and the intense interest in lipoprotein A, the emphasis placed on fibrinolytic links to atherosclerosis is likely to increase.

Hyperhomocyst(e)inemia

Homocyst(e)ine, represented here with an (e) because it can be present in either the oxidized or reduced form, is an intermediate in the metabolic cycle that converts the essential, sulfur-containing amino acid, methionine, into S-adenosylmethionine. This product is then converted to homocyst(e)ine, which may be remethylated back to methionine. Homocyst(e)ine may also be converted to cysteine.

Several inborn genetic defects in this pathway result in homocyst(e)inemia. People afflicted with severe hyperhomocyst(e)inemia are at markedly increased risk for occlusive vascular disease. This raises the question of whether a moderate degree of homocyst(e)inemia is a risk factor for vascular disease. The prospective physician's health study (1985)²² demonstrated an association between homocyst(e)ine and the risk for coronary artery disease. Other studies have confirmed that a moderately increased plasma concentration of homocyst(e)ine is an independent

risk factor for the development of atherosclerotic diseases.²³ A survey pooling all of the relevant investigations suggested that elevated concentrations of homocyst(e)ine were less predictive of coronary artery disease than peripheral and cerebrovascular arterial diseases. In these studies, the incidence ratios between hyperhomocyst(e)inemic patients and controls ranged from 2.6 to 5.3 for coronary artery disease, and from 2.2 to 9 for peripheral and cerebrovascular arterial diseases.²⁴

It has been proposed that homocyst(e)ine promotes development of atherosclerotic lesions by damaging endothelial cells and possibly smooth muscle cells. It should be noted that hyperhomocyst(e)inemia is also associated with coagulation abnormalities and platelet activation.

Obesity

Obese subjects have a higher incidence of atherosclerotic diseases than do nonobese individuals, although it is not known whether this enhanced risk is related specifically to obesity. The importance of obesity as an independent risk factor is complicated by the common occurrence of hypertension, diabetes, hypertriglyceridemia, and hypercholesterolemia in these subjects. Nevertheless, the National Cholesterol Education Program has classified obesity, defined as body weight greater than 30% of ideal, as being a risk factor for atherosclerosis. A 26-year follow-up of the Framingham study demonstrated that obesity was an independent risk predictor of coronary artery disease.²⁵ Weight gain was associated with increased LDL cholesterol and VLDL triglyceride plasma concentrations, and decreased HDL cholesterol concentrations. Thus, increased body weight is often associated with an exacerbation of several risk factors. It has yet to be established that weight loss reduces the risk of atherosclerosis in moderately obese individuals, or indeed, that maintenances of weight loss for prolonged periods is possible.

Smoking

Cigarette smoking is the single most important modifiable risk factor for atherosclerotic diseases.²⁶ The detrimental effect of smoking is directly proportional to the number of cigarettes smoked. It appears that smokers of cigars and pipes are at less risk for coronary artery disease, their decreased risk being attributed to a reduction in the amount of smoke they inhale.

Smokers of cigarettes have a death rate from coronary artery disease that is 70% higher than that for nonsmokers, with heavy smokers (those who smoke two or more packs per day) having an even higher risk. The increased risk for coronary artery disease is also seen in women although it is less dramatic than

in men. The exception to this statement is that women older than 35 who take oral contraceptives have a markedly increased risk for coronary artery disease. Smoking is also associated with increased cerebrovascular disease, especially in the younger age groups, and with a greater incidence of peripheral vascular disease.

Risk for coronary disease appears to be related to the current level of smoking, and risk can be dramatically reduced by smoking cessation in subjects younger than 65. Indeed, the pooling project research group (1978)²⁷ demonstrated that the incidence of coronary events in middle-aged males was only slightly greater in those who stopped smoking than in those who had never smoked. The decrease in risk is relatively prompt and may be apparent within a year of smoking cessation. The MRFIT also identified passive smoking as a risk factor. Mortality in spouses of smokers was two times greater than that for spouses married to nonsmokers.²⁸

The mechanism by which cigarette smoking contributes to the development of atherosclerosis-related diseases is unknown. It is unknown whether smoking increases the atherogenic process or exacerbates ancillary events that lead to the manifestation of the disease. Suggested mechanisms for the increase in coronary events associated with smoking include coronary vasoconstriction, enhanced platelet aggregation, and transient vascular hypoxemia.

Behavior and Personality

It is widely believed that personality traits and excessive stress are related to the development of atherosclerosis, but little data support this hypothesis. Personality and stress studies have been hindered by the inability to quantify behavior. Early studies suggested that type A personalities, characterized by such traits as competitiveness, impatience, and compulsiveness over deadlines, have an increased incidence of atherosclerotic disease compared with the more "relaxed" type B personalities. Little recent evidence substantiates these earlier thoughts, however.

More recent studies have focused on how individuals respond to stress through anger and frustration. Excessive anger has been linked to premature coronary artery disease. In addition, those individuals who react to stress with marked increases in arterial blood pressure and heart rate also appear to be candidates for the occurrence of premature atherosclerosis.

The mechanisms by which stress may be related to the acceleration of atherosclerosis have not been defined. Furthermore, convincing evidence has been lacking to support the contention that stress and personality have any decisive effect on the outcome of atherosclerotic diseases.

Physical Inactivity

As in the case of personality, there is a widely held belief that a sedentary life-style is linked to the onset of coronary heart disease. Unlike for personality, however, there is more solid support for the benefits of exercise. The detriments of a sedentary life-style have been shown by studies of physical activity and physical fitness, and population studies. Studies of Harvard alumni²⁹ and in MRFIT³⁰ subjects have demonstrated a lower incidence of coronary artery disease in people who exercised regularly. All these studies demonstrated a benefit of moderate exercise, whereas the Harvard alumni study demonstrated a further benefit of vigorous exercise.

Physical activity has several potential benefits relative to the atherogenic process. One of the most frequently cited is the elevation of HDL cholesterol concentrations. It has been suggested that significant elevation of HDL cholesterol requires a minimum of 15 min of aerobic exercise at least 3 days a week. In addition, a generally reported benefit of cardiovascular conditioning is a decrease in arterial blood pressure.

It should be noted that the benefits to patients with cardiovascular diseases have not been demonstrated in any large, well-controlled, prospective clinical trial. Physical inactivity may be a risk factor for atherosclerotic diseases, but implementation of rigorous exercise may not be a panacea to overcome the disease process.

SUMMARY

Atherosclerosis-related cardiovascular disease is common and represents a large burden on the American health care system. A large number of risk factors have been proposed for the development of atherosclerosis, many of which, however, do not fit into the criteria needed to define them as causal influences as described at the opening of this chapter. At present, researchers have been able to specify a small number of risk factors that fit some of these criteria despite the complexity and chronicity of the disease. Despite these solid associations in population studies, it is still difficult to determine risk in an individual who does not have a blatant risk factor such as severe hypercholesterolemia.

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