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Inflammation and Cardiovascular Disease: The Role of Colchicine

Maria Elizabeth Ferreira,MD
Department of Internal Medicine, Estácio de Sá University, Rio de Janeiro, Brazil.

Abstract
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. Different stimuli can cause the activation of cell types – lymphocytes and mast cells – leading to release proinflammatory cytokines, which modulate the activity of monocytes and its migration from the bloodstream to the vessel wall. Colchicine – an anti-inflammatory drug used in rheumatologic disease has been emerged as an option to reduce inflammation in cardiovascular diseases.

Key words: *inflammation;atherosclerosis; cardiovascular disease; coronary artery disease; colchicine*

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I. Introduction

Inflammation has been recognized as an important issue in the pathophysiology of atherosclerosis and consequently, cardiovascular diseases and its complications (arterial hypertension, heart failure, stroke)[1]. It involves morphological and functional damages into the endothelium and platelets. This articleaims at raising the value of the inflammatory process in cardiovascular disease, bringing to surface this knowledge, and analysing the role of colchicine as anti-inflammatory therapy target to decrease cardiovascular events[1,2].

II. Methods

It was performed a systematic search of Medline, PubMed and American/European Societies of Cardiology websites, American Heart Association site for all studies in humans and written in English. The research included the search strings “coronary artery disease”, “cardiovascular diseases” AND “biomarkers”, “C-reactive protein”, “predictor”, “mortality”, “outcomes”, “colchicine”, “major adverse cardiovascular event-MACE”. Relevant selected studies, reviews, guidelines, and meta-analysis were hand-searched included.

PATHOPHYSIOLOGY

Although disorders of lipoprotein metabolism and the accumulation of its products in the arterial wall are important causes of atherosclerosis and thrombosis, they are far to be the only mechanism[1,2]. Inflammatory pathways cover both components in the innate and acquired activated immune systems, which participate in the initiation and progression of atherosclerotic plaques. Different stimuli can lead to the activation of cell types – lymphocytes and mast cells – giving rise to proinflammatory cytokines, which modulate the activity of monocytes and its migration from the bloodstream to the vessel wall[3].

As leucocytes migrate, its infiltration at the atheromatous plaque site produces molecules, such as proteases, inflammatory cytokines (tumour necrosis factor α, interleukin (IL)1, IL6, IL18, reactive oxygen species) and procoagulant factors, modulating thrombus formation and destabilization of the lesion (Figure 1). These inflammatory cells, released from the vessel wall by vascular damages, become potential endothelial proinflammatory mediators[3].

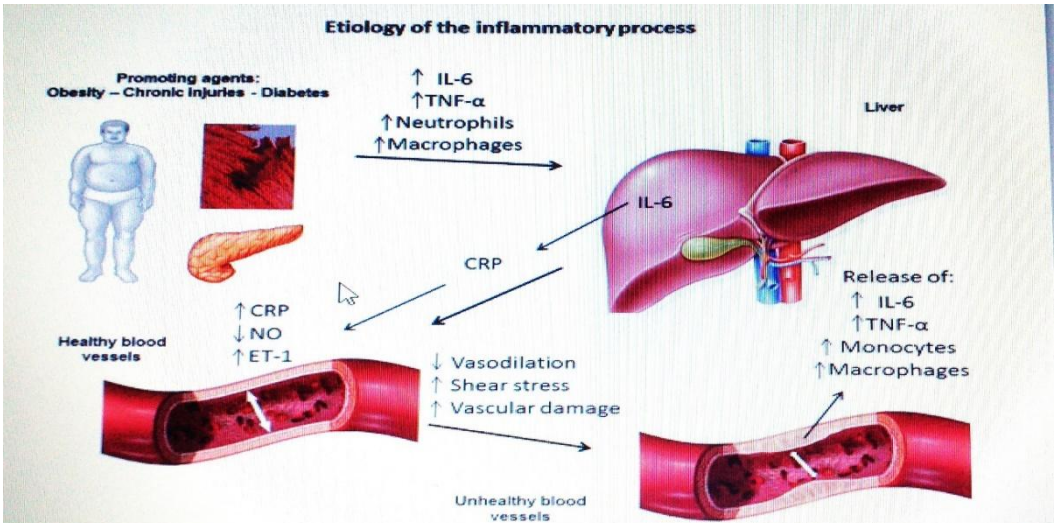

Figure 1. Pathophysiology of inflammation and its interaction with pancreas, liver, and vessel wall. Chronic inflammation increases inflammatory cells migration, leading to augmentation of C-reactive protein (CRP in response to interleukin 6 (IL-6), which provoke vascular damage and diminish vasodilatation. TNF-α, tumour necrosis factor-alfa; IL-6, interleukin 6; CRP, C-reactive protein; NO, nitric oxide; ET-1, endothelin1. From Camm et al, 2019.

Among the cytokines involved, there is a balance between anti-inflammatory (IL 10) and proinflammatory (IL1, IL6, IL18). In this balance, NLRP3 inflammasome – a macromolecular protein complex – which is activated by cholesterol crystals, hypoxia, and molecular damages, activates IL1β with consequent activation of IL6 and C-reactive protein[3,4,5].(Figure 2).

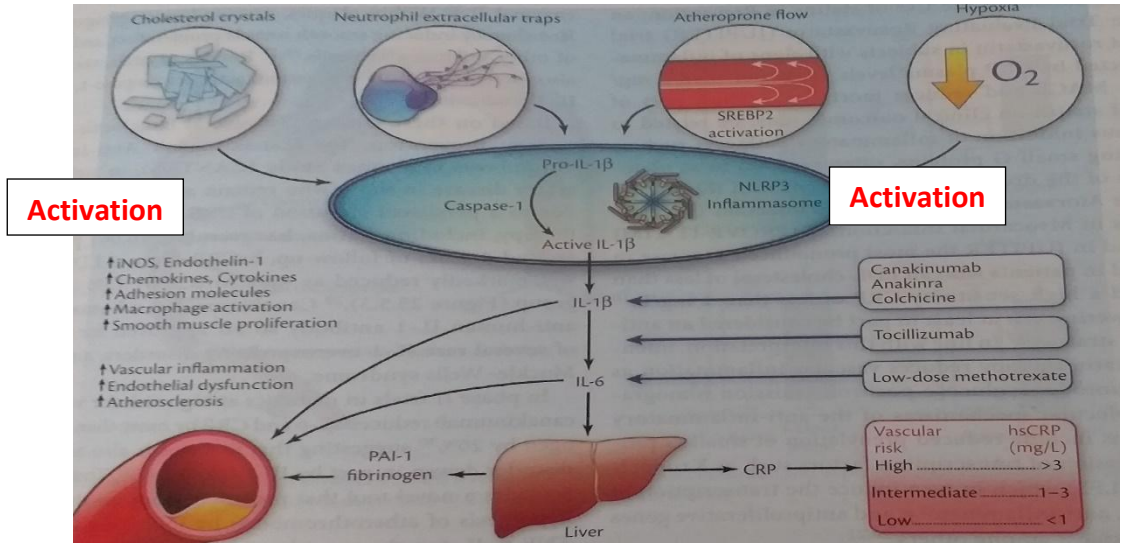

Figure 2. Schematic representation of activation of the containing NLRPE inflammasome by cholesterol crystals neutrophil cells, hypoxia, resulting in production of interleukin 1β with consequent activation of interleukin 6 and C-reactive protein, as well as increased vascular atheroma. Canakinumab, Anakinra, colchicine, tocilizumab and methotrexate, nitric oxide synthase are all potential interventions in this inflammatory cascade. PAI-1, plasminogen activator inhibitor 1; SREBP2, sterol regulatory binding protein 2. Illustration credit by Ben Smith, Sarwar N et al, 2012 (modified by the author).

C-reactive protein (CRP) is one of the most studied proinflammatory protein and has emerged as important tool in the association between inflammation and cardiovascular events, making an interesting biomarker for assessing the intensity of atherosclerotic process. This protein is mainly synthetized in hepatocytes and whose mRNA transcription is influenced by IL6 e IL1β is released in respond to infections (or trauma), forming part of an innate defence mechanism.

Inflammation and coronary artery disease

Inflammation is closely associated with coronary artery disease (CAD) and acute coronary syndrome (ACS) as part of innate and adaptive immunity, increased metabolism, and neovascularization. According to Alman and colleagues, augmentation of inflammatory markers levels is associated with the progression of calcification in coronary arteries in humans with or without type 1 diabetes. This finding shows a causal relationship between inflammation and cardiovascular disease[4,6].

Several studies have shown the closely relationship between high-sensitivity CRP (hs-CRP) and ischemic events, providing arguments of hs-CRP levels and cardiovascular (CV) risk factors in the general population and in individuals with CAD[3,4,5,6]. This biomarker can discriminate CV risk independently of lipid levels. Many reports have demonstrated that after an acute event, inflammation has a potential role in residual risk. Inflammation and atherosclerosis, and consequently acute coronary syndrome. Both systemic (traditional CV risk factors) and local factors (ischemiaand cholesterol plaques) can triggerthe activation of inflammatory pathways. Activation of the NLRP3 inflammasome has a substantial role to proinflammatory cytokines imbalance and various cell types in a progressing inflammatory signalling. Several drugs have the capable to modulate steps of this process. Among these, colchicine has emerged promising results in major cardiovascular outcome trials as an anti-inflammatory therapy to hinder the progression of coronary disease[7,8].

Colchicine: an anti-inflammatory drug

Colchicine is a microtubule inhibitor with potential anti-inflammatory effects. It was initially extracted from the *autumn crocus* (*Colchicum autumnale*). Colchicine reduces expression of adhesion molecules and leucocyte recruitment on endothelial cells, reduces tissue factor expression (reduce thrombotic potential), reduces fibrinogen and plasminogen activator inhibition 1 (PAI-1) levels, alter leucocyte responsiveness, as well as diminish inflammatory chemokines and NLRP3 inflammasome and increase fibrinolytic potential.

From the last five years, recent trials demonstrated the possibility of anti-inflammatory therapy to improve cardiovascular events. This acquaintance was firstly analysed in the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS)[9] involvingabout 10.000 patients from 39 countries with a history of myocardial infarction and elevated CRP levels; its results showed a lower risk of CV events with canakinumab group (150 mg every three months) comparing to placebo group. But it proved no difference in total mortality,as well higher risk of fatal infections than placebo.

In contrast, colchicine has multiple different types of anti-inflammatory effects. The Colchicine Cardiovascular Outcomes Trial (COLCOT) was conducted to evaluate the properties of colchicine on major adverse cardiovascular events (MACE) comparing to placebo in recently myocardial infarction patients. This study was randomized, double-blind, placebo-controlled trial to receive either colchicine (0,5mg once daily) or placebo in patients with myocardial infarction within 30 days who had completed any revascularization procedures and were treated according to guidelines[8,10]. As results, the percentage of patients who had the composite endpoint of CV death, Myocardial infarction, stroke, and coronary revascularization was lower among those who received colchicine 0,5mg once daily than placebo group (Figure 3).

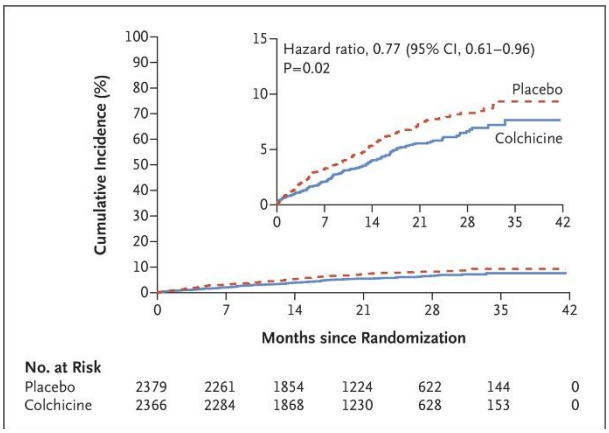

Figure 3. COLCOT Trial - results. Tardif et al, 2019.

In the Low-dose Colchicine in Patients with Chronic Coronary Disease (LoDoCo 2) trial, Nidorf and colleagues conducted an investigator-initiated, randomized, double-blind, placebo-controlled trial of low-dose colchicine (0,5mg once daily) compared with placebo, to analyse if colchicine prevents MACE in patients with chronic CAD[11]. This trial showed the magnitude of benefit of low-dose colchicine, being consistent with previous studies, reducing 31% the risk of CV death, myocardial infarction, stroke, or coronary revascularization as primary endpoint, comparing to placebo.

III. Conclusion

It is very important to recognize the strong relationship between inflammation and cardiovascular diseases in worldwide countries – industrialized and in development nations. Despite the great arsenal treatment, mortality rate is still high. Anti-inflammatory drugs, especially colchicine, had evidenced a significant benefit to patients with chronic coronary diseases, allowing interventions to mitigate inflammation and reducing risk of cardiovascular events. Further studies will be necessary to corroborate to the next chapter of cardiovascular science.

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