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Nutrition

Why is LDL-cholesterol bad cholesterol?

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Summary

The high circulating LDL-cholesterol levels seen in the inherited disease familial hypercholesterolaemia cause high rates of cardiovascular disease whereas the low circulating LDL-cholesterol levels following statin treatment cause low rates of cardiovascular disease. This is why LDL-cholesterol is referred to as bad cholesterol by the media. Atherosclerosis is caused not by native circulating LDL particles but rather by oxidized LDL particles in the arterial wall. Oxidized LDL particles unlike native particles are taken up by macrophages via scavenger receptors to form foam cells and are treated as autoantigens by the immune system provoking inflammation. Hence many of the characteristics of the atherosclerotic plaque including its tendency to rupture and cause thrombosis and heart attacks can be explained in molecular detail by the effects of oxidized LDL particles.

Introduction

As discussed in my last article, the media has taken to referring to low density lipoprotein (LDL)-cholesterol as bad cholesterol and to high density lipoprotein (HDL)-cholesterol as good cholesterol. In my last article I explained why HDL-cholesterol can be considered to be good cholesterol and promised to explain why LDL-cholesterol can be considered to be bad cholesterol in my next article.

The circulating LDL-cholesterol concentration is regulated by the activity of the LDL receptor. This protein is found on the surface of all cells and is responsible for taking up LDL-cholesterol from the circulation. When the activity of the receptor is high, LDL-cholesterol is removed from the circulation at high rates and as a result circulating concentrations of LDL-cholesterol are comparatively low. By contrast, when the activity of the receptor is low, LDL-cholesterol is removed from the circulation at low rates and as a result circulating concentrations of LDL-cholesterol are relatively high.

There are a number of reasons for believing that a high circulating concentration of LDL-cholesterol has detrimental effects on the health of the cardiovascular system. First, patients with inherited defects in the LDL receptor, a condition known as familial hypercholesterolaemia (FH), have very high circulating concentrations of LDL-cholesterol and very high rates of cardiovascular disease. Second, treatment with statins which are drugs specifically designed to competitively inhibit the key enzyme of cellular cholesterol synthesis result in an adaptive increase in the activity of the LDL receptor aimed at restoring cellular cholesterol levels. As a result, statin treatment results in a fall in circulating cholesterol levels and a reduced risk of developing cardiovascular disease. Third, dietary saturated fatty acids are known to raise circulating LDL-cholesterol levels whereas dietary monounsaturated or omega-6 (*n*-6) polyunsaturated fatty acids are known to lower them. In addition, epidemiological studies have demonstrated that the intake of saturated fat is associated with a high risk of developing cardiovascular disease whereas intakes of monounsaturated or *n*-6 polyunsaturated fats are associated with low rates of developing cardiovascular disease. As a result dietary recommendations include advice to reduce intake of saturated fat and increase intakes of monounsaturated and *n*-6 polyunsaturated fat in an attempt to reduce risk of developing cardiovascular disease. For this and other reasons it is widely believed that high circulating concentrations of LDL-cholesterol are bad for cardiovascular health.

However, none of the above evidence explains why a high circulating LDL-cholesterol concentration is bad for cardiovascular health, why HDL-cholesterol and LDL-cholesterol levels have opposite effects on the risk of developing cardiovascular disease or why an essential cellular nutrient such as cholesterol can be bad for health at all. It is the purpose of the present article to explain why LDL-cholesterol can be considered to be bad for cardiovascular health.

Atherosclerosis, atherosclerotic plaques and cardiovascular disease

As observed recently "atherosclerosis involves the formation in the arteries of lesions that are characterized by inflammation, lipid accumulation, cell death and fibrosis" (1). The inside surface of all arteries is lined with a single cell layer of endothelial cells. Beneath this layer lies the intimal layer of the arterial wall itself, consisting of smooth muscle cells embedded in connective tissue. Atherosclerosis is a disease of the intimal layer of the arterial wall.

The arterial lesions, otherwise known as atherosclerotic plaques, pass through various stages of complexity beginning with the so-called fatty streak and ending in the mature atheroma. The atherosclerotic plaque consists of a core region surrounded by a fibrous cap. The core region consists of foam cells, extracellular lipid some of which may be crystalline cholesterol and debris from dead cells. This is surrounded by a fibrous cap consisting of smooth muscle cells and the fibrous protein collagen. The plaque also contains many other types of cell which originate in the circulation including dendritic cells, mast cells, B cells, natural killer T cells, monocytes and monocyte-derived macrophages. The presence of so many inflammatory and immune

cells in the plaque is one reason for believing that atherosclerosis is a chronic inflammatory condition.

It used to be thought that atherosclerotic plaques cause fatal heart attacks by gradually reducing the diameter of the artery leading to a progressive limitation of blood flow. However, it is now recognised that thrombosis or the formation of a blood clot is the key event. Rupture of the fibrous cap of the plaque leading to thrombosis accounts for two-thirds to three-quarters of fatal heart attacks while superficial erosion of the plaque accounts for one-fifth to one-quarter (2). The causes of plaque rupture are clearly critical in this process and the induction of proteases which gradually hydrolyse the collagen and weaken the fibrous cap is emerging as the determining factor.

However, the main question for this article is how high circulating levels of LDL-cholesterol initiate the process of atherosclerosis.

LDL particle oxidation

The LDL particle is the major cholesterol carrier in the circulation. The surface of the LDL particle consists of phospholipids, free cholesterol and apolipoprotein (apo) B100 surrounding a core of cholesterol esters and triacylglycerols. The LDL particle is not prone to oxidation while it is in the circulation.

However, once the LDL particle crosses the endothelial cell layer lining the artery it can be oxidised in the subendothelial space (3). This process is somewhat ill-defined but it is assumed that reactive oxygen species such as superoxide, hydrogen peroxide and hydroxyl radicals produced by the surrounding endothelial cells and smooth muscle cells initiate a lipid peroxidation chain reaction which results in damage to both the lipid and protein components of the LDL particle. During this process, lipid hydroperoxides are formed that fragment to reactive aldehydes such as malondialdehyde and 4-hydroxynonenal. These species can then be conjugated to the ε-amino groups of lysine residues in apo B100 and to LDL phospholipids such as phosphatidylethanolamine and phosphatidylserine. In addition, histidine, lysine and proline residues in apo B100 are oxidatively damaged leading to fragmentation of the apo B100 molecule.

Clearly the oxidative changes to the LDL particle are complex. However, the important point is that oxidised LDL particles are handled differently to native LDL particles in at least two ways. First, oxidised LDL particles are taken up into cells by scavenger receptors rather than LDL receptors. Second, oxidised LDL particles unlike native LDL particles are treated as autoantigens by the immune system. These differences between the handling of oxidised LDL and the handling of native LDL, account for many of the features of the atherosclerotic plaque.

Uptake of oxidised LDL by scavenger receptors

Migration of circulating monocytes into the arterial wall is mediated by adhesion molecules on the surface of endothelial cells called vascular cell-adhesion molecule 1 (VCAM1). The expression of VCAM1 and hence the ability of monocytes to migrate into the arterial wall is highest in areas of the circulation with the greatest turbulence of blood flow. This explains why atherosclerotic plaques have the greatest tendency to form in parts of the circulation with the greatest turbulence.

Once inside the arterial wall, monocytes differentiate into macrophages under the influence of macrophage colony-stimulating factor (M-CSF). This process of differentiation includes increased expression of scavenger receptors which comprise a large family of at least eight classes of cell surface molecules with the ability to take up oxidised LDL particles (4). The uncontrolled uptake of oxidised LDL particles by macrophages results in the formation of lipid engorged cells called foam cells which are one of the characteristics of atherosclerotic plaques.

Oxidised LDL as an autoantigen

The idea that atherosclerosis is a chronic inflammatory condition was revolutionary 20 years ago but has now gained widespread acceptance. This idea has further evolved recently with the suggestion that atherosclerosis is at least in part an autoimmune condition (5). However, it is not at present clear whether the immune response is pro- or anti-atherogenic. Indeed, it is possible that some aspects of the immune response are pro-atherogenic while others are anti-atherogenic.

Migration of T cells into the arterial wall is also mediated by VCAM1. Once inside, T cells undergo activation after interacting with antigen presenting cells such as macrophages and dendritic cells. Among the antigens presented by these cells to the T cells are oxidised LDL particles. This stimulates T cell formation of pro-inflammatory cytokines including interferon-γ (IFNγ) and tumour-necrosis factor (TNF). These cytokines in turn stimulate macrophage production of proteases which hydrolyse collagen and inhibit smooth muscle collagen synthesis. Both of these processes would be expected to weaken the plaque fibrous cap and ultimately cause plaque rupture or erosion leading to thrombosis and heart attack.

Conclusions

It can be concluded that arterial wall oxidized LDL particles and not circulating native LDL particles promote atherosclerosis. The molecular details of how arterial wall oxidized LDL particles cause the formation of atherosclerotic plaques and how these plaques rupture to provoke thrombosis and heart attack is becoming clearer and clearer. However, what is not clear is why a high circulating concentration of native LDL particles triggers the processes of atherosclerosis. The assumption seems to be that a high circulating concentration of native LDL particles inevitably leads to a high concentration of arterial wall oxidized LDL particles. This assumption may turn out to be justified but little if any evidence has been produced to support it.

In addition, the above account of how oxidized LDL particles damage arterial walls and cause atherosclerosis fails to address one very important area. It is beginning to be appreciated that processes for repairing arterial walls also exist. Consequently, the progression of atherosclerosis may turn out to represent the balance between the processes of damaging and the processes of repairing arterial walls. Perhaps it is this balance that is altered in favour of damage by risk factors for cardiovascular disease. Until the processes of repairing arterial walls are understood, there will still be much to learn about the relationship between circulating native LDL particles, arterial wall oxidized LDL particles and the progression of atherosclerosis.

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