Abstract

Atherosclerotic disease has been a feature of more affluent societies since ancient times. Currently, cardiovascular disease accounts for almost half of all mortality across Europe, causing over two million deaths within the EU and costing EU health economies €192 billion per year. The pathogenesis of atherosclerosis is complex, and our understanding of it has come a long way over the last 50 years. The public and many health professionals have an image of cholesterol that is probably over-simplistic. The oxidation of low-density lipoprotein (LDL) cholesterol to form oxLDL is the first molecular step in atherosclerosis pathogenesis, and it appears that oxLDL levels may act as a useful biomarker in identifying individuals at greatest risk of cardiovascular events. Inhibition of oxLDL or its active removal may represent a useful new therapeutic strategy. Antioxidants such as lycopene may offer another approach to prevention or treatment, and emerging evidence around the role of anti-*Chlamydia pneumoniae* antibodies in LDL oxidation could open up another avenue of preventative and therapeutic options.

Keywords

Atherosclerosis, cholesterol, oxidised low-density lipoprotein (oxLDL), lycopene, Chlamydia pneumoniae, abzyme

Disclosure

The author has no conflicts of interest to declare.

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For many years cardiovascular disease has been a major cause of morbidity and mortality across the developed world, and its incidence is also increasing in many developing countries. Indeed, it has recently been shown that even Egyptian mummies, representing the more affluent members of their society several thousand years ago, had established atherosclerosis in multiple blood vessels.[1] Cardiovascular disease has been extensively researched and has been the subject of considerable media interest and campaigns to promote lifestyle changes, such as stopping smoking, reducing alcohol consumption, avoiding obesity and taking regular exercise. Medical interventions are principally targeted at lowering cholesterol levels and reducing platelet activity, as well as treating, for example, hypertension and arrhythmias.

In spite of the many advances in our understanding of the pathogenesis of atherosclerotic disease, cardiovascular disease remains responsible for nearly half of all deaths in Europe.[2] The same report highlights the fact that cardiovascular disease is estimated to kill over two million people in the EU and to cost the EU economy some €192 billion a year. The bulk of these costs relate to healthcare (57%), but there are also significant losses of productivity (21%) and informal care costs (22%). Add to this the UN predictions that the number of people over 65 years of age in the EU is due to increase by some 45% over the next two decades and it is clear that our health economies face an unprecedented challenge for the future.

How, then, should we be responding to this challenge? While there have been a number of improvements in the management of acute myocardial infarction and, more recently, cerebral infarction over recent years, including thrombolytic therapy, manual thrombus removal and primary percutaneous intervention with stenting, there has been far less progress in the primary and secondary prevention of atherosclerotic disease. For the last few decades the general population and health professionals have been given an image of cholesterol as being something of a public enemy. Indeed, Pfizer's lipid-lowering statin drug Lipitor (atorvastatin) was the world's top-selling pharmaceutical product for at least the first five years of the millennium. While lowering low-density lipoprotein (LDL) lipids with statins certainly saves lives when used in high-risk individuals, half of all heart attacks and strokes occur in people whose cholesterol level is not considered to be elevated. Most professionals and large swathes of the public have an understanding that high-density lipoprotein (HDL) cholesterol is 'good' and that LDL cholesterol is 'bad'. This somewhat over-simplistic view may now be one of the factors impeding our current progress against cardiovascular disease.

The Importance of Cholesterol

Cholesterol is a crucial component of our biochemistry. It is needed by all cells to build and maintain cell membranes. It is also essential for the normal functioning of our nervous systems and the production of hormones such as testosterone, oestrogen, progesterone and cortisol, as well as bile acids, which assist in the emulsification and absorption of dietary fats.

Cholesterol is not water-soluble and must therefore be transported around the body in the form of a lipoprotein. While there are a number of lipoproteins, the two that predominate are the HDL and LDL fractions. Normal LDL is the main transporter of cholesterol within the circulation, taking it from the liver out to cells, where it is recognised by receptors and incorporated into cells. HDL takes

cholesterol that has been used peripherally back to the liver in the circulation for safe disposal. Thus, both normal HDL and normal LDL cholesterol are essential to the proper functioning of the body.

The Role of Oxidised Low-density Lipoprotein Cholesterol

Since the mid-1950s it has been suspected that the oxidation of LDL cholesterol by free radicals was the first molecular step in the process of atherosclerosis,[3] a condition characterised by arterial wall stiffening and formation of plaques containing a complex mixture of oxidised LDL (oxLDL), foam cells, collagen and smooth-muscle cells. Now, over half a century later, many of the details in this story have been elucidated, although a number of finer details still need further clarification. The problem starts when LDL cholesterol is modified, principally by the process of oxidation, to form oxLDL. This oxLDL is no longer recognised by cell membranes and thus builds up in the circulation. There is a strong correlation between oxLDL levels in the circulation and atherosclerosis formation, with oxLDL forming a significant proportion of the complex make-up of atherosclerotic plaques.[4] oxLDL is taken up by macrophages, which would normally recycle the damaged components, and ultimately becomes incorporated into atherosclerotic plaques within macrophage-induced foam cells (macrophages that have become overwhelmed by the excessive amount of oxLDL). Over the last decade oxLDL has been the subject of intensive research, and it now appears that oxLDL levels may provide a biomarker and useful predictor of risk of future cardiovascular events in otherwise apparently healthy men.[5,6]

However, most laboratories do not currently measure oxLDL levels and so the main focus up to now has been to reduce total LDL levels – hence the 'bad cholesterol' image of LDL cholesterol. Once the atherosclerotic plaques become large enough, the luminal surface may become fragile and easily disrupted. If the endothelium should be breached at all, platelets will immediately start to adhere and thrombus formation will begin, potentially leading to myocardial or cerebral infarction if this takes place within a coronary or cerebral vessel.
Thus, oxLDL levels may enable the identification of individuals at higher risk of atherosclerosis and atherosclerotic plaque formation, potentially giving an opportunity to target resources more effectively towards those at higher risk, who would benefit more from primary preventative measures being offered. Furthermore, it has been suggested that lowering levels of oxLDL might prove to be a promising therapeutic strategy in the battle against atherosclerosis.[7,8]

Antioxidants

LDL cholesterol oxidation appears to be related to an imbalance of oxidants and antioxidants in which oxidants predominate, resulting in a situation termed oxidative stress. The oxidation of LDL cholesterol probably takes place within the arterial wall.[4] There is evidence that antioxidants may play a protective role in atherosclerosis. Diets rich in fruit and vegetables that contain arytenoids have for some time been known to be associated with a protective effect against cardiovascular disease and cancers. The 'Mediterranean diet', rich in monounsaturated fat, plant proteins, fish and whole grains and low in red meat, refined grains and sweets, with moderate intake of alcohol, is associated with a significantly reduced incidence of coronary heart disease (CHD) and stroke. The main antioxidant component of the Mediterranean diet is lycopene, the red pigment found in sun-ripened tomato skins, although it is also found in watermelon, grapefruit and some seafoods, such as lobster and crab. Low levels of serum lycopene have been found to be associated with increased risk of acute coronary events and stroke in men,[9] and conversely higher levels of serum lycopene are

associated with a protective effect against CHD and stroke. For most of the population living outside the Mediterranean area, the dietary intake of lycopene is probably not sufficient to exert a significant protective effect, as the largest source of lycopene, tomatoes, are not sufficiently sun-ripened to be of much benefit. Furthermore, dietary lycopene has a large crystalline structure that renders it relatively difficult to absorb.

It appears that, in the Mediterranean diet, the act of cooking tomatoes in olive oil produces a more bioavailable form of lycopene. There are a number of lycopene supplements available, and in 2009 Cambridge Theranostics Ltd. launched Ateronon (see *Figure 1*), a capsule containing lactylycopene, a form of lycopene that has been combined with milk whey protein and that has been shown to be more bioavailable. Early studies in both healthy volunteers and individuals with established atherosclerotic disease have suggested that levels of LDL oxidation are reduced by up to 95% within two months of commencing the supplement; further studies are under way to test these results.

Chlamydia pneumoniae and Low-density Lipoprotein Cholesterol Oxidation

Over recent years the role of lipoprotein immune complexes has generated increasing interest. For some time it has been known that the immune system recognises oxLDL as 'foreign', with the production of antilipoprotein antibodies. However, recently it has been found that some of the immunoglobulin G (IgG) antibodies found in atherosclerotic plaques actually cause LDL oxidation.[10] *Chlamydia pneumoniae*, a common respiratory tract pathogen, has been recognised for the last two decades to be associated with the development of atherosclerosis. It now seems likely that antibodies produced by the immune system following immunological challenge with *C. pneumoniae* may also cause LDL cholesterol oxidation. The same study also found that, in patients with established atherosclerotic disease showing evidence of these anti- *C. pneumoniae* and LDL cholesterol oxidising antibodies (abzymes, from antibody + enzyme), treatment with an antimicrobial active against *C. pneumoniae* (azithromycin) for two months caused the abzyme levels to drop to undetectable levels and produced an improvement in the symptoms of atherosclerosis. This might suggest that appropriate antimicrobial treatment in those individuals with established atherosclerosis who show evidence of the specific anti-*C. pneumoniae* abzyme might go some way to slowing disease progression. The question also needs to be asked of whether individuals who are at risk of developing atherosclerosis should be screened for abzyme activity so that they could be targeted as a higher-risk group. Indeed, it is possible that those individuals who are positive for this abzyme could account for the half of all heart attacks and strokes that occur in people with a cholesterol level that does not appear to be elevated.

Conclusions

It is clear from the above that the processes involved in the development of atherosclerosis are complex, but that much progress has been made over the last half-century in understanding the pathogenesis of this disease. While lipid-lowering drugs have made a significant contribution to saving lives, cardiovascular disease currently costs the EU more than €0.5 billion each day, and these costs are likely to escalate over the next few years. If health economies are to make the best use of resources, a more targeted approach to primary and secondary prevention and treatment probably needs to be adopted. As a first step, the public and many healthcare workers will need to begin to understand that atherosclerosis is more complex than simply good versus bad cholesterol; clearly, the media have an important role here, perhaps along with the pharmaceutical industry. It would

appear that oxLDL levels and the abzymes producing them could provide an important biomarker for identifying higher-risk individuals, and inhibition of oxLDL production or its active removal might present another credible treatment strategy in individuals with established atherosclerosis. Diet continues to play an important role, and antioxidants such as lycopene also seem likely to prove useful in the future. Further work will be required in some of these areas, particularly the anti- *C. pneumoniae*/antilipoprotein abzyme story and their potential role as biomarkers, as well the place of antimicrobials. If future healthcare is to remain affordable, there is still considerable work to be done in this field in terms of identifying and targeting at-risk groups more accurately than at present so that primary and secondary preventative measures, as well as active treatments, can be focused more effectively on those at greatest risk. Ôûá

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