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Cholesterol Update

Many researchers are re-evaluating the past 70 years of animal experiments that examined relationships between dietary factors and atherosclerosis. Recent findings indicate that because of the contamination of cholesterol with certain oxidation products, earlier feedings trials may have been flawed.

Many of the early cholesterol feeding studies involved large quantities of cholesterol in the diets of chickens and rabbits, and typical findings were that high levels of dietary cholesterol resulted in the type of injury to coronary arteries typically seen in atherosclerosis. Thus, the hypothesis developed that dietary cholesterol increases levels of blood cholesterol, thereby increasing the severity of atherosclerosis and CHD. Studies such as these resulted in recommendations by the American Heart Association and the U.S. Senate Select Committee that Americans reduce the amount of cholesterol in their diets.

These studies were criticized on the basis of two major points: (1) the experimental animals were strict herbivores and, as such, did not normally eat cholesterol, and (2) levels of cholesterol used in the diet were unrealistic (equivalent of 30 to 60 eggs per day), and when animals were fed levels of cholesterol similar to levels found in the human diet, atherosclerosis was not produced.

The conclusion that cholesterol in the diet caused atherosclerosis was incorrect because it was based on the assumption that cholesterol is a stable molecule. Actually, cholesterol can react with oxygen to undergo numerous types of oxidation reactions resulting in many new compounds, many of which appear to be angiotoxic.

Review of the Diet-CHD Hypothesis

Numerous factors in the human diet can be related to CHD. Total calories, salt, sugar, fat, degree of saturation and unsaturation of dietary fat, and cholesterol have all been suspected of playing a role in human coronary disease. But conclusions based on experiments with laboratory animals are controversial--the most controversial being those that fed cholesterol to rabbits, chickens, and pigeons.

Cholesterol is used by the body to synthesize vitamin D and make sex hormones and hormones of the adrenal gland. It is a component of cellular membranes, the sheath around each cell. Cholesterol is also used to make bile salts to aid in digestion of fat. Cholesterol forms an important part of the body's biological functioning system and yet is not an essential dietary nutrient since it can be made by the body from food.

Research has demonstrated that it is difficult to increase blood cholesterol by changing dietary cholesterol. An estimate of dietary effects indicated that within the average consumption range (250-750 mg per day), blood cholesterol would change by less than 10 mg/dl. Oliver (1981) concludes that "the association (epidemological) between dietary cholesterol and CHD is weak." Even among persons who are unusually sensitive to dietary alterations, dietary cholesterol would be far less important than intake of saturated and unsaturated fat, because the body compensates for consumption of cholesterol by reducing the synthesis and increasing the excretion of cholesterol. The net result is that blood cholesterol is difficult to alter by dietary cholesterol changes. In this regard, rabbits and people are very different.

Definitions

Angina pectoris - often results from partial blockage of arteries by plaque; shows up as pain, usually in the chest.
Angiotoxicity - toxic to blood vessels.
Arteriosclerosis - group of diseases characterized by thickening and loss of elasticity of arterial walls; commonly called hardening of the arteries.
Atherosclerosis - specific and common type of arteriosclerosis in which deposits of yellowish plaques containing cholesterol, fatty material, and other factors are formed in arteries.
Cholesterol - fat-soluble, sterol type of chemical compound produced in tissues of humans and animals; also found in meat, egg yolks, and milk products.
Hypercholesterolemia - a condition of high blood cholesterol.
Ischemia - a deficiency of blood flow through a tissue caused by clogging of blood vessels.
Coronary heart disease (CHD) - deficiency of blood flow through the heart tissue caused by atherosclerosis of coronary arteries that nourish the heart.
Myocardial infarction - damage to heart caused by near or total blockage of one or more coronary arteries; constitutes a heart attack.
Cholesterol oxidation products - formed from cholesterol when it is allowed to react with oxygen.

The relationships between diet and CHD are exceedingly complicated and often conflict with prevailing theories. In a study by Gordon and coworkers, research involved over 16,000 men, aged 45-64. This was a prospective study in that the occurrence of CHD was monitored for four to six years after dietary habits had been determined. Men who incurred CHD actually consumed less sugar, fewer total calories, and more alcohol than non-CHD men, and their dietary cholesterol intake was not associated with CHD. Dietary polyunsaturated/saturated (P/S) fat intake was not related to CHD except in one section of the study (8,218 men) in which a higher P/S ratio was associated significantly with higher morbidity and mortality due to CHD! Physical activity was inversely correlated with CHD. CHD men ate more protein and fat than non-CHD men. Finally, statistical calculations revealed a "protective" effect of starch: 72 grams per day increase in starch intake was associated with a 20% lower risk for CHD.

Another argument used against the dietary cholesterol-CHD hypothesis is that no real evidence has ever been found in humans to indicate that dietary cholesterol causes heart disease. Cholesterol is only one of many dietary factors that has been related to the disease. And diet, overall, is but one of several major risk factors that has been correlated with CHD.

Finally, the importance of the ratio of high-density lipoprotein (HDL) to low-density lipoprotein (LDL) in the blood has only recently been appreciated. Cholesterol must be carried by proteins in the blood, and HDL and LDL have opposing functions. LDL takes cholesterol from the liver and distributes it to the body's tissues. Unfortunately, LDL also deposits cholesterol in the coronary arteries and, therefore, tends to promote atherosclerosis. In contrast, HDL tends to reduce atherosclerosis since it carries cholesterol from the various tissues (and arteries) back to the liver for the manufacture of bile salts and excretion from the body. Those who have a high level of HDL and a low level of LDL in their blood tend to have a lower risk of heart disease. (Diet is only one of many factors controlling the overall HDL/LDL ratio in our blood. Smoking and dietary saturated fat tend to raise LDL; exercise tends to raise HDL. Women generally have higher levels of HDL).

Because of the importance of the HDL/LDL ratio and other previously discusses factors, it seems rather simplistic to some scientists to say that dietary cholesterol per se is a major risk factor in coronary disease.

Instability of Cholesterol

Reasearchers have found a total of 32 different oxidation products from cholesterol. The only means available of inhibiting these types of oxidation reactions is to flush the cholesterol container with nitrogen and keep it at a very low temperature. Previous studies using cholesterol feeding did not take these precautions and are now suspected of having led some researchers to an incorrect conclusion concerning the ability of native cholesterol to promote atherosclerosis.

Another more recent study reported the following additional facts concerning the instability of cholesterol in relationship to earlier feeding trials: (1) purchasing fresh cholesterol from suppliers does not ensure that oxidation has not already taken place, (2) allowing cholesterol to remain in the laboratory for a few months allows significant oxidation of cholesterol, (3) further oxidation occurs after cholesterol is mixed into the feed, (4) oxidized products of cholesterol are highly angiotoxic, and (5) native (unoxidized) cholesterol expresses little or no angiotoxicity in side-by-side comparisons to some of the oxidation products of cholesterol.

These findings raise significant questions about the dietary cholesterol-CHD hypothesis. It appears that the atherogenic properties of the diets of the animals were not due to the cholesterol content but rather to the contaminating oxidation products of cholesterol. Native cholesterol appears to be a much safer chemical compound than was previously recognized. This appears logical since it is a multi-use compound in the body, is made by the body, and is, in fact, an essential component of many parts of the body.

Detrimental Effects of Oxidized Cholesterol Products

The relative angiotoxic effects of native cholesterol and the oxidation products of cholesterol, an interesting and relevant study, was conducted comparing drugs with dietary cholesterol as a means of inducing hypercholesterolemia. In one treatment, hypercholesterolemia was induced by a drug; in the other treatment, hypercholesterolemia was caused by a high-cholesterol diet.

Both treatments were about equal in their ability to elevate blood cholesterol. What was facinating, however, was that the degree of atherosclerosis was much higher in the diet-induced hypercholesterolemia than in that produced by the body. It seems likely that the difference in the degree of atherosclerosis was due to the fact that the dietary treatment also included oxidation products of cholesterol, whereas the cholesterol synthesized by the body was protected against oxidation and involved only hypercholesterolemia due to native cholesterol.

Another study showed that purified cholesterol is quite unstable when stored at room temperature. The end products of cholesterol oxidation were concentrated from commercially available cholesterol, and the biological activities were studied using cultured rabbit's aortic smooth muscle cells. This type of bioassay measured the ability of chemical compounds to produce atherosclerosis. The researchers concluded that the concentrate of the autoxidation products of cholesterol "showed remarkable in vitro cytoxic effects, whereas purified cholesterol at the same concentration produced no toxic effects."

These studies provide further evidence that the atherosclerosis noted in feeding trials was due to oxidation products and not to cholesterol itself.

New Hypothesis on Dietary Cholesterol and CHD

The foregoing studies necessitate a re-evaluation of the previous hypothesis on dietary cholesterol and heart disease. A different role must be found for native cholesterol, which numerous studies have now shown does not produce the initial insult to blood vessels that causes conditions permitting atherosclerosis to occur. The initial damage is clearly not caused by cholesterol, but may be spontaneous, occurring with aging, or caused by other unknown, toxic factors.

Hypercholesterolemia may play a role, however, in the total build-up of plaque in the blood vessel subsequent to the initial damage. Many of the previous warnings against conditions that elevate cholesterol would still appear to be pertinent. It is doubtful, though, that the amount of native cholesterol in the diet is as important a factor in hypercholesterolemia as was originally thought. Other factors such as dietary saturated fat intake, obesity, hypertension, sex, lack of exercise, smoking, and other types of risk factors are still relevant. Native cholesterol, as a dietary factor, essentially plays no role in atherosclerosis.

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