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EDITORIAL

Arterial ageing and atherosclerotic risk: new perspectives

Envejecimiento arterial y riesgo arteriosclerotico: nuevas perspectivas

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The ageing process involves numerous changes and modifications in the structure and function of virtually all organs of the human body, including the arterial system. Arterial ageing is associated with endothelial dysfunction, proliferation and phenotypic changes of smooth muscle cells (SMCs), development of calcifications, alterations in wall protein composition (less elastin and increased percentage of collagen) and changes in the structure of the adventitia, leading to progressive arterial stiffness and accelerated arteriosclerosis.[1]

The vascular endothelium plays a key role in the maintenance of vascular homeostasis by being involved in the control of virtually all functions related to the homeostasis of the vascular wall and its interactions with the blood. Regulation of endothelial permeability and its barrier function, regulation of the growth of all cell types in the wall, relaxation and contraction of vascular smooth muscle cells (VSMCs), white blood cell adhesion, platelet aggregation and activation, plasma coagulation and fibrinolysis are some of the functions in which endothelial cells are fundamentally involved. These functions are performed through the release of numerous factors with autocrine and paracrine actions.[2]

Arterial ageing is associated with endothelial dysfunction, considered to be the initial process of atherosclerotic development, and where the aforementioned functions are impaired.[1] The Framingham study demonstrated that ageing is the most important independent correlate of endothelial dysfunction (Mitchell et al. 2004), as in the absence of clinical disease both older men and women showed endothelial dysfunction.[3] Oxidative stress and inflammation are the most important pathological mechanisms responsible for endothelial dysfunction in healthy older adults. Risk factors such as hypertension, dyslipidaemia and alterations in blood glucose may exacerbate endothelial dysfunction in ageing through oxidative stress and inflammation.[2,3]

In addition to endothelial dysfunction, the normal structure of the arterial wall undergoes structural and functional changes with age. Ageing is frequently accompanied by increased thickness and alterations in the media VSMCs.[4] These changes are associated with an increase in collagen and a decrease in elastin content.[4] This imbalance increases arterial stiffness, reduces elasticity and distensibility of the arterial wall, leading to increased pressure differential, increased pulse wave velocity, increased afterload and reduced coronary flow. Increased arterial stiffness may reflect a dissociation between chronological age and biological age of the arteries, and is considered an independent predictor of cardiovascular disease in both subjects at high cardiovascular risk and the general population. Aging VSMCs have a higher proliferation rate than young cells, which correlates with increased expression of growth factors and decreased antiproliferative mechanisms. In addition, there is a change in the phenotype of aged smooth muscle cells from a contractile to a synthetic phenotype, which

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together with increased oxidative and inflammatory factors promotes atherosclerotic development.[4,5]

In the current issue of Clínica e Investigación en Arteriosclerosis, Hamczyk and Nevado write a special article on vascular smooth muscle cell ageing from the perspective of Hutchinson-Gilford progeria syndrome (HGPS).[6] HGPS presents with premature ageing characterised among other signs by accelerated atherosclerosis, high prevalence of myocardial infarction or stroke, and death in adolescence. Post-mortem examination of arteries from patients with HGPS revealed atheroma plaques with calcifications, erosions and plaque rupture.[6]

Patients with HGPS show signs resembling physiological ageing, the most relevant being those related to cardiovascular disease, including increased carotid-femoral pulse wave velocity indicating arterial stiffness. In the smooth muscle cells of these patients, increased extracellular matrix, elastin fragmentation, calcifications in the medial layer, thickening of the adventitia and fibrotic lesions are observed, despite the fact that most patients with HGPS do not have a high prevalence of classical vascular risk factors.[7]

The main cause of HGPS is an accumulation of the mutant lamin A protein called progerin. Lamin A is encoded by the LMNA gene which plays a key role in the regulation of nuclear structure and numerous essential cellular functions, such as gene transcription, DNA replication, DNA damage repair response, or signal transduction. Studies in elderly individuals without HGPS have shown detectable levels of progerin in cells and tissues including arteries, indicating that progerin may play a role during normal ageing.[7]

Mouse models with LMNA gene modifications showed alterations in VSMCs, suggesting a link to the accelerated vascular ageing process in HGPS. Progerin causes alterations in VSMCs that result in increased arterial stiffness, calcification and atherosclerosis. Progerin also causes low proliferation and replication rate, due to prolonged mitosis and impaired DNA repair, which is associated with premature senescence and death of VSMCs.[8,9] There are important differences in the development and progression of atherosclerotic disease between people with and without HGPS, with the onset of disease development being the main difference. Endothelial dysfunction is at the origin of atherosclerotic development in people without HGPS, whereas alterations in VSMCs seem to be more related to disease development in patients with HGPS. Based on the information provided in the article, the authors suggest that vascular disease associated with progerin production shares characteristics with age-related atherosclerosis, although extrapolation of some results may be limited by the existence of progeria-specific mechanisms.[10]

In the current issue of Clínica e Investigación en Arteriosclerosis, Zuriaga and Fuster write a review article on clonal haematopoiesis and atherosclerotic disease.[11] Clonal haematopoiesis is a situation in which a significant proportion of an individual's blood cells are derived from a single dominant clone of haematopoietic stem cells, as opposed to normal haematopoiesis, which is polyclonal. Clonal haematopoiesis is due to acquired mutations, but also to non-mutation-related mechanisms. In clonal haematopoiesis, the presence of a mutation provides a competitive advantage to the mutant haematopoietic stem cell, leading to its clonal expansion. The most widespread definition is clonal haematopoiesis of undetermined potential or CHIP, which is defined as the presence in blood or bone marrow of an expanded single nucleotide variation or insertion/deletion of a gene associated with a known haematological malignancy.[12] Although CHIP mutations can be acquired at any time in life, the likelihood of acquiring such mutations increases as an individual ages. It has been estimated that CHIP is present in 2%–3% of middle-aged individuals and 10%–20% of those over 70 years of age,[10] although these figures appear to be underestimated.[12,13] Recently it has been suggested that CHIP may be an independent risk factor for the development of atherosclerotic disease. There is evidence suggesting an association between CHIP and the development of atherosclerotic disease in older age, where it is also considered a risk factor for haematological tumour diseases.[13]

Experimental studies suggest that mutations in TET2 and JAK2, some of the most common in clonal haematopoiesis, promote the inflammatory process and may be related to the progression of atherosclerosis, which would explain the association between clonal haematopoiesis and increased cardiovascular risk. TET2, which codes for an epigenetic regulator of gene transcription, was the first gene with mutations in blood cells in individuals with clonal haematopoiesis without haematological cancer.[14] Studies in TET2-deficient mice suggest that accelerated atherosclerosis under these conditions is mainly due to the proinflammatory activity of TET2-mutant macrophages, which is characterised by up-regulation of IL-1 production.[14] The CHIP-associated JAK variant is a mutation associated with myeloproliferative neoplasms, but is also detected in individuals without haematological abnormalities, in whom it is associated with a high risk of atherosclerotic disease.[15]

The differences in atherosclerosis phenotypes and underlying molecular mechanisms observed in TET2-mutated and JAK2-mutated mouse models of clonal haematopoiesis suggest that mutations in different genes are not equivalent, and that the clinical significance of CHIP most likely depends on the specific mutated gene. In view of the available results, research is needed to determine whether other CHIP mutations, in addition to the aforementioned TET2 and JAK2, are causally related to the accelerated development of atherosclerosis and increased cardiovascular risk.[16] Although speculatively, a vicious circle between CHIP and atherosclerotic disease has been proposed, whereby atherosclerosis would facilitate clonal haematopoiesis, which in turn would accelerate the progression of atherosclerosis and its outcomes. However, there are no studies related to the prevention of increased cardiovascular risk in CHIP, and there is insufficient information to assess whether classical strategies to prevent atherosclerotic progression also prevent increased cardiovascular risk in patients with CHIP.[16]

In summary, the two articles discussed above open up new perspectives related to atherosclerotic development in pathological situations such as HGPS and CHIP.

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