The Cause of Atherosclerosis
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*Nutr Clin Pract* 2008; 23: 464
DOI: 10.1177/0884533608324586

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Most physicians, I believe, consider atherosclerosis to be a multifactorial disease, and the greater the number of atherosclerotic risks factors present, the greater the chance of having an atherosclerotic event. I am in the minority in believing atherosclerosis to be a unifactorial disease, the result of abnormal serum or plasma cholesterol levels. If dyslipidemia is present, then systemic hypertension, diabetes mellitus, cigarette smoking, inactivity, and excessive body weight increase the likelihood of an atherosclerotic event, but none of them in and of themselves is required for severe atherosclerosis to occur. In contrast, atherosclerosis does not occur if dyslipidemia is not present, irrespective of the blood pressure level, blood glucose level, the degree of obesity, the degree of activity, or the number of cigarettes smoked daily.

There are 4 factors supporting the proposition that cholesterol is the cause of atherosclerosis:

1. Atherosclerosis is easily produced in nonhuman herbivores (eg, rabbits, monkeys) by feeding them a high cholesterol (eg, egg yolks) or high saturated fat (eg, animal fat) diet. These studies initially were done by some Russian physiologists beginning in 1908. And atherosclerosis was not produced in a minority of rats fed these diets, it was produced in 100% of the animals! Indeed, atherosclerosis is one of the easiest diseases to produce experimentally, but the experimental animal must be an herbivore. It is not possible to produce atherosclerosis in a carnivore but with one exception, and that is in carnivores that have hypothyroidism due to thyroidectomy. The only condition that is easier to produce experimentally than atherosclerosis is an endocrine deficiency. If the thyroid gland is removed, the consequence is hypothyroidism, unless the thyroid hormone is replaced. In contrast to feeding cholesterol and/or saturated fat, it is not possible to produce atherosclerotic plaques in herbivores by raising the blood pressure chronically, by blowing cigarette smoke in their faces for their entire lifetimes, or by somehow raising the blood glucose levels without simultaneously feeding them an atherogenic diet. Presently, it is commonly stated that “atherosclerosis is an inflammatory disease.” Inflammatory cells, however, are infrequent in plaques of coronary arteries studied at necropsy or in endarterectomy specimens. When present, the few mononuclear cells—even giant cells—appear to be present due to a reaction to the deposits of lipid (pultaceous debris) present in the plaque. “Inflammation” appears to be a surrogate for elevation of serum C-reactive protein or various cytokines (interleukins 1 and 6, tumor necrosis factor, etc), not for inflammatory cells in plaques. Thus, it is a definition situation, and the morphologic definition of inflammation is not applicable.

2. Cholesterol is present in the plaques. Several studies in the 1930s nicely demonstrated that experimentally produced plaques in herbivores were similar to plaques in humans.

3. Populations with relatively high serum cholesterol levels compared to populations with relatively low serum cholesterol levels have a much higher frequency of atherosclerotic events, a much higher frequency of dying from these events, and a much greater quantity (burden) of plaque in their arteries. This factor was nicely supplied by the 7-country study and the Framingham study among others.

4. Lowering serum total cholesterol and low-density lipoprotein (LDL) cholesterol levels decrease first and repeat atherosclerotic events. Additionally, plaque size may decrease.

In summary, the connection between cholesterol elevation and atherosclerotic plaques is clear and well established. Atherosclerosis is a cholesterol problem! If one has elevated cholesterol, has an elevated blood pressure, smokes cigarettes, or has an elevated blood sugar, these additional factors serve to amplify the cholesterol damage but they by themselves do not produce atherosclerotic plaques! Societies with a high frequency of systemic
hypertension or a high frequency of cigarette smoking but low cholesterol levels rarely get atherosclerosis.

**Differences Between Herbivores and Carnivores**

Because humans get atherosclerosis, and atherosclerosis is a disease only of herbivores, humans also must be herbivores. Most humans, of course, eat flesh, but that act does not make us carnivores. Carnivores and herbivores have different characteristics. (a) The teeth of carnivores are sharp; those of herbivores, flat (humans have some sharp teeth but most are flat for grinding the fruits, vegetables, and grains we are built to eat). (b) The intestinal tract of carnivores is short (about 3 times body length); that of herbivores, long (about 12 times body length). (Because I am 6-feet tall my intestinal tract should be about 60-feet long. As a consequence if I eat bovine muscle [steak], it could take 5 days to course through those 20 yards.) (c) Body cooling for carnivores is done by panting because they have no ability to sweat; although herbivores also can pant, they cool their bodies mainly by sweating. (d) Drinking fluids is by lapping them for the carnivore; it is by sipping them for the herbivore. (e) Vitamin C is made by the carnivore’s own body; herbivores obtain their ascorbic acid only from their diet. (f) the appendages are different: Carnivores have claws; herbivores have hands or hooves. Thus, although most human beings think we are carnivores or at least conduct their lives as if they were, basically humans are herbivores. If we could decrease our flesh intake to as few as 5 to 7 meals a week, our health would improve substantially.

**Conditions Uncommon in Human Non–Flesh Eaters**

Some extremely common conditions in the Western world are relatively uncommon in purely or predominately vegetarian fruit-eating societies. These include (a) severe atherosclerosis and its devastating consequences (heart attacks, strokes, etc); (b) systemic hypertension: in societies that eat not enough salt for it to be measurable, the systemic arterial blood pressure is usually about 90/60 mm Hg, a level near what it is at birth, but a level in the Western world often associated with shock; (c) stroke; (d) obesity; (e) diabetes mellitus; (f) some common cancers (colon, breast, prostate gland); (g) constipation, cholecystitis, gallstones, appendicitis, diverticulosis, hemorrhoids, inguinal hernia, varicose veins; (h) renal stones; (i) osteoporosis and osteoarthritis; (j) salmonellosis and trichinosis; and (k) cataracts and macular degeneration.

**Cholesterol Numbers Needed to Prevent and Arrest Atherosclerotic Plaques**

The guidelines for cholesterol-modifying therapy published in 1988, 1993, and 2001, and modified subsequently, brought some rationale into the arena of who should and who should not be treated with “lifestyle changes” and/or lipid-lowering drugs or both. These guidelines, however, were based exclusively on the concept of “decreasing risk” of events, not decreasing the formation of plaques. Because atherosclerosis is rarely genetic in origin (1 in 500), and because the pharmaceutical industry has provided us with truly miracle drugs for lowering serum LDL cholesterol levels, it is time to switch gears from the concept of decreasing risk of atherosclerotic events to actual prevention of atherosclerotic plaques. To make this change, the guideline-recommended numbers must be lowered substantially.

According to the published guidelines, initiation of lipid-modifying drug therapy should be based on the serum LDL cholesterol level and the presence or absence of other atherosclerotic risk factors. Lipid-lowering drug therapy is recommended in people with only 1 or no non-LDL-cholesterol risk factors if the LDL cholesterol is >190 mg/dL with a goal of <160 mg/dL. But the most common LDL cholesterol number in people with heart attacks is about 140 mg/dL, so this recommendation is not “preventive.” If >1 non-LDL-cholesterol risk factor is present, then the LDL cholesterol drug-treatment number is >160 mg/dL with a goal of <130 mg/dL. If a patient has a coronary event, however (or is at high risk of an atherosclerotic event such as having diabetes mellitus or a previous non–coronary atherosclerotic event), the LDL cholesterol goal is <100 mg/dL (with an “option” of <70 mg/dL). If it is useful for the LDL cholesterol to be <100 mg/dL after a heart attack, surely it must be useful for the LDL cholesterol to be <100 mg/dL before a heart attack! Therefore, in my view, the goal for all populations—not just those with heart attacks or strokes, diabetes mellitus, or non–coronary atherosclerotic events—must be LDL cholesterol <100 mg/dL and ideally <70 mg/dL. If such a goal was created, the great scourge of the Western world would be essentially eliminated, “primary” and “secondary” prevention would be the same, and >100 million Americans—rather than the present 13 million—would need to be on a statin drug with or without ezetimibe or be pure vegetarian fruit eaters.

Thus, although not clearly established at this time, to prevent atherosclerotic plaques, the serum LDL cholesterol must be <70 mg/dL, the serum total cholesterol certainly <150 mg/dL, and the high-density lipoprotein (HDL) cholesterol >20 mg/dL. The latter—surely a surprise to most readers—is in patients with a serum total cholesterol level about 130 mg/dL and a LDL cholesterol.
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<th>Statin (mg)</th>
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<th>Atorvastatin (Lipitor)</th>
<th>Simvastatin (Zocor)</th>
<th>Lovastatin (Mevacor)</th>
<th>Pravastatin (Pravacol)</th>
<th>Fluvastatin (Lescol)</th>
<th>Reduction of TCa</th>
<th>Reduction of LDLa</th>
<th>Reduction of LDL by Ezetimibe 10 mg</th>
<th>Total LDL Reduction by Statin + Ezetimibe 10 mgb</th>
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aThese reductions are ±3%.
bNot available.
cThe 2.5-mg tablet is available in Japan but not in Western countries.
Crestor: AstraZeneca, Wilmington, DE; Lescol: Novartis, Basel, Switzerland; Lipitor: Pfizer, New York, NY; Mevacor: Merck, Whitehouse Station, NJ; Pravacol: Bristol-Myers Squibb, New York, NY; Zocor: Merck, Whitehouse Station, NJ.
level of about 60 mg/dL. Exactly what HDL cholesterol level is required to prevent plaques is unclear at this time, but clearly if the LDL cholesterol is very low (eg, 50 mg/dL), then a low HDL cholesterol—as long as it is >20 mg/dL—appears not to be dangerous. Ideal may be equal serum HDL and LDL cholesterol levels or an HDL cholesterol > LDL cholesterol. In summary, the recommended guideline numbers—particularly those for primary prevention—are intended for decreasing the risk of atherosclerosis events, not for preventing formation of atherosclerotic plaques.

The Rule of 5 and the Rule of 7 in Lipid-Lowering Therapy and the Goal for All

The statin drugs, in my view, are the best cardiovascular drugs ever created in that they have the greatest potential to prevent atherosclerotic plaques and therefore their complications; statin drugs also have the greatest potential to arrest plaque formation and therefore to prevent additional atherosclerotic events. The statin drugs are to atherosclerosis what penicillin was to infectious diseases. Despite being truly miracle drugs, they are terribly underused and underdosed.

The average serum LDL cholesterol level in American adults is about 130 mg/dL. Therefore, if we want to prevent plaque formation in the United States, most of us will need a 50% LDL cholesterol reduction! As shown in Table 1, that goal can be achieved by 3 doses of statin monotherapy (rosuvastatin 20 and 40 mg daily or atorvastatin 80 mg daily) or by adding ezetimibe 10 mg to all statin doses except the lowest level of recommended statin doses. Because titration is often neglected, starting the dose from the beginning, which achieves the preventive goal (LDL cholesterol <70 mg/dL), appears reasonable. Most American adults have life insurance, which, in actuality, is death insurance. The insured pays for the policy, dies, and then someone else gets the money. The statin drugs—with or without ezetimibe—represent true life insurance. The taker of the drug lives longer and is able to provide for his/her family longer. These drugs are safe. (Myopathy occurs in only 1 in 10,000 persons.) The risk of taking the drug is far less than the atherosclerotic consequences that might occur from not taking the drug! Of course, a vegetarian fruit diet is the least expensive and safest means of achieving the plaque-preventing LDL goal, but few in the Western world are willing to live on the herbivore diet. If we did so, however, we would prevent the daily killing in the United States of 100,000 cows, of 300,000 pigs, and of 15 to 20 million chickens!

Conclusion

Thanks to the pharmaceutical industry, we now have the armamentarium to change our cardiovascular health. We will not do so by waiting to treat our serum LDL cholesterol levels until an atherosclerotic event occurs, or by using guidelines such as LDL cholesterol >190 or >160 mg/dL before lipid-lowering drug therapy is initiated. The blowing up of balloons, the placing of stents in our arteries, or the performing of bypass operations (with all of their damaging incisions, such as median sternotomy) can be prevented or their need enormously reduced if the statin drugs with or without ezetimibe are used in proper doses to produce serum LDL cholesterol levels low enough to where atherosclerotic plaques do not form. Life insurance policies are often purchased by individuals in their 20s. Statin drugs with or without ezetimibe can be started at the same time because they—along with antihypertensive drugs—represent true life insurance. And to smoke cigarettes, to eat excess calories, not to put on a seatbelt in an automobile or airplane, or to ride a motorcycle or not to control our cholesterol numbers is simply not to use our brain as it was intended to be used!