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Cholesterol and Coronary Heart Diseases- A Review Article

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ABSTRACT *Atherosclerosis is a disease whose causes are multifactoral, and alterations in plasma lipids and lipoproteins are one facet of the problem. A major achievement of research has been to show how the various risk factors interact in atherogenesis. Low density lipoprotein levels in the plasma are highly correlated with levels of plasma cholesterol. The role of LDL-cholesterol for atherosclerosis growth has been exaggerated, a finding with consequences for the prevention of cardiovascular disease. For instance, as the statins exert their beneficial influence on the cardiovascular system by several mechanisms, it may be wiser to search for the lowest effective dose instead of the dose with maximal effect on LDL-cholesterol. While there is considerable evidence that high density lipoprotein levels are negatively correlated with risk, there are as yet no data on the effects of altering these levels in individuals or in populations.*

Introduction

Atherosclerosis is a disease whose causes are multifactoral, and alterations in plasma lipids and lipoproteins are one facet of the problem. A major achievement of research has been to show how the various risk factors interact in atherogenesis. To focus solely on lipids and specifically on dietary cholesterol provides a narrow view of the problem. Various factors are cooperative and operate together to produce the disease.

According to the low-density-lipoprotein (LDL) receptor hypothesis, development of atherosclerosis is caused by a high concentration of LDL-cholesterol in the blood, and lowering LDL cholesterol reverses, or at least retards, atherosclerosis, thus preventing cardiovascular disease.[1] As a scientific hypothesis, it is open to falsification: if the concentration of LDL-cholesterol or total cholesterol and the degree of atherosclerosis do not correlate, or if there is no exposure-response, e.g. if there is no association between the cholesterol changes and atherosclerosis progression.

Very low density lipoproteins have been described in the Food and Nutrition Board Report' as neutral, but the meaning of neutrality is not clear. High density lipoproteins are now in vogue and are unique in that their levels in the plasma are negatively correlated with coronary heart disease.

Low density lipoprotein levels in the plasma are highly correlated with levels of plasma cholesterol. Since the latter is far easier to measure, most clinical and epidemiologic data are in terms of total cholesterol which, however, reflects low density lipoprotein levels. I have taken data from the Lipid Research Clinics Prevalence Study[2] and plotted low density lipoprotein cholesterol versus plasma cholesterol. There is a high degree of correlation, except at the lower levels of plasma cholesterol where high density lipoproteins make a relatively greater contribution to total cholesterol. There is now abundant evidence demonstrating that low density lipoprotein is a risk factor[3].

Intravascular ultrasound (IVUS) allows transmural visualization of coronary arteries and direct measurements of lumen, plaque, and vessel dimensions.[4-7] As a consequence, IVUS is an ideal tool for the assessment of the mechanisms that may be involved in the progression or regression of coronary artery disease.

A correlation between the pathological findings seen on coronary angiography and cholesterol has been found in many studies. Many studies have found an association between LDL- or total cholesterol and peripheral atherosclerosis, depicted by angiography or ultrasonography, but only in dichotomous analyses, and again, differences have been found mainly between individuals with very high cholesterol concentrations and the rest. In ultrasonographic studies, where degree of carotic atherosclerosis was graded as a continuous variable, no correlation was found with individual LDL-cholesterol concentrations. [8, 9] in similar studies using aortic[10] and femoral[11] angiography, no correlation were found either.

Hypercholesterolemia

Familial hypercholesterolemia is, as its name implies, a hereditary form of hypercholesterolemia. In the homozygous form, low density lipoprotein levels are extremely high, and mortality from coronary heart disease is very high. Survivors past age 25 are rare, and myocardial infarction is not at all infrequent in children six or seven years of age. In the more common heterozygous form, low density lipoprotein levels are not as high, but nevertheless the incidence of coronary heart disease in these subjects is high. Fifty percent of men with heterozygous familial hypercholesterolemia have myocardial infarctions before age 50.'"

In the course of studies of cholesterol metabolism by cultured cells, Brown and Goldstein'" found that cells from normal subjects bind low density lipoproteins when they are grown in their absence. However, cells from patients with homozygous familial hypercholesterolemia do not bind low density lipoproteins, and heterozygotes are intermediate in their binding. These studies led to the conclusion that cells have specific receptor sites for low density lipoproteins and that these are absent in patients with homozygous familial hypercholesterolemia. The failure to bind and to catabolize low density lipoproteins leads to elevation of their plasma levels. Originally, receptors were found only in peripheral cells, but more recently they have been found in liver cells. It appears that about half of the low density lipoproteins is cleared from the plasma

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through the liver, although not necessarily by the high affinity receptor mechanism. 'These studies clearly demonstrate that a genetic defect in receptor production leads to elevated plasma low density lipoprotein levels.

It has already been pointed out that low density lipoprotein levels are affected by levels of saturated fatty acids in the diet so that reducing saturated fatty acids in the diet will lead to reduction of low density lipoproteins. In the Indians studied by Dr. Connor in Mexico, [12] he found a good correlation between dietary cholesterol and plasma cholesterol. It is pointed out that these subjects ate diets with a high P:S ratio, and it could well be argued that this may not be applicable to the American population. Dr. Ahrens and his associates demonstrated clearly that substitution of polyunsaturated fat for saturated fat in the diet lowered serum cholesterol. Substitution of coconut oil, which does not contain saturated fatty acids, causes the cholesterol level to return to baseline levels and corn oil caused cholesterol to decrease. This is an unequivocal proof that by altering the diet we can change levels of low density lipoproteins. Studies have been performed in free living Scandinavian populations on a diet low in saturated fat and high in polyunsaturated fatty acids. In almost all instances, serum cholesterol levels in these individuals fell.

There is considerable disagreement as to the significance of very low density lipoprotein as a risk factor. Epidemiologists using multivariate analysis state that hypertriglyceridemia is not a primary risk factor, and some do not believe it useful to measure plasma triglycerides.[13] However, it has long been known that patients with coronary heart disease have, on average, higher levels of triglyceride. Thus, in the study of Goldstein et al[14] the patients with coronary heart disease had higher levels of triglycerides than did the control subjects. In some populations, such as in Sweden, [15] prospective studies have shown a high correlation between plasma triglyceride concentrations and the incidence of myocardial infarction.

Conclusion

'The more LDL there is in the blood, the more rapidly atherosclerosis develops.' Low density lipoprotein is clearly a major risk factor for coronary heart disease. There are less definitive data regarding the role of very low density lipoprotein, but it does have a strong association with coronary heart disease.

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