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Inflammation And Cardiovascular Disease

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ABSTRACT
Background: Inflammation has been recognized as an important issue in the pathophysiology of atherosclerosis, and consequently, cardiovascular diseases and its complications. Inflammatory pathways cover both components in the innate and acquired activated immune systems, which participate in the initiation and progression of atherosclerotic plaques and the incoming concept - thromboinflammation. Methods: it was performed a systematic search of Medline, PubMed, and American/European Societies of Cardiology websites (and respective guidelines), SCOPUS, Clinicaltrials.gov and references from published reviews/meta-analysis/trials and web (scholar.google.com), according to PRISMA checklist for all studies in human and written in English. Results: Different stimuli can cause the activation of cell types, leading to release pro-inflammatory cytokines, modulating the activity monocytes/macrophages and its migration from the bloodstream to the vessel wall.Conclusion:A better insight into the pathophysiology of thromboinflammation and immune inflammation and strategies to transform bad outcomes into good outcomes is necessary, thus further reducing the residual burden of cardiovascular disease.
Key words: thromboinflammation; immunoinflammation; atherosclerosis; cardiovascular diseases; anti-inflammatory therapies.
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I. INTRODUCTION

One of the major consequences of chronic inflammation is the activation of prothrombotic signalling pathways in vascular cells. Inflammation is a cascade of mechanisms that evolved in multicellular organism to neutralize injurious agents that entered the tissues. It can precipitate or exacerbate thrombotic complications of atherosclerosis. Immunoinflammation has emerged as a term to describe the inner connection between the immune system and the coagulation activation, aiming at allowing trapping of invaded pathogens and to improve host defence[1,2]. The initial recognition of such agents is mediated by molecular sensor on membranes of host defence cells, in cellular cytoplasm, or in extracellular fluid. The activation of these molecular sensors generates mediators that augment the clinically detectable manifestations of inflammation. Additionally, inflammation may develop because of immune dysregulation in autoimmune or malignant disorders (e.g., rheumatologic diseases, inflammatory bowel diseases and Hodgkin's lymphoma)[1,2,3].

Inflammation entails many blood cells and molecules. Many systems mediate the immune response and are classified as non-cellular (cytokines, chemokines, and complement) as well as cellular (neutrophils, monocytes/macrophages). Cells derived from monocyte/macrophage are involved in atherogenesis, as numerous chemokines, cytokines (including alpha tumour necrosis factor – TNFα, interleukin-1, interleukin-6, interferon γ), activation of myeloid cells and adhesion molecules expressed in the vasculature or adipose tissue, are produced by inflammation cells within the first hours after the onset of inflammation; these cytokines restrict erythropoiesis[4,5]. It occurs even in the absence of a pathogen, but is triggered mainly by endothelial dysfunction, in a so-called "thromboinflammation". This may lead to release of pro-inflammatory molecules, besides decryption of tissue factor on the surface of neutrophils and monocytes, release of von Willebrand factor (vWF) from platelets and endothelial cell Weibel-Palade bodies, netting of neutrophils with activation of the coagulation cascade and Factor Xa (FXa)/thrombin activation, implying thrombin propagation via factor XI (FXI)activation as well as increased fibrin deposition (Figure 1)[5,6,7].

Figure 1. Mechanism of thromboinflammation in cardiovascular disease.

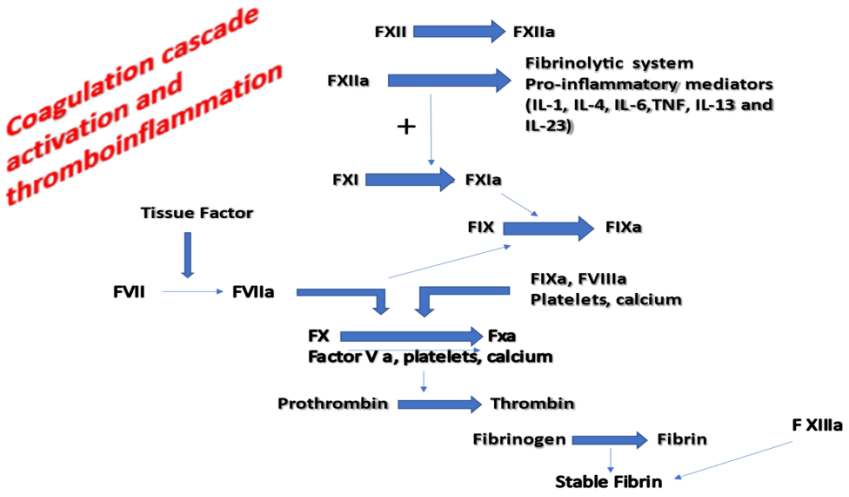

Figure 1. Pathophysiology of thromboinflammation in atherosclerosis, and its repercussion in cardiovascular diseases. Inflammation cells may lead to release of pro-inflammatory molecules (cytokines, interleukins 1,4,6, 13 and 23, tumour necrosis factor-α, TNF-α), release of von Willebrand factor (vWF) from platelets and netting of neutrophils with activation of the coagulation cascade and Factor Xa (FXa)/thrombin activation, implying thrombin propagation via factor XI (FXI)activation as well as increased fibrin deposition. By the author.

This article aims at raising the value of the inflammatory process in cardiovascular diseases, bringing to surface this knowledge, and summarizes current understanding of established and emerging mechanisms contributing to prothrombotic state, as well as analysing the role of anti-inflammatory therapy target to decrease cardiovascular burden.

II. METHODS

Initially, it was performed a systematic search of Medline, PubMed, and American/European Societies of Cardiology websites (and respective guidelines), SCOPUS, Clinicaltrials.gov and references from published reviews/meta-analysis/trials and web (scholar.google.com), for all studies in human and written in English. The research included the search strings "inflammation", "cardiovascular diseases", "coronary artery disease" "thrombosis", "thromboinflammation", "immune system" AND "biomarkers", "C-reactive protein, "cytokines", "outcomes", "major adverse cardiovascular events- MACE". Studies were developed from the last decade need to obtain a continuous response for correlating inflammatory process and cardiovascular diseases. Relevant selected studies, reviews, guidelines, and meta-analysis were hand-searched included, as seen Figure 2.
Figure 2. Flow of information with the different phases of a systematic review

Figure 2. The flow of information about the different phases of the selected studies, reviews, guidelines, and systematic meta-analysis.

III. MECHANISM OF ACTION

Atherosclerosis is a chronic inflammatory disease of the vessel wall driven by the progressive intimal accumulation of leucocytes. There are mechanisms which inflammation can accelerate or worse thrombotic complications of atherosclerosis[1,3,4]. It is well recognized that immune response play a critical role in atherogenesis. Monocytes differentiate into macrophages and take up oxidized low-density lipoprotein (oxLDL) to transform into foam cells. In addition, adaptive immune responses are activated, and a balance between pro-inflammatory and regulatory T-cell (Treg) responses control atherosclerosis [8].Activated type 1 helper T cells (Th1) secrete interferon γ and CD4+ T cells of the Th1 type promote inflammation, they were identified as the dominant lymphocyte subset in human atherosclerotic plaques. Increased numbers of a distinct T-cell subset termed CD4+, CD 28 null T cells producing high levels of interferon γ were detected in blood from patients with acute coronary syndromes and were found to be independent predictors of future coronary events. Among CD4+ T cells, interferon γ producing T-helper 1 (Th1) cells promote atherosclerosis, Th 2 responses contribute to atheroprogression or protection, dependent on the context and model[8]. In contrast, regulatory T cells (Treg) – including interleukin-4 and interleukin 13 – play a role in arterial inflammation, consumption of interleukin-2 (IL2), triggering the release of M2 macrophages, and production of anti-inflammatory cytokines interleukin 1-(IL-10), interleukin 4 (IL-4), interleukin 13 (IL-13), transforming growth factor-β (GF-β) andInterleukin 35 (il-35), which counterbalance the proinflammatory activity of the macrophages, promoting tissue repair(Figure 3)[5,6,9].

Figure 3. The role of cytokines in atherosclerosis

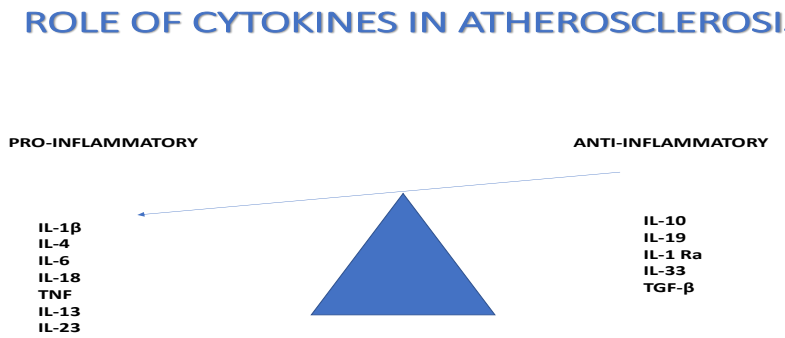

Figure 3. Role of Cytokines, showing an imbalance between pro-inflammatory and anti-inflammatory cells in the atherosclerosis process and its complications. IL, interleukin; TNF tumour necrosis factor, IL-1Ra, interleukin-1 receptor activated; TGF-β, tumour growing factor-beta. By the author.

IV. INFLAMMATION AND CARDIOVASCULAR DISEASES

From the first indication that atherosclerosis and acute coronary syndromes (ACS) are inflammatory diseases, an increasing body of evidence has grown and supports the notion that atherosclerosis shares pathogenic mechanisms with other inflammatory and/or autoimmune diseases[10,11,12].

Atherosclerosis is a chronic inflammatory disease of the vessel wall driven by the progressive intimal accumulation of leucocytes. It is well recognized that immune responses play a critical role in atherogenesis. Different inflammatory pathways have been considered in the prevention and treatment of cardiovascular diseases (CVD). Plasma levels of these molecules provide prognostic information about future major adverse cardiovascular events (MACE) in healthy subjects and patients with cardiovascular (CV) conditions – referred to as residual inflammatoryrisk[10,12].

Activated monocytes, neutrophils, eosinophils, and C-reactive protein (CRP) are present not only at the site of coronary plaque, but also in the entire coronary circulation of patients with ACS. Monocytes accumulate within thrombi and specifically overexpress toll-like receptor 4 (TLR4). TLRs are key receptors expressed by innate immunity cells. An outburst of the inflammatory process within the atherosclerotic plaque may lead to plaque rupture with thrombosis resulting in myocardial ischaemia and necrosis. Patients in whom plaque instability is caused by an inflammatory outburst present hyperreactivity to the inflammatory stimulus represented by myocardial necrosis, which, in turn, promotes plaque instability: inflammation beget inflammation. Interestingly, the intensity of this inflammatory surge predicts short and long-term outcomes[4,6,11,12]. These data suggest that specific anti-inflammatory treatment might improve the outcome of ACS, as shown inFigure 4.

Figure 4. The intensity of the inflammatory process within the atherosclerotic plaque.

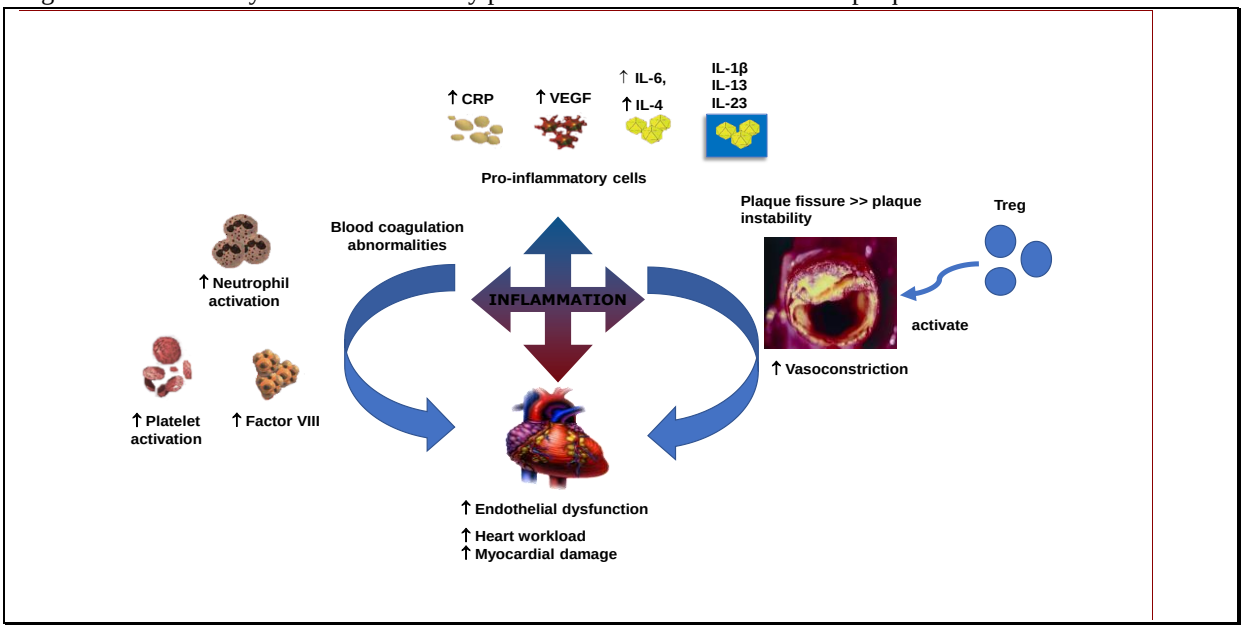

Figure 4. The outburst of the inflammatory process within the atherosclerotic plaque, leading to plaque rupture with thrombosis and coronary artery disease. Patients in whom plaque instability is caused by inflammatory outburst present hyperreactivity to the inflammatory stimulus represented by myocardial necrosis , which promotes plaque instability . The intensity of the inflammatory surge predicts short and long-term outcome. IL-1β, interleukin 1β; IL-6, interleukin 6; IL-1R, interleukin 1 receptor; IL-6R, interleukin 6 receptor; CRP, C-reactive protein; VEGF, vascular endothelial growth factor (Permitted by the author).

Interleukin-1 (IL-1) has important role as therapeutic target, once it acts at the beginning of inflammatory cascade, activating interleukin-6 (IL-6) synthesis. IL-1 presents two activators – alpha and beta – while its endogenous inhibitor (IL-1 Ra) blocks the two forms. Monocytes product IL-1β through their inactive precursor – pro-IL 1β), which is cleaved to give rise to IL-1β[10,11]. Commonly this process is mediated by intracellular proteins, known as nucleotide-binding leucine-rich repeat-containing pyrin receptor 3 (NLRP3) inflammasome, which, in response to cholesterol crystals, activate caspase-1. Within plaques, activated macrophages express IL-1 inducing smooth muscle proliferation, and recruitment of other inflammatory cells. Besides cholesterol crystals, oscillatory flow also increases NLRP3 expression, activates caspase-1, and consequently stimulate IL-1 production[10,13,14].

According to ACC/AHA and ESC guidelines (2022 and 2021, respectively)[14,15], high-sensitivity C-reactive protein (hs-CRP) in primary CV prevention predicts future CV events with a significance similar to that of total and low-density lipoprotein cholesterol (LDL-c). The hs-CRP in secondary prevention predicts the risk of recurrent myocardial infarction (MI), stroke, and CV death. Patients with ST-segment elevation myocardial infarction (STEMI), IL-6 are increased at the site of thrombotic coronary occlusion, while CRP is not, suggesting that IL-6 plays a role in that process.

Pro-inflammatory cytokines – such as IL-6 – provide a unique window to detect and quantify systemic inflammation in clinical practice. IL-6 is a pro-inflammatory cytokine secreted by T-lymphocytes in response to a variety of stresses in the body and the primary stimulus for the production of CRP in the liver. Michou et al[16] affirmed in their study that IL-6 concentrations are a strong independent predictor of all-cause mortality in all CVD patients, particularly with heart failure. Patients who maintained high levels of IL-6 or increased their IL-6 levels during hospital stay exhibited the worst prognosis. According to the same authors inflammation and heart failure seem to have a bidirectional causal relationship. Increased wall stress in the failing heart exposes cells to enlarge biomechanical strain and stimulates different cellular responses including inflammation. They concluded that inflammatory cytokines are overexpressed in stretched myocytes, as well as in conditions of pressure and volume overload. In their study NT-proBNP – a biomarker known to be produced in response to increased myocardial and haemodynamic stress – was an independent predictor of elevated IL-6 concentrations.

V. ANTI-INFLAMMATORY THERAPIES IN CLINICAL PRACTICE

The emerging association of inflammatory mediators with the pathogenesis and progression of chronic cardiovascular diseases has already resulted in the development of new anti-inflammatory strategies, used as adjunctive therapy in CVD patients.

Some drugs used in the treatment of chronic cardiovascular diseases may also influence the persistent immune activation and inflammatory pathways. Treatment with high doses of angiotensin converting enzyme inhibitors (ACEI) reduces circulating levels of IL-6, may affect TNF-α and reduce macrophage infiltration. Angiotensin- II receptor antagonists (ARB) downregulate inflammation by reducing plasma levels of TNF-α, IL-6 and brain natriuretic peptide (BNP) in mild-to-moderate heart failure,p.ex.

A novel addition to the pharmaceutical management of CVD (and so, heart failure) is angiotensin receptor- neprilysin inhibitor (ARNI); it reduces inflammatory myocardial infiltration in addition to preserving cardiac function and reducing fibrosis. Amlodipine reduces IL-6 levels, as well as carvedilol (beta-blocker).

Current evidence insinuate that an anti-inflammatory treatment might improve the outcome of ACS. Blockade of IL-1β and IL-6 have been investigated in the field of ACS using biological response modifiers that inhibit inflammatory cytokines. Lipid-lowering therapy can be considered an anti-inflammatory strategy, since statins reduce vascular inflammation through reduced prenylation of small G proteins, which induce anti-inflammatory and antiproliferative genes such as nitric oxide (NO), among others. Statins may attenuate inflammatory responses and promote plaque stability independent ofcholesterol-lowering effects. Statins also reduce CRP levels and is effective in the prevention of coronary events. It has been increasingly confirmed that therapies directed towards inflammatory process crucially reduce CVD morbidity and mortality[5,10,11].
Some of the effects on the immune system may be secondary to improved left ventricular function and not a direct effect of the drugs.

VI. CLINICAL TRIALS CONCERNING ABOUT INFLAMMATORY RISKS

A secondary prevention trial, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study – CANTOS trial – in stable coronary artery in high inflammatory risk patients, approached 10061 patients during four years of follow-up, with persistent elevation of CRP despite usual therapy, including statins. In this trial, hs-CRP (but not LDL-c) reduced MACE by 15%. Canakinumab provides a tool for the inflammatory risk in atherothrombosis by inhibiting IL-1, IL-6, and TNF-α without effects on lipids or coagulation[17].

The Colchicine Cardiovascular Outcomes Trial (COLCOT) was conducted to analyse the properties of colchicine (an anti-inflammatory drug that reduces expression of adhesion molecules and leucocyte recruitment on endothelial cells, as well as diminish inflammatory chemokines and NLRP3 inflammasome) on MACE comparing to placebo in recently myocardial infarction patients. This study was randomized, double-blind, placebo-controlled trial to received colchicine (0,5mg once daily) or placebo within 30 days, with reduction of CV death, MI, stroke, and coronary revascularization in colchicine group, compared to placebo group.[18]

In the Low-dose Colchicine in Patients with Chronic Coronary Disease (LoDoCo2) trial, Nidorf and colleagues brilliantly conducted an investigator-initiated, randomized, double-blind, placebo-controlled trial of low-dose colchicine (0,5 mg once daily) compared to placebo, to analyse if colchicine prevents MACE in patients with chronic coronary artery disease (CAD). This study showed the magnitude of benefit of low-dose colchicine, reducing 31% the risk of CV death, MI, stroke, or coronary revascularization as primary endpoint, comparing to placebo[19].

A number of studies evaluate the effect of anti-inflammatory therapies, including IL-1β antagonist Canakinumab and low-dose colchicine, in reducing the risk of recurrent ACS[5,17,18]. Their positive effects on clinical outcomes are due not only the prevention of atherosclerotic progression and thrombotic complications, but also to an improvement in plaque healing capacity. Blockade IL-1β may inhibit leucocyte adhesion, reduce thrombosis, and promote fibrinolysis. Low-dose colchicine favourably modifies the morphologic features of coronary plaques, producing more stable and fibrous phenotype.

In summary, we have learned a lot about mechanisms of inflammation and thromboinflammation, and this knowledge has driven the traditional approaches to therapy for atherosclerosis. But it is not enough yet. Recent data have led to an improved understanding of the underlying prothrombotic mechanisms contributing to chronic inflammation and impaired fibrinolysis. A better insight into the pathophysiology of thromboinflammation and immune inflammation and strategies to transform bad outcomes into good outcomes is necessary, thus further reducing the residual burden of cardiovascular disease.

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