Atherosclerosis and aging

Newton Luiz Terra

Professor of the Biomedical Gerontology Graduate Program, Pontifical Catholic University of Rio Grande do Sul (PUCRS), Brazil.
Director of the Institute of Geriatrics and Gerontology, PUCRS, Brazil

In 2050 Brazil will be ranked 6th in the world in terms of elderly population, behind China, India, Russia, the United States and Japan. In this year, the population older than 60 years will be near by 64 million inhabitants, according the world health organization. Good nutrition, the improvement of sanitary conditions in cities, advances in diagnostic medicine, medications and vaccines, and a decline in infant mortality and birth rates, all contribute to population aging. This is a global and irreversible phenomenon with great impact on social, political, economic and cultural structures. This trend has caused a huge diversity of social and health needs in many different contexts. Drastic consequences will be observed in the health field; there will be a lower prevalence of infectious diseases and higher rates of mortality due to cardiovascular and cerebrovascular diseases. These diseases have atherosclerosis as their common denominator, with this being responsible for approximately 12 million deaths per year worldwide.

Atherosclerosis is a chronic inflammatory disease of multifactorial and polygenic origin that occurs in response to endothelial aggression, primarily affecting the intima of medium and large arteries. It is a systemic disease that may affect one or more vascular territories simultaneously. Coronary artery disease (CAD) is often associated with peripheral artery occlusive disease (PAOD), cerebrovascular disease (stroke) and aneurysmal disease. When this disease does not kill, it leaves behind sequelae that change drastically the quality of life of individuals and their families. Thousands of elderly people die every year of a disease that could have been prevented.

Over the years, much evidence has led to the understanding that atherosclerotic plaques are actually an active collection of different types of cells that migrate and infiltrate in association with inflammatory and possibly infectious agents. Currently, it is known that this disease involves multiple processes that include endothelial dysfunction, vascular inflammation and proliferation.

The endothelium is the name given to the layer of cells that line the inner walls of arteries. The formation of the atheromatous plaque begins through an attack on the endothelium of the artery due to various risk factors, such as increased cholesterol, high blood pressure, or smoking. After this attack, there
is a dysfunction of the endothelium by increasing the permeability of the inner layer of the vessel, favoring the penetration and retention of small particles of cholesterol – LDL (low-density lipoprotein) cholesterol – in the endothelium. When these particles of LDL-cholesterol are retained, they undergo a process called oxidation. It is important to note that the deposit of this lipoprotein (LDL) in the artery wall occurs in proportion to its concentration in the blood. In other words, the more the LDL-cholesterol circulates, the greater the chances it will have of forming plaques. This deposit is the key process in early atherosclerosis.

In addition to increased lipoprotein permeability, other manifestations also occur. Adhesion molecules appear on the surface of the endothelium, responsible for attracting monocytes and lymphocytes, which are inflammatory cells to the artery wall. Monocytes migrate into the subendothelial space where they differentiate into macrophages. These macrophages capture the LDL that has undergone oxidation (oxidized LDL). Lipid-loaded macrophages, called foam cells, are the main component of fatty streaks, which are the first evidence of early atherosclerosis. After this stage, some mediators of inflammation stimulate the migration and proliferation of smooth muscle cells of the tunica media of the artery. When these smooth muscle cells migrate to the intima, they form a fibrous cap that contributes to the increase of plaque.

In reality, the plaque formed comprises of a lipid core and necrotic debris, enveloped by foam cells. The separation between this material and the blood is done by the fibrous cap, which consists of smooth muscle fibers. These plaques begin to form very early in life and will accumulate and form real lumps that protrude into the artery, reducing blood flow and causing ischemia. As the atheromatous plaques increase, they thicken and weaken the wall of the artery, gradually reducing the amount of blood that can pass through it.

Plaques can be unstable and soft, or stable and hard. The soft fatty plaques are the most harmful because they cause no symptoms and do not show up in regular tests. The soft plaques are within the walls of the arteries and coated with a very fragile membrane that can easily rupture. When this happens, the fat cells break through the wall behind which they were hidden and mix with the blood and existing cells of the immune system. A clot is then formed, which interrupts the arrival of blood to the heart, causing a heart attack. The mechanism is the same for a stroke (cerebrovascular accident). These soft plaques are responsible for around 70% of heart attacks. Unlike hard plaques, soft plaques do not compromise circulation.

Most diagnostic tests do not detect soft plaques. Intravascular ultrasound is one of the exams that can visualize soft plaque, although it is an expensive exam. On the other hand, two simple tests can help to indicate an association with these plaques: ultra-sensitive C-reactive protein and Coronary Computed Tomography Angiography (CCTA).

There are non-modifiable factors of the disease such as age, male gender and family history. Age is an independent risk factor for atherosclerosis, in which we consider the increased risk over 45 years for men and 55 years for women. Around the age of 75, the number of cases in men and women is almost the same. In terms of family history, the first-degree relatives of people with the disease have a higher risk than the general population.

It is of extreme value to highlight the other group of risk factors as they are preventable or modifiable: dyslipidemia, systemic hypertension, diabetes mellitus, smoking, obesity, sedentary lifestyle, and stress. Once initiated, atherosclerosis is difficult to treat. Our greatest weapon for defeating it is in fact to prevent it, something that should be started as early as possible. An enormous effort must be made by geriatricians, gerontologists and social educators to prevent the formation of these plaques and avoid their complications. It is of the utmost importance not only to identify those people at a higher or lower risk of developing the disease, but also to identify, stratify and control the risk factors for atherosclerosis.

Beyond the cited classic predictors, there are also emerging risk factors such as: Lipoprotein(a), a modified form of LDL that appears to play an important role in atherosclerosis; homocysteine, an excess of which has been indicated as an independent risk factor for atherosclerosis; and fibrinogen, a protein produced by the liver that participates in coagulation mechanisms, which in excess should also participate in atherosclerosis.

High-sensitivity C-reactive protein (hs-CRP), an indicator of inflammatory activity in the body, has been identified as a potent and useful determining factor for the risk of developing atherosclerosis. It has been shown to identify those people who are more prone to the disease. Ultra-sensitive C-reactive protein is currently widely studied and the most correlated with cardiovascular risk. Coagulation factors VII, VIII and X have been considered to be able to increase the risk of developing atherosclerosis; fibrinolysis and plasminogen activator inhibitor decrease the plasma fibrinolytic capacity as a result of various reasons, but particularly from high levels of plasminogen, functioning as a risk factor for atherosclerosis. The possible role of infectious
agents in the origin of atherosclerosis has also been studied, with *Helicobacter pylori*, cytomegalovirus and *chlamydia pneumoniae* being among those investigated.

More studies are needed to confirm the importance of these new factors as risk indicators and their potential applicability in clinical practice. Nonetheless, it is felt important that such findings be disseminated to the scientific community to raise awareness of the many risk factors for this disease, some of which are being studied and some of which have yet to be discovered. However, it is essential that we also direct our attention to those causes that we can currently deal with and can change the history of atherosclerotic disease.

The prevalence of atherosclerosis remains high, even with new drugs to treat the disease and the advances in molecular biology and genetic engineering. There is a trend toward an increasing prevalence of risk factors for atherosclerosis with population aging and increased longevity, due to adverse changes in lifestyle in combination with industrialization and urbanization. Thus, mortality and disability rates will drastically increase over the coming years in our country. Preventive measures are urgently required. Generating the right conditions and working proactively will help to prevent many hospitalizations, deaths and disabilities, as well as reduce the costs generated by cardiovascular diseases. Unfortunately, our provision of preventive care is very limited, with healing and rehabilitation measures predominating. It is necessary to invest more in preventive geriatrics aimed at healthy aging with quality of life. Simple and applicable measures, even in scenarios of limited financial resources, such as encouraging the adoption of healthier eating habits, regular exercise, stress management, diagnosis and treatment of high blood pressure, tobacco and obesity control, diagnosis and treatment of high cholesterol and diabetes control can substantially reduce the incidence of and mortality rates for atherosclerosis. In order to achieve this goal, we need integrated actions throughout the country, conducted by the government, medical societies and the private sector to help in the prevention of atherosclerosis, a chronic inflammatory disease that is most feared by geriatricians around the world.