2.4.4

Atherosclerosis

Arteriosclerosis or hardening of the arteries, is a generalized condition that describes the progressive loss of arterial elasticity, or compliance, ultimately leading to greater resistance to blood flow. Normal aging can cause structural changes in the vessel cell walls that lead to arteriosclerosis, as well as other causes/risk factors such as smoking, high cholesterol, diabetes or inflammation from disease. The hardening that occurs in the vessel walls can lead to chronic hypertension, or increased blood pressure as the heart must pump harder to compensate for this decrease in arterial elasticity. Hypertension due to arteriosclerosis contributes to several damaging effects on blood vessels if left untreated. Arteries may be weakened by the constant high blood pressure and enlarge to form a bulge, or aneurysm, that can potentially rupture, causing life-threatening internal bleeding. Damage to your heart may occur due to hypertension leading to coronary artery disease, an enlarged heart and eventual heart failure. High blood pressure that damages blood vessels in your brain can lead to strokes, dementia or cognitive impairment as blood flow is reduced to your brain. Kidneys are also negatively affected. We will be learning more about the kidneys ability to autoregulate blood pressure as we study the urinary system and kidneys, but in short, damage to the arteries in the kidneys due to hypertension and arteriosclerosis will decrease the blood flow inside the kidneys and their ability to filter waste from the body.

Atherosclerosis is a specific kind of arteriosclerosis also known as coronary heart disease. It is the leading cause of death for both men and women in the United States. It occurs when a lipid laden plaque builds up within the tunica intima and media. As both fats and cholesterol are insoluble in blood, they must be transported throughout the body via special lipoproteins. There are various types of lipoproteins, one of which is called low-density lipoproteins (LDL or "*bad cholesterol*"). In high concentrations, this lipoprotein is thought to promote inflammation and damage in the walls of arteries.

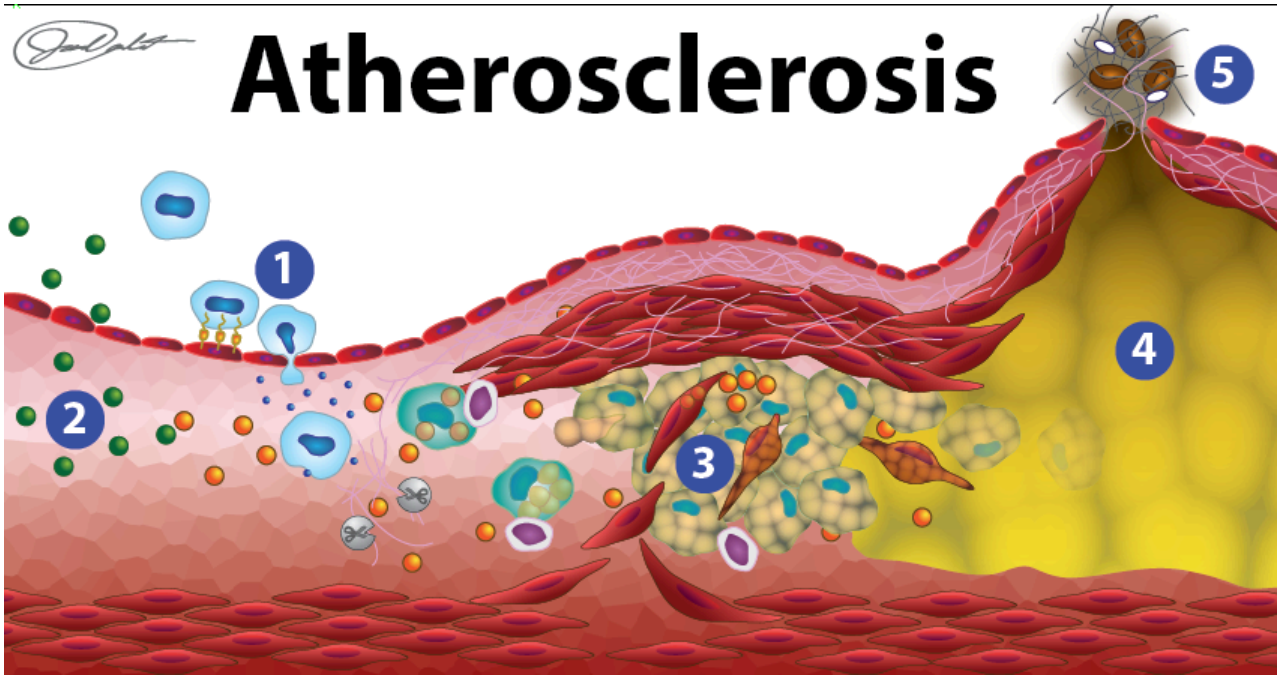

Image drawn by BYU-I student - Jared C Fall 2013

The image above shows a blood vessel wall. The blood vessel lumen is located where the numbers 1 and 5 are. The blood vessel wall is located where the numbers 2,3 and 4 are. This image depicts the disease process that may occur in a blood vessel wall called Atherosclerosis.

The numbered areas in the image are described below.

1. White blood cells normally move freely through blood vessels and do not attach to endothelial cells as they stream past. However, when endothelial cells are exposed to irritating stimuli or damage they will express adhesion protein molecules that can capture nearby white blood cells. These white blood cells undergo morphological changes that allow them to flatten and squeeze between endothelial cells that are themselves undergoing changes that make the vessel wall more permeable. This movement of white blood cells out of the bloodstream and into the tunica intima is called **diapedesis.**

2. The permeability changes of the affected vessel also promotes increased entry of LDL particles to the underlying matrix of the tunica intima. Normally, LDL particles attach to LDL receptors and enter cells through endocytosis. The cells then extract the lipids and use them in normal cell processes. When endothelial cells are damaged, LDL particles can enter the underlying basement membrane and smooth muscle tissue that surrounds the vessel.

White blood cells and endothelial cells have the ability to produce oxygen free radicals. It is not known what all the reasons are that these cells do this, but it is likely part of a protective response to foreign antigens that are sometimes introduced to the circulation. Also, it appears that these free radicals may play a role in some intracellular signaling mechanisms. Whatever the reason for producing these free radicals, they can become a problem when they interact with LDL particles. When this happens, we say that the LDL is "oxidized" or "modified". While oxidation of some LDL particles is likely happening all the time, it becomes greatly increased in areas of tissue damage and white blood cell activation. Oxidized LDL particles are particularly effective at attracting and activating white blood cells. White blood cells engulf the modified LDL particles which stimulates them to produce more oxygen free radicals. From this it becomes easy to imagine that an area of endothelial damage will lead to an accumulation of modified LDL particles and migrating white blood cells. A positive feedback situation begins to arise when accumulating immune cells and modified LDLs lead to more immune cells and more modified LDLs.

3. Macrophages and nearby smooth muscle cells engulf modified LDL particles in a non-specific mechanism. The modified LDL particles are not recognized by their proper receptor on the cell surface but rather by immune receptors on the cells. The lipid laden LDL particles are then engulfed but not properly processed as LDL particles. Ultimately, this leads to a cell called a "foam cell". A foam cell is saturated with LDL particles and the excessive amount of lipid in the cell gives the cytoplasm a "foamy" appearance. Foam cells ultimately die and release their contents which are quickly engulfed by other nearby white blood cells and smooth muscle cells.

4-5. Eventually, the accumulating lipid from the processes explained above and the fragments of dead cells produce an area with a lipid core that begins to form a "plaque". Endothelial cells cover the plaque. The plaque accumulates calcium salts and more dead cells over time and it will harden. This plaque in the arterial wall is what we generally refer to as atherosclerosis. If the endothelial cells over the plaque are compromised, blood clots can form on the vessel wall. Over time, ruptured areas of plaque may create a situation where an area of plaque may jut out into the vessel lumen. A clot that forms and attaches to the wall is called a **thrombus.** If the clot breaks loose and floats downstream to ever smaller vessels it is called an **embolus.**

****Note, it is currently thought that it is a combination of endothelial damage, high concentrations of LDL particles and time that develops dangerous levels of plaque. The greatest causes of endothelial damage appear to be toxic chemicals such as those in cigarette smoke. High blood pressure is another dangerous factor as this can cause mechanical damage to endothelial cells. High LDL concentration occurs because of one's genes and lifestyle choices that include poor diet and lack of exercise.**