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Understanding Risk in Hypercholesterolemia

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Summary: Atherosclerosis was relatively uncommon 100 years ago, when researchers first established its link to elevated cholesterol. As the twentieth century progressed, however, factors such as high-fat diets, sedentary lifestyles, cigarette smoking, and urbanization combined to increase the prevalence of both hypercholesterolemia and coronary heart disease (CHD) throughout the developed world. Atherogenesis begins at an early age and progresses throughout life, and cholesterol levels during young adulthood strongly predict the risk of CHD and related mortality during the ensuing decades. The total cholesterol level in youth also determines the actual age at which a critical level of atherosclerosis will be reached. Early studies on the primary and secondary prevention of CHD failed to identify a linear relationship between lipid lowering and risk reduction, primarily because older lipid-lowering agents lacked the potency to reduce cholesterol levels significantly enough to achieve lower cardiovascular event and mortality rates. The introduction of the statins, with their powerful lipid-lowering activity, overcame this limitation. Several large-scale trials of statins firmly established the efficacy of these agents in both primary and secondary CHD prevention. With the availability of statin therapy, we are now able to reduce the risk of major adverse CHD events by an average of 30%, regardless of patient age or gender.

Key words: atherosclerosis, hypercholesterolemia, statins

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Introduction

Atherogenesis has been the subject of investigation for more than 300 years, yet our understanding of cholesterol-deposition and plaque-formation processes continues to evolve. In 1695, Johann Conrad von Brunner illustrated autopsy-identified changes that he referred to as "hardening" of the aorta and major blood vessels. William Heberden penned a description of angina pectoris based on 20 cases in 1768, then expanded his observations to 100 cases in 1782.

The next milestone was Karl Freiherr von Rokitansky's 1852 description of atheroma pathology, which elucidated the "thrombogenic" or "encrustation" theory of atherosclerosis. A few years later, in 1856, Rudolf Virchow presented the "inflammatory" theory, which held that atherosclerosis is the result of intimal inflammation and subsequent fibrosis. Between 1909 and 1913, A. Ignatowsky, S. Saltykow, and N. N. Anitschkow developed the "lipid" theory of atherosclerosis, which linked dietary cholesterol to elevated circulating cholesterol and, in turn, to subintimal cholesterol deposits. In 1910, however, Sir William Osler contended that angina pectoris was a rare disease. "Indeed," he noted, "I had reached Fellowship before I saw a case in hospital or private practice."[1]

The theories of atherogenesis that occupy us today, then, have clearly been around for a while. Even so, as Osler noted, angina pectoris was an unusual finding in the early 1900s. As the twentieth century unfolded, this relatively rare condition[2] became the leading cause of mortality in the world.

Risk Factor Interactions

Studies carried out in recent decades have documented a clear relationship between serum cholesterol levels and the risk of coronary heart disease (CHD) in the developed world. As shown in Figure 1, curves depicting coronary artery disease (CAD) risk ratios from the landmark Multiple Risk Factor Intervention study (MRFIT) and a series of retrospective epidemiologic investigations in Japan are nearly identical.[3] These findings suggest that despite some degree of individual susceptibility, genetic predisposition plays only a minor role in

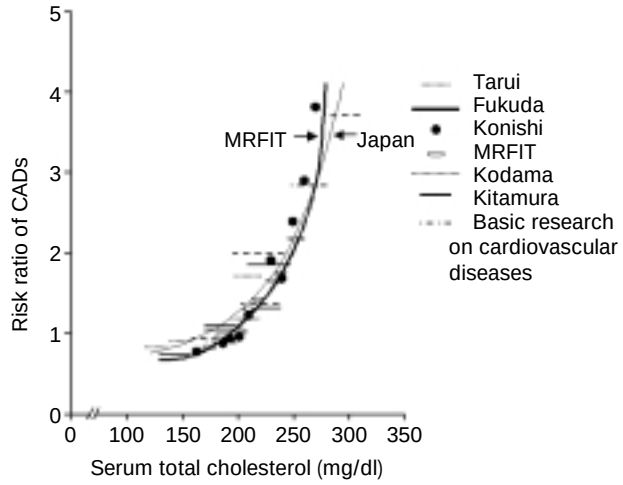

FIG. 1 Relationship between serum total cholesterol and risk ratio for coronary artery disease in the United States vs. Japan. Reprinted from Ref. No. 3 with permission. CAD = coronary artery disease, MRFIT = Multiple Risk Factor Intervention Trial.

determining the development of CAD as the result of elevated serum cholesterol. Rather, in the aggregate, this risk represents the influence of a constellation of factors, including high-fat diets, sedentary lifestyles, cigarette smoking, urbanization, and, most likely, others that have not yet been identified.

A study of Japanese patients—half living in Hiroshima, half living in Hawaii, and all having a 10- to 19-year history of type 2 diabetes—clearly illustrated the influence of diet, as opposed to genetics, on the development of CHD.[4] The incidence of retinopathy was similar in the two groups, affecting 57% of the Hiroshima residents and 50% of the Hawaiians. However, postmortem studies in individuals > 40 years old revealed that CHD was far more prevalent in Hawaii (33%) than in Hiroshima (14%). These data indicate that diabetes is an important risk factor for CHD in the presence of the factors that cause Western societies to have higher cholesterol levels—most prominently, high-fat diets.

Patterns of Atherogenesis

Pivotal data reported in the 1950s revealed that the process of atherogenesis begins early in life. Analyzing autopsy findings from 300 U.S. soldiers killed in action in the Korean conflict (mean age, 22 years), Enos *et al.* found that 35% had "fibrous" coronary arterial plaque with insignificant luminal narrowing, 12% had more than 50% occlusion of one or more vessels, and 3% had complete occlusion of one or more vessels.[5] Similar figures of 42, 12, and 0%, respectively, were reported by McNamara *et al.* in a 1971 analysis of data from 105 comparably aged casualties of the Vietnam War.[6]

For almost half a century, therefore, we have been aware that atherosclerosis is fairly well advanced by early adulthood. More recent confirmation of this pattern came from 1990s reports published by the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group.[7,8] Autopsy data from 2,876 individuals (15 to 34 years old) who had died of traumatic causes revealed the presence of raised lesions or fatty streaks even among teenagers; the percentage of intimal surface with such involvement increased with age. Fatty streaks were more extensive in black than in white subjects, but the prevalence of raised lesions did not differ by race. The extent of raised lesions in the aorta was similar in women and men, but raised lesions in the right coronary arteries were less common in women. Atherosclerotic damage to the intimal surface was positively associated with elevated serum levels of low-density lipoprotein (LDL) cholesterol and very-low-density lipoprotein (VLDL) cholesterol and negatively associated with high-density lipoprotein (HDL) cholesterol. Smoking was strongly associated with a greater prevalence of raised lesions—an effect that occurred independent of lipoprotein levels. Hypertension and diabetes also increased the risk of atherosclerotic changes. Assessing the clinical implications of this analysis, the investigators pointed out that the primary prevention of atherosclerosis, as opposed to the primary prevention of clinically manifest atherosclerotic disease, must begin in childhood or adolescence.

Other work showed that a single measurement of cholesterol in early adulthood does, in fact, predict which individuals will develop CHD as they grow older. In a prospective study of 1,017 men with a mean age of 22 years, Klag *et al.* found a strong relationship between the baseline serum cholesterol level and the occurrence of CHD, as well as CHD mortality and total mortality, during the subsequent 40 years (Fig. 2).[9]

Based on the strong association between cholesterol and CHD risk, one can reasonably conclude that consistently low cholesterol levels confer protection against heart disease. In Western societies with high-fat diets and sedentary habits, "low" indicates well below average. The median cholesterol level in the United States and Japan is 200 to 210 mg/dl (5.17 to 5.43 mmol/l),[10] which is probably 50 to 60 mg/dl (1.29 to 1.55 mmol/l) higher than the ideal in terms of preventing

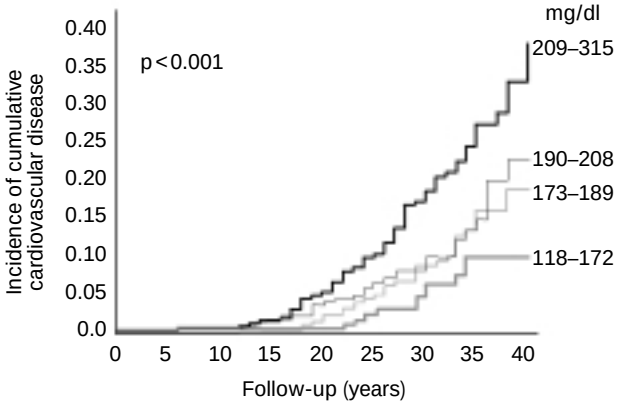

FIG. 2 Cumulative incidence of cardiovascular disease by cholesterol level at 22 years of age in men. Reprinted from Ref. No. 9 with permission.

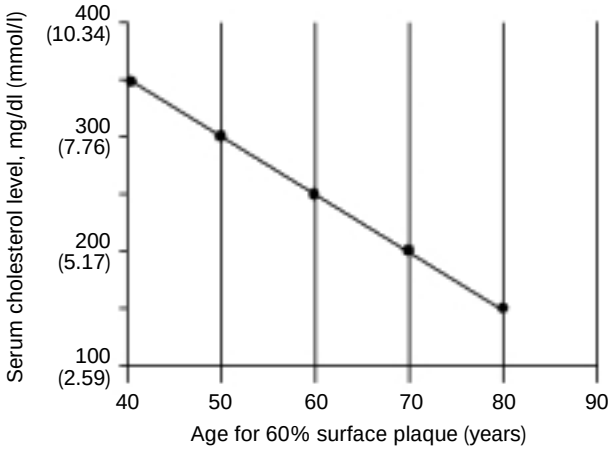

FIG. 3 Relationship of age to cholesterol level and extent of coronary artery plaque involvement. Reprinted from Ref. No. 11 with permission.

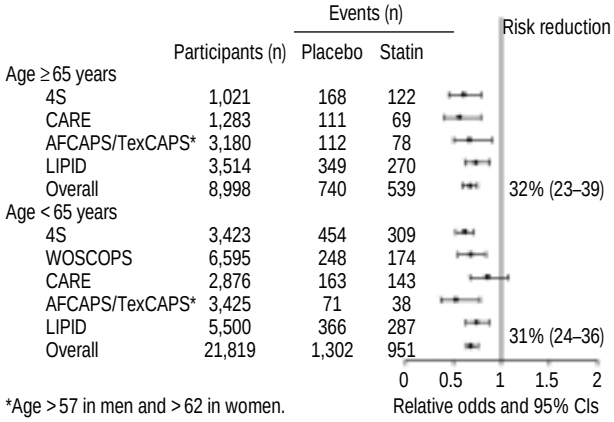

FIG. 4 Reduction in coronary heart disease risk by age in major statin trials. Reprinted from Ref. No. 18 with permission. 4S = Scandinavian Simvastatin Survival Study, CARE = Cholesterol and Recurrent Events Trial, AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study, LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease study, WOSCOPS = West of Scotland Coronary Prevention Study, CI = confidence interval.

atherosclerosis. A truly normal cholesterol level, from the standpoint of the process of atherogenesis, would be approximately 150 mg/dl (3.88 mmol/l).

The atherogenesis that begins at an early age progresses throughout life. The point at which an individual reaches a critical level of atherosclerosis depends on the cholesterol level. From a pathologic perspective, evidence of plaque formation on 60% of the coronary artery surface area could be considered significant atherosclerosis. An individual who maintains a total cholesterol level of 150 mg/dl (3.88 mmol/l) would reach the age of 80 before developing that degree of atherosclerosis (Fig. 3).[11] On the other hand, an individual with a steady total cholesterol level of 300 mg/dl (7.76 mmol/l) would reach this critical point at around the age of 50.

Primary and Secondary Prevention

Early studies of the primary and secondary prevention of CHD failed to identify a linear relationship between the degree of cholesterol reduction and the extent of CHD risk reduction.[12] In hindsight, it became apparent that the lipid-lowering agents used in the early trials (clofibrate, colestipol, cholestyramine, gemfibrozil, and niacin) simply lacked the cholesterol-lowering power needed to produce significant reductions in CHD risk.

Any doubt about the linear relationship between total cholesterol levels and CHD risk evaporated with the development of the statins, the most powerful agents for reducing cholesterol. Five pivotal, large-scale trials firmly established the efficacy of these agents in terms of both primary and secondary prevention of CHD morbidity and mortality.[13–17] A meta-analysis of data from these trials, representing a total of 30,817 participants, demonstrated that statin therapy reduces the risk of major adverse CHD events by approximately 30% regardless of patient age or gender (Figs. 4 and 5, respectively).

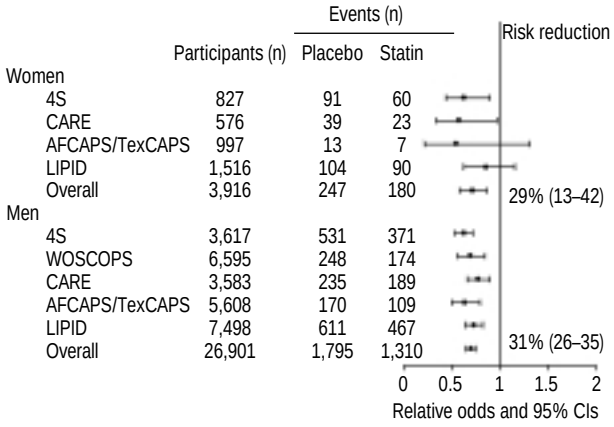

FIG. 5 Reduction in coronary heart disease risk by gender in major statin trials. Reprinted from Ref. No. 18 with permission. Definition of acronyms and abbreviations as in Figure 4.

Conclusion

Our understanding of the link between serum cholesterol and atherogenesis has been evolving for nearly 100 years. This association has become ever more striking during the past century as factors that raise atherogenic blood lipids—high-fat diets, sedentary lifestyles, cigarette smoking, and urbanization—have spread to affect every segment of society. With the understanding that atherogenesis begins early in life and that total cholesterol levels predict CHD risk, the goal of effective prevention through pharmacologic and behavioral interventions seems well within reach.

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