Twenty questions on atherosclerosis

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1. Is atherosclerosis a disease affecting all animals or only certain animals?

Atherosclerosis affects only herbivores. Dogs, cats, tigers, and lions can be saturated with fat and cholesterol, and atherosclerotic plaques do not develop (1, 2). The only way to produce atherosclerosis in a carnivore is to take out the thyroid gland; then, for some reason, saturated fat and cholesterol have the same effect as in herbivores.

2. Are human beings herbivores, carnivores, or omnivores?

Although most of us conduct our lives as omnivores, in that we eat flesh as well as vegetables and fruits, human beings have characteristics of herbivores, not carnivores (2). The appendages of carnivores are claws; those of herbivores are hands or hooves. The teeth of carnivores are sharp; those of herbivores are mainly flat (for grinding). The intestinal tract of carnivores is short (3 times body length); that of herbivores, long (12 times body length). Body cooling of carnivores is done by panting; herbivores, by sweating. Carnivores drink fluids by lapping; herbivores, by sipping. Carnivores produce their own vitamin C, whereas herbivores obtain it from their diet. Thus, humans have characteristics of herbivores, not carnivores.

3. Is atherosclerosis genetic in origin?

Infrequently. Although many physicians and the lay public believe that atherosclerosis is genetic, the evidence for that is slim. One way to define the genetic variety of atherosclerosis is by the presence or absence of low-density lipoprotein (LDL) receptors in the liver (3–5). Patients with homozygous familial hypercholesterolemia have no LDL receptors in the liver, and their total cholesterol levels from birth are usually >800 mg/dL. The frequency of this genetic defect is 1 in 1,000,000. Patients with heterozygous familial hypercholesterolemia have only 50% of the normal number of LDL receptors in the liver. These patients generally have total cholesterol levels about 300 mg/dL, and they generally die (without lipid-lowering therapy) in their 40s or early 50s. The incidence of this familial defect is 1 in 500. The rest of us apparently have normal numbers of LDL receptors in the liver. Of course, a few patients have genetic defects involving high-density lipoprotein (HDL) cholesterol and triglyceride production and uptake, but these individuals are relatively few in number (6). Thus, the genetic defect producing atherosclerosis occurs in no more than 1 in 200 and possibly as low as 1 in 400 or 500 persons. This means, of course, that most persons with atherosclerosis acquire it by the types of calories they consume.

4. Is atherosclerosis a consequence of aging and therefore a degenerative disease?

No. When I was in medical school, I was taught that atherosclerosis was a disease of aging and that it was to be expected as we got older. It is true that symptomatic and fatal atherosclerosis is usually a problem of older people. But, not too old. Patients with homozygous familial hypercholesterolemia, however, may have lipid plaques in their arteries at the time of birth.

It appears that atherosclerosis requires certain serum cholesterol levels over certain periods of time. Therefore, if one has a serum total cholesterol of 1000 mg/dL, death usually occurs by age 15 (without lipid-lowering therapy). Those with total cholesterol levels of approximately 300 mg/dL live into their 30s and 40s. The average age of death from coronary artery disease in the USA is 60 years in men and 68 years in women (7). Sudden death is primarily a problem of young men. Therefore, those who make it to the hospital are usually older than these ages. Nevertheless, atherosclerosis is a disease of relatively young people as well as a disease of older persons. The point here is that atherosclerosis does not have to occur just because of aging. The more years we live, the longer the time period we have to keep our cholesterol levels elevated and thus to develop plaques. Multiplying our serum cholesterol level by our age in years may provide a rough indication of when we have developed enough atherosclerotic plaque to have symptomatic or fatal atherosclerosis.

5. What risk factors predispose to atherosclerosis?

Risk factors include hypercholesterolemia, systemic hypertension, diabetes mellitus, obesity, low HDL cholesterol, cigarette smoking, and inactivity.

6. Of the various atherosclerotic risk factors, which one is an absolute prerequisite for development of atherosclerosis?

The answer is hypercholesterolemia. What level of total cholesterol and specifically LDL cholesterol is required for atherosclerotic plaques to develop? Symptomatic and fatal atherosclerosis is extremely uncommon in societies where serum total cholesterol levels are <150 mg/dL and serum LDL cholesterol levels are <100 mg/dL (8). If the LDL cholesterol level is <100—and possibly it needs to be <80 mg/dL—the other previously mentioned risk factors in and of themselves are not associated with atherosclerosis. In other words, if the serum total choles-

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terol is 90 to 140 mg/dL, there is no evidence that cigarette smoking, systemic hypertension, diabetes mellitus, inactivity, or obesity produces atherosclerotic plaques. Hypercholesterolemia is the only *direct* atherosclerotic risk factor; the others are indirect. If, however, the total cholesterol level is >150 mg/dL and the LDL cholesterol is >100 mg/dL, the other risk factors clearly accelerate atherosclerosis.

7. What evidence connects atherosclerosis to cholesterol?

The connection between cholesterol and atherosclerosis is strong (9, 10):

a) Atherosclerotic plaques similar to those in humans can be produced in nonhuman herbivores by feeding them large quantities of cholesterol and/or saturated fat. It is not possible to produce atherosclerotic plaques experimentally in carnivores.

b) Cholesterol is found within atherosclerotic plaques.

c) In societies where the serum total cholesterol is <150 mg/dL, the frequency of symptomatic and fatal atherosclerosis is exceedingly uncommon; in contrast, in societies where the total cholesterol level is >150 mg/dL, the frequency of symptomatic and fatal atherosclerosis increases as the level above 150 increases.

d) The higher the serum total cholesterol level, and specifically the higher the serum LDL cholesterol, the greater the frequency of symptomatic atherosclerosis, the greater the frequency of fatal atherosclerosis, and the greater the quantity of plaque at necropsy.

e) In placebo-controlled, double-blind, lipid-lowering studies of adults without symptomatic atherosclerosis, the group with lowered serum LDL cholesterol developed fewer symptomatic and fatal atherosclerotic events compared with controls.

f) In placebo-controlled, double-blind, lipid-lowering studies of adults with previous symptomatic atherosclerosis, the group with lowered LDL cholesterol levels after the event had fewer subsequent atherosclerotic events than did the group that did not lower their cholesterol levels (controls).

g) LDL receptors were discovered in the liver by Brown and Goldstein, and the absence or decreased numbers of LDL receptors in patients with quite elevated serum cholesterol levels indicates a genetic defect in an occasional patient (3–5).

8. What are the major sources of cholesterol in calories?

Cholesterol comes from animals and their products. Therefore, if we do not eat animals and their products, we do not take in cholesterol. Most Americans now take in only about 300 to 400 mg of cholesterol daily. This amount is hardly enough to obtain a calorie from it. A toothpick weighs 100 mg, so most in the USA take in the equivalency of 3 or 4 toothpicks of cholesterol every day. There are 2 major sources of cholesterol in our diet: 1) *cows,* including their muscle (beef), milk, butter, and cheese, and 2) *eggs*. About 45% of the cholesterol we obtain in our diet comes from the visible and nonvisible eggs we eat, and about 40% comes from bovine muscle and bovine milk and its products.

9. What are the major sources of fat in calories?

Fat comes from many sources. A major source in the USA is bovine muscle (beef). Cows naturally do not have so much fat, but in the USA most are fattened before slaughter. They are placed in feed lots their last 4 to 6 months of life and fed 20 to 25 pounds of various grains and soybeans every day, and the result is a huge increase in body fat. Cows slaughtered directly from pasture have far less fat between their muscle fibers and that overlying them. In the USA most adults now consume approximately 140 grams of fat daily. Our upper limit should be 75 grams. (A deck of cards weighs 75 grams.) If we were to limit our fat intake to 50 grams a day, the health of the US population would skyrocket.

10. Which of the 3 components of fatty acids raise the serum total and LDL cholesterol levels?

Each triglyceride particle contains a saturated, a monounsaturated, and a polyunsaturated fatty acid. There is no such thing as a pure saturated fatty acid or a pure monounsaturated or a pure polyunsaturated fatty acid. The question is which one is dominant in the triglyceride particles. The saturated portion, when dominant, clearly raises our total and LDL cholesterol levels; the mono- and polyunsaturated, when dominant, either lower them or have a neutral effect. Saturated fatty acids are solid at room temperature, and that fact is easy to remember by the "s" in saturated. The fatty acids with the highest saturated component are coconut oil, palm kernel oil, beef tallow, and butter. Olive oil has the highest monounsaturated percentage (approximately 75%); peanut oil has approximately 50% monounsaturated fatty acids. Grundy and colleagues (11) have demonstrated that monounsaturated fatty acids have healthier features than do polyunsaturated fatty acids.

11. What percentage of reduction in the serum total and LDL cholesterol levels can be expected by decreasing the percentage of calories from fat by 25%, 50%, and 75%?

Hunninghake and colleagues (12) demonstrated that reducing the percentage of calories from fat from 40% to 30%, a 25% reduction, reduces *on average* the serum total cholesterol level by 5% and the LDL cholesterol level by 5%. Getting 30% of calories from fat is the most commonly prescribed diet by physicians in the USA, and its effect on cholesterol levels is relatively small. There is great individual variability, so that it is not possible to predict what drop in cholesterol levels will occur in a single individual. The drop in a single individual may be as high as 20%, but in some individuals the total and LDL cholesterol levels increase by as much as 20% (12). A reduction in percentage of calories from fat from 40% to 20%, a 50% reduction, generally leads to approximately a 20% reduction in both serum total and LDL cholesterol levels (13). A drop in percentage of calories from fat from 40% to 10%, a 75% reduction, generally leads to reductions in total and LDL cholesterol levels of about 40% (14). The 10% of calories from fat is a vegetarian-fruit diet.

12. What are the equivalent efficacious doses of the 6 statin drugs, and what are the average reductions in serum total and LDL cholesterol and average increase in HDL cholesterol from the various doses?

These are illustrated in the *Table* (15). These reductions in cholesterol are baseline independent—i.e., the percentage of reduction does not depend on what the baseline total cholesterol or baseline LDL might be. Furthermore, at the lower doses of the statin drugs, the increase in HDL cholesterol, which is generally about 6% to 7%, is also not baseline dependent. At the higher doses, the HDL becomes more baseline dependent, i.e., the lower the HDL, particularly when it is <35 mg/dL, the greater the increase in HDL produced by some statins but not by others (16, 17). Reductions in serum triglyceride levels by the statin drugs

Table. Comparative efficacy of the 6 currently available statin drugs

Statin drug (mg)						Cholesterol levels		
Cerivastatin (Baycol)	Atorvastatin (Lipitor)	Simvastatin (Zocor)	Lovastatin (Mevacor)	Provastatin (Pravachol)	Fluvastatin (Lescol)	Total	LDL	LE↑ >3 × ULN*
0.3	5	10	20	20	40	22%↓	27%↓	0.25%
0.4	10	20	40	40	80	27%↓	34%↓	0.50%
	20	40	80			32%↓	41%↓	1%
	40	80				37%↓	48%↓	2%
	80					42%↓	55%↓	2.3%

*LE↑ >3 × ULN = liver enzyme increase >3 times upper limit of normal.
Modified from Roberts WC. The rule of 5 and the rule of 7 in lipid-lowering by statin drugs. *Am J Cardiol* 1997;80:106–107. Used with permission.

are baseline dependent, i.e., the higher the serum triglyceride level, the greater the reduction in triglycerides by the statin drugs. If the triglyceride level is >350 mg/dL, the statin drugs have the capacity to lower the triglyceride level by up to 40%; if, however, the serum triglyceride level is 100 mg/dL, even the higher doses of the statin drugs have essentially no effect on the triglyceride level.

13. What is the LDL cholesterol goal of lipid lowering?

The goals proposed by the National Cholesterol Education Committee are variable, depending on the baseline LDL cholesterol and the presence or absence of other atherosclerotic factors (18). Persons without an atherosclerotic event have LDL cholesterol goals of <160 or <130 mg/dL. The goal in persons with previous atherosclerotic events is LDL cholesterol <100 mg/dL. If it is useful to lower the LDL to <100 mg/dL after a heart attack, surely it must be useful to lower the LDL cholesterol level to <100 before a heart attack! Therefore, in my view, the LDL cholesterol goal for all persons should be <100 mg/dL.

Atherosclerosis might best be viewed as the pediatricians view measles, mumps, and pertussis. They are not satisfied with decreasing the risk of these 3 contagious diseases; their goal is complete prevention of these infectious diseases. I think the same philosophy needs to be applied to atherosclerosis (19). Because it is infrequently a disease related to defective genetic makeup, we should all try to get our serum LDL cholesterol levels down to the point where atherosclerotic plaques do not form, and that level is clearly <100 mg/dL and maybe <70 or 80 mg/dL. My goal for both primary and secondary prevention is the same—namely, serum LDL cholesterol <100 mg/dL.

The minimal HDL goal of therapy in men is >35 mg/dL and for women >45 mg/dL. Raising the HDL cholesterol, however, is usually more difficult than lowering the LDL cholesterol. And, finally, the ideal fasting serum triglyceride goal for everybody is <150 mg/dL.

14. How safe are the statin drugs?

These are some of the safest drugs that have been produced (20–28)! They are considerably safer than aspirin or nonsteroidal anti-inflammatory drugs. They are safer than many drugs presently available over the counter. At the lower doses there is no evidence that statin drugs have detrimental effects on the liver. The frequency of liver enzyme elevation at the lower doses is the same as in placebo groups (20). Evidence is now accumulating that possibly even at the higher doses the statin drugs do not in themselves affect the liver detrimentally. Individuals with elevated liver enzymes associated with the intake of statin drugs have never had permanent damage to the liver produced by the statin drug. The only serious side effect of the statin drugs is myopathy, and that occurs in 1 of 10,000 persons taking the drug. The toxicity is not the statin drug; the toxicity is atherosclerosis! The risk-benefit ratio of using statin drugs in patients with atherosclerosis, either to prevent further plaque formation or to prevent its formation in the first place, favors drug use.

15. Who should be treated with the statin drugs?

Everyone who has had an atherosclerotic event, be it from involvement of the coronary arteries, carotid arteries, aorta, or peripheral arteries. The goal in patients with symptomatic atherosclerosis is LDL cholesterol <100 mg/dL. The goal in persons without symptomatic atherosclerosis should be the same. There is simply more time to work on dietary change in persons who have not had atherosclerotic events compared with persons who have. If dietary interventions are unsuccessful in lowering cholesterol levels in persons without atherosclerotic events, these drugs can be useful and should be used more freely as long as the users are >15 years of age. They also have proven benefit in the elderly.

16. Is it important to lower elevated serum triglyceride levels?

Yes. The most important lipoprotein to lower is the LDL cholesterol. The most important lipoprotein to raise is the serum HDL cholesterol. The third most important lipoprotein to alter is the serum triglyceride level (29). Although the LDL particles are the most atherogenic, the very-low-density lipoprotein particles contain atherogenic components as well. In general, the higher the serum triglyceride level, the lower the HDL cholesterol level. Thus, by lowering the serum triglyceride level, the effect often is to raise the serum HDL cholesterol level, and the higher the HDL cholesterol, the lower the risk of atherosclerotic events. When the triglyceride level is elevated, the LDL cholesterol particles tend to be small and dense, and these are the most atherogenic ones. When the triglyceride level is lowered, the LDL particle size tends to increase, and the larger and more buoyant LDL particles are not as atherogenic as the small dense ones. A third reason to lower the triglyceride levels is that elevated ones are associated with coagulation factors that promote thrombosis or retard thrombolysis. Platelet aggregation and therefore thrombosis is accelerated in patients with elevated triglyceride

levels. And finally, elevated triglyceride levels are commonly associated with the metabolic syndrome (insulin-resistance syndrome). The components of this syndrome include obesity, systemic hypertension, the lipid triad (increased triglyceride, decreased HDL cholesterol, and predominance of small, dense LDL particles), glucose intolerance, insulin resistance, increased serum insulin levels, and diabetes mellitus.

The fibrates (fenofibrate and gemfibrozil) and niacin are the best triglyceride-lowering drugs. In my view, however, neither a fibrate nor niacin should be used as monotherapy. I think these drugs should be added to a statin drug, which in and of itself can reduce the triglyceride levels up to 40%, depending on the baseline level.

17. Can niacin and fibrates be used effectively and safely in combination with the statin drugs?

Yes. Liver enzyme elevations occur more frequently when either niacin or a fibrate is combined with a statin drug, and these enzyme levels should be checked more frequently in patients on this combination. The combination, however, is quite effective.

18. How effective are statin drugs compared with aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and calcium antagonists in preventing repeat atherosclerotic events?

At least among patients who have had an acute myocardial infarction and survived, daily aspirin decreases the chance of recurrence of an atherosclerotic event within a 5-year period by 25% (30), beta-blockers by 25% (31), angiotensin-converting enzyme inhibitors (at least the tissue inhibitors) by 25% (32), calcium antagonists by probably 0%, and statin drugs by >40% (21). Thus, if a person could take only 1 drug after a heart attack, the most effective one would be a statin.

19. How effective are the statin drugs in preventing strokes?

Very effective. The statin drugs decrease the frequency of strokes in a 5-year period by approximately 30% (33). Until recently the statin drugs were the only drugs other than an antihypertensive drug demonstrated to decrease the frequency of stroke. Recently, the angiotensin-converting enzyme inhibitor ramapril has been shown to decrease the frequency of strokes also by approximately 30% (32).

20. Do statin drugs have to be taken every day for the remainder of life?

Yes. Some patients apparently believe that the statin drugs need to be taken for only a few months—until the cholesterol levels come down. I believe that it is important to tell patients when they are first placed on a statin drug that they will need to take the drug every day for the remainder of their lives. Of course, if a patient subsequently becomes a pure vegetarian-fruit eater it might be possible to discontinue the statin drug, but few Americans are willing to go the vegetarian route.

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