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The “cholesterol paradox” in patients with mastocytosis

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To the Editor,

Indhirajanti et al. have documented that in some patients with mastocytosis there is a higher prevalence of cardiovascular events. This basic data serves the authors to highlight how mast cells contribute to the destabilization of atherosclerotic lesion and cardiovascular events, despite the low levels of total cholesterol and LDL cholesterol [1].

Two data are provided in apparent contradiction:

- the increase in cardiovascular events in subjects with mastocytosis;
- the paradox of low levels of total cholesterol and LDL cholesterol.

Other researchers, in addition to the authoritative studies cited by Indhirajanti S et al., confirm the emerging responsibility of mast cells. These responsibilities are also extended to cardiovascular diseases other than plaque rupture, such as hypertension and heart failure [2].

The authors abstained from a true analysis of the apparent “paradox”, resulting from the pathogenic responsibility of mast cells in the increase in cardiovascular events and the low levels of total cholesterol and LDL.

We are far from accepting that low levels of total cholesterol and LDL cholesterol are a protective factor for atherosclerotic lesions and cardiovascular events, as we have already supposed in the case of the “atrial fibrillation paradox” [3]. On that occasion, we stressed that low levels of LDL cholesterol and total cholesterol are pathogenetically related to the increase in atrial fibrillation, through the increased inflammation caused by endotoxins and the consequent altered immune response [4].

This hypothesis is based on the fact that all lipoproteins within a few minutes are able to complexate lipopolysaccharides and transport them to the liver for their detoxification 4.

Since the availability of sufficient levels of lipoproteins is lacking, the inflammatory tone increases and immune responses are altered, including the homeostatic capacity of mast cells.

Broad support for this hypothesis also comes from recent epidemiological work, where it is confirmed that atrial fibrillation is clearly associated with low levels of total cholesterol and LDL cholesterol [5].

Moreover, in subjects with advanced heart failure, increased bacterial lipopolysaccharides and decreased lipoprotein levels heavily affect the abnormal response of macrophages [6].

From a pathogenic point of view, in the formation of atherosclerotic plaque:

- first, the residues of LDL lipoproteins found in the atherosclerotic plaque are the result of the previous formation of foam cells and subsequent macrophage apoptosis: the epilogue of a long battle against the presence of foreign substances, and not the result of native cholesterol, deposited therein;
- second, all lipoproteins, together with macrophages, in fact, contribute to the elimination of undesirable substances from the circle, including the Gram-negative lipopolysaccharides, through the reverse cholesterol transport [5];
- third, lipoprotein cholesterol is essential for the physiology and functionality of all cell membranes, including those of mast cells;
- fourth, lipoproteins also carry sphingosine-1-phosphate (S1P), a substance that stabilizes mast cells, with consequent anti-inflammatory and cardioprotective effects [7].

It is known that lipopolysaccharides, increasing the inflammatory tone, are mainly responsible for the increase of serum amyloid A (SAA) at the expense of apolipoprotein A1 (Apo-A1), in lipoproteins, with mobilization of mast cells and neutrophils [8]. This would explain the decreased presence of Apo-A1, documented by the authors.

Furthermore, we know that in the course of infections and inflammations, the role of HDL decreases, while the increasing role of VLDL/LDL becomes the true protagonist in the defense against lipopolysaccharides [9].

Consequently, we confirm our hypothesis that cardiovascular pathology, chronic and acute, depends on the excessive presence of

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circulating lipopolysaccharides, which primarily alter the functionality of lipoproteins and, in the long run, reduce cholesterol synthesis. Such lipidic, quantitative and qualitative modifications, such as the decreased transport of S1P, can contribute to the increase in the inflammatory tone and destabilization of mast cells.

The low levels of total cholesterol and LDL cholesterol, reported by the authors, are to be considered a key pathogenetic moment in the beginning and progression of atherosclerotic plaque. The increase in the number of mast cells and their causal contribution to plaque destabilization can also be linked to the presence of lipopolysaccharides and decreased levels and/or dysfunction of total cholesterol and LDL cholesterol. The link between low levels of cholesterol and mastocytosis can be identified, for example, in the lack of S1P and in the decreased presence of Apo-A1.

In conclusion, the precious signaling of the “cholesterol paradox” (low levels of total cholesterol and LDL and higher incidence of cardiovascular events) in patients with mastocytosis could definitively indicate the “rehabilitation” of LDL cholesterol (bad cholesterol) and direct research of the etiopathogenetic responsibility of cardiovascular diseases to other causes, including microbial agents, also recognized by mast cells.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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