

Atheroma

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In pathology, an **atheroma** (plural: atheromata) is an accumulation and swelling (-oma) in artery walls that is made up of cells (mostly macrophage cells), or cell debris, that contain lipids (cholesterol and fatty acids), calcium and a variable amount of fibrous connective tissue. In the context of heart or artery matters, atheromata are commonly referred to as atheromatous **plaques**. It is an unhealthy condition, but is found in most humans.


These anatomic lesions usually begin in some children younger than age 1 year and all children older than age 10 regardless of geography, race, sex or environment. Veins do not develop atheromata, unless surgically moved to function as an artery, as in bypass surgery. The accumulation (swelling) is always between the endothelium lining and the smooth muscle wall central region (media) of the arterial tube, see IMT. While the early stages, based on gross appearance, have traditionally been termed fatty streaks by pathologists, they are not composed of fat cells, i.e. adipose cells, but of accumulations of white blood cells, especially macrophages that have taken up oxidized low-density lipoprotein (LDL). After they accumulate large amounts of cytoplasmic membranes (with associated high cholesterol content) they are called foam cells. When foam cells die, their contents are released, which attracts more macrophages and creates an extracellular lipid core near the center to inner surface of each atherosclerotic plaque. Conversely, the outer, older portions of the plaque become more calcific, less metabolically active and more physically stiff over time.

Collectively, the process of atheroma development within an individual is called atherogenesis and the overall result of the disease process is termed atherosclerosis.

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Atheroma
Classification and external resources



Atherosclerotic plaque from a carotid endarterectomy specimen. This shows the bifurcation of the common into the internal and external carotid arteries.

ICD-10	I70.9
ICD-9	440
DiseasesDB	1039
MeSH	C14.907.137.126.307

Difficulty of Tracking, Researching and Better Understanding Atheroma

For most people the first clinical symptoms result from atheroma progression within the heart arteries, most commonly resulting in a heart attack and ensuing debility. However, the heart arteries, because (a) they are small (from about 5 mm down to invisible), (b) they are hidden deep within the chest and (c) they never stop moving, have been a difficult target organ to track, especially clinically in individuals who are still asymptomatic. Additionally all mass applied clinical strategies focus on both (a) minimal cost and (b) the overall safety of the procedure. Therefore existing diagnostic strategies for detecting atheroma and tracking response to treatment have been extremely limited. The methods most commonly relied upon, patient symptoms and cardiac stress testing, do not detect any symptoms of the problem until atheromatous disease is very advanced.

Evolving Concepts and Understanding

In developed countries, with improved public health, infection control and increasing life spans, atheroma processes have

become an increasingly important problem and burden for society. Atheroma continue to be the number one underlying basis for disability and death, despite a trend for gradual improvement since the early 1960s (adjusted for patient age). Thus, increasing efforts towards better understanding, treating and preventing the problem are continuing to evolve.

In the mid-twentieth century, it was assumed (incorrectly) that atheromata simply expanded into the lumen and produced stenoses as they grew, since the disease always developed between the inner endothelial lining and the muscular wall. This belief was based on angiographic views of the blood column within arteries and a belief that the smooth muscle wall of an artery (the thickest and strongest portion of the artery wall in a healthy artery) would not change in size and structure over time. This belief continued despite increasing contradicting evidence that this was an overly simplistic theory and did not explain many empirical observations. Most artists' illustrations of atheromata and the atherosclerosis process in 2004 still portray this concept, even though quite incorrect. By the late 1980s and early 1990s, careful pathology work and research using intravascular ultrasound (IVUS) showed clearly that this angiographic assumption was incorrect.

Since the early to mid 1990s, better research has led to a somewhat wider recognition that one of two changes typically occur in the artery wall structure as an atheroma develops and progresses: (a) wall thickening and external enlargement with associated lumen (blood flow opening) preservation until late in the process; or (b) wall thickening with both external and lumen enlargement. These processes both have survival value, as they reduce and hide some of the effects of the atheroma process and help prevent symptoms, for a time. However they also prevent detection of the disease process by most conventional diagnostic tests, (*e.g.* cardiac stress tests and angiography), until advanced stages.

According to United States data, 2004, for about 65% of men and 47% of women, the first symptom of cardiovascular disease is heart attack or sudden death (death within one hour of symptom onset.)

Most artery flow disrupting events occur at locations with less than 50% lumen narrowing. From clinical studies published in the late 1990s to IVUS (in-the-artery-ultrasound) to visualize disease status, the typical heart attack occurs at locations with about 20% stenosis (narrowing), prior to sudden lumen closure and resulting heart attack. Cardiac stress testing, traditionally the most commonly performed non-invasive testing method for blood flow limitations generally only detects lumen narrowing of ~75% or greater, although some physicians advocate that nuclear stress methods can sometimes detect as little as 50%.

Actual Artery/Atheroma Behavior:

1. External Artery Enlargement; Eventual Possible Stenosis and/or Closure

Over time, atheromata usually progress in size and thickness and induce the surrounding muscular central region (the media) of the artery to stretch out, termed remodeling, typically just enough to compensate for their size such that the caliber of the artery remains unchanged until typically over 40-50% of the artery wall cross sectional area consists of atheromatous tissue (see: Glagov, below).

If the muscular wall enlargement eventually fails to keep up with the enlargement of the atheroma volume, then the lumen of the artery begins to narrow, commonly as a result of repeated ruptures of the covering tissues separating the atheroma from the blood stream. This becomes a more common event after decades of living, increasingly more common after people are over 40 years old.

The endothelium (the cell monolayer on the inside of the vessel) and covering tissue, termed fibrous cap, separate atheroma from the blood in the lumen. If a rupture occurs of the endothelium and fibrous cap, then a platelet and clotting response over the rupture rapidly develops. Additionally, the rupture may result in a shower of debris. Platelet and clot accumulation over the rupture may produce narrowing/closure of the lumen and tissue damage may occur due to either closure of the lumen and loss of blood flow beyond the ruptured atheroma and/or by occlusion of smaller downstream vessels by debris. See vulnerable plaque.

This is the principal mechanism of heart attack, stroke or other related cardiovascular disease problems. As research has shown, this process is not a result of stenosis. Prior to the rupture, there may have been no lumen narrowing, even aneurysmal enlargement, at the atheroma. On average, by clinical research using IVUS, there is a minor stenosis, about 20%, present over those unstable atheroma which rupture and result in major disability or death. Comparatively, stenoses of about 75% are required to produce detectable abnormalities during cardiac stress tests.

2. External Artery Enlargement and Lumen Enlargement

If the muscular wall enlargement is overdone over time, then a gross enlargement of the artery results, usually over decades of living. This is a less common outcome. Atheroma within aneurysmal enlargement (vessel bulging) can also rupture and shower

debris of atheroma and clot downstream. If the arterial enlargement continues to 2 to 3 times the usual diameter, the walls often become weak enough that with just the stress of the pulse, a loss of wall integrity may occur leading to sudden hemorrhage (bleeding), major symptoms and debility; often rapid death. The main stimulus for aneurysm formation is pressure atrophy of the structural support of the muscle layers. The main structural proteins are collagen and elastin. This causes thinning and the wall balloons allowing gross enlargement to occur, as is common in the abdominal region of the aorta.

Evolution of Strategies and Changing Focus

The sudden nature of the complications of pre-existing atheroma, vulnerable plaque, have led, since the 1950s, to the development of intensive care units and complex medical and surgical interventions. Angiography and later cardiac stress testing was begun to either visualize or indirectly detect stenosis. Next came bypass surgery, to plumb transplanted veins, sometimes arteries, around the stenoses and more recently angioplasty, now including stents, most recently drug coated stents, to stretch the stenoses more open.

Yet despite these medical advances, with success in reducing the symptoms of angina and reduced blood flow, atheroma rupture events remain the major problem and still sometimes result in sudden disability and death despite even the most rapid, massive and skilled medical and surgical intervention available anywhere today. According to some clinical trials, bypass surgery and angioplasty procedures have had at best a minimal effect, if any, on improving overall survival. Typically mortality of by-pass operations is from 1-4%, of angioplasty about 1-1.5%.

Additionally, these vascular interventions are often done only after an individual is symptomatic, often already partially disabled, as a result of the disease. It is also clear that both angioplasty and by-pass interventions do not prevent future heart attack.

The older methods for understanding atheroma, dating to before World War II, relied on autopsy data. Autopsy data has long shown initiation of fatty streaks in later childhood with slow asymptomatic progression over decades.

One way to see atheroma is the very invasive and costly IVUS ultrasound technology; it gives us the precise volume of the inside intima plus the central media layers of about 2.5 cm of artery length. Unfortunately, it gives no information about the structural strength of the artery. Angiography does not visualize atheroma; it only makes the blood flow within blood vessels visible. Alternative methods that are non or less physically invasive and less expensive per individual test have been used and are continuing to be developed, such as those using computed tomography (CT; lead by the Electron Beam Tomography form, given its greater speed) and magnetic resonance imaging (MRI). The most promising since the early 1990s has been EBT, detecting calcification within the atheroma before most individuals start having clinically recognized symptoms and debility. Interestingly, statin therapy (to lower cholesterol) does not slow the speed of calcification as determined by CT scan. Most visualization techniques are used in research, they are not widely available to most patients, have significant technical limitations, have not been widely accepted and generally are not covered by medical insurance carriers.

From human clinical trials, it has become increasingly evident that a more effective focus of treatment is slowing, stopping and even partially reversing the atheroma growth process. However, this effort has been slow, partly because the asymptomatic nature of atheromata make them especially difficult to study. Promising results are found using B-vitamins that reduce a protein corrosive, homocysteine and that reduce neck carotid artery plaque volume and thickness, and stroke, even in late-stage disease.

Additionally, understanding what drives atheroma development is complex with multiple factors involved, only some of which, such as lipoproteins, more importantly lipoprotein subclass analysis, blood sugar levels and hypertension are best known and researched. More recently, some of the complex immune system patterns that promote, or inhibit, the inherent inflammatory macrophage triggering processes involved in atheroma progression are slowly being better elucidated in animal models of atherosclerosis.

Detection and Diagnosis Options

Arterial wall fixation, staining and thin section: historically this has been the gold standard for detection and description of atheroma, though only done after autopsy. With special stains and examination, micro calcifications can be detected, typically with smooth muscle cells of the arterial media near the fatty streaks within a year or two of fatty streaks forming.

IVUS is the current most sensitive method detecting and measuring more advanced atheroma within living individuals, though it is typically not used until decades after atheroma begin forming due to cost and body invasiveness.

CT Scans using state of the art higher resolution spiral, or the higher speed EBT, machines have been the most effective method for detecting calcification present in plaque. However, the atheroma have to be advanced enough to have relatively large areas of

calcification within them to create large enough regions of ~130 Hounsfield units which the CT scanner software can recognize as distinct from the other surrounding tissues. Typically, such regions start occurring within the heart arteries about 2-3 decades after atheroma start developing.

Arterial ultrasound, especially of the carotid arteries, with measurement of the thickness of the artery wall, offers a way to partially track the disease progression. As of 2006, the thickness, commonly referred to as IMT for intimal-medial thickness, is not measured clinically though it has been used by some researchers since the mid 1990's to track changes in arterial walls. Traditionally, clinical carotid ultrasounds have only estimated the degree of blood lumen restriction, stenosis, a result of very advanced disease. More progressive clinicians have begun using IMT measurement as a way to quantify and track disease progression or stability within individual patients.

Angiography, since the 1960s, has been the traditional way of evaluating for atheroma. However, angiography is only motion or still images of dye mixed with the blood within the arterial lumen and never shows the wall of arteries, including atheroma with the arterial wall remain invisible. The limited exception to this rule is that with very advanced atheroma, with extensive calcification within the wall, a halo-like ring of radiodensity can be seen in most older humans, especially when arterial lumens are visualized end-on. On cine-fluoro, cardiologists and radiologists typically look for these calcification shadows to recognize arteries before they inject any contrast agent during angiograms.

Treatment Options

Many approaches, including food choices, staying slender (especially in the abdominal area), aerobic exercise and many different supplements have been promoted as methods to reduce atheroma progression. For most people, changing their internal physiologic behaviors, mostly hidden within, from the usual ones which promote atheroma progression (i.e. high risk, meaning high event rates for symptomatic cardiovascular disease) to reduced risk, requires a combination of strategies, including taking several compounds, on a daily basis and indefinitely. More and more human treatment trials have been done and are ongoing which demonstrate improved outcome for those people using more complex and effective treatment regimens which change physiologic behavior patterns to more closely resemble those which humans more commonly exhibit in childhood at a time before fatty streaks begin forming. Calculated LDLipoprotein cholesterol levels at this time of life are usually in the 20 to 40 mg/dL range, far below what are usually considered "normal" adult concentrations.

The group of medications referred to as statins, originally discovered in 1972 by a Japanese researcher as a compound produced by certain strains of fungi, e.g. *Aspergillus terreus*, *Monascus ruber* and *Monascus purpureus*, have been the most successful single approach, with the lowest rates of undesirable side-effects, to reducing atherosclerotic disease events. However, current research evidence continues to support using a combination of several approaches, including: (a) food choices (such as consuming omega-3 containing fats), (b) abdominal fat reduction, (c) low normal blood glucose levels (glycosylated hemoglobin, also called HbA1c, values < 5.0), (d) aerobic exercise and (e) micronutrient (multivitamin and magnesium) supplements to improve the odds of maintaining better health with absence of either symptoms or worse, catastrophic disease events.

The latest statin approved in the United States but not in some other countries, rosuvastatin, showed regression of atherosclerotic plaque (in fact, a decrease in intima + media volume) in the coronary arteries by IVUS evaluation^[1] in the prospective treatment ASTEROID study which utilized IVUS to directly visualize volume plaque changes with treatment. Page 8, shows an artery before and after about 2 years of 40 mg/day treatment; the relevant wall volume is reduced to about half by a decrease in the volume of atheroma. However, keep in mind that the IVUS images on page 8 are only for illustration and are not presented as typical for the group. A careful read of the article provides a clearer, though still more favorable than other trial views of the outcomes. This is the first human clinical trial, with any treatment agent available within the USA, that has produced some plaque regression (as opposed to only slowed rates of increase in quantified volume).

Controversy over treatments continues and reportedly Health Canada issued a "Dear doctor" warning concerning the dose used in the ASTEROID study. There have been concerns after the PROSPER trial,^[2] which used another statin, showed no all-cause mortality reduction. A 2008 Bayesian meta-analysis concluded however that statins would reduce all-cause mortality in elderly patients with a relative risk reduction of 22% over 5 years (absolute mortality rate of 15.6% with statins and 18.7% with placebo). Bayesian inference methods are criticized for the use of "a priori distributions," which some view as artificial; however the authors conducted a sensitivity analysis using several conservative a priori distributions, as well as a more conventional Frequentist analysis, and in all cases found a consistent benefit of statins in elderly patients.^[3]

A key issue is that there is no magic pill. The important issues are multiple internal physiologic behaviors within each of us; supplements, including the far more rigorously researched prescription agents, are simply tools, which if used with wisdom, in careful combinations with a goal of dramatically changing physiologic behaviors to emulate patterns known to be much healthier,

often work very well. As always, no single approach is perfect or applicable to everyone, at least not without careful attention to detail and individual adjustments.

Footnotes

- [^] JAMA, "Effect of Very High-Intensity Statin Therapy on Regression of Coronary Atherosclerosis".
- [^] Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG; PROSPER study group. PROSpective Study of Pravastatin in the Elderly at Risk. PMID 12457784
- [^] Afilalo J, Duque G, et al. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. *J Am Coll Cardiol*. 2008;51(1):37-45. PMID 18174034

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- Vos E, Rose CP: *Questioning the benefits of statins* CMAJ • Nov. 8, 2005; 173(10)[2]

See also

- Atherosclerosis
- Coronary circulation
- Coronary catheterization
- Angiogram
- EBT
- Lipoprotein
- LDL, HDL, IDL and VLDL
- ApoA-1 Milano

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