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From bench to bedside: Chronic inflammation and cardiovascular risks

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Cardiovascular disease is the leading global cause of death, accounting for 17.3 million deaths per year, a number that is expected to grow to >23.6 million by 2030 [1]. In 2008, CVD deaths represented 30% of all global deaths [2].

The pathogenesis of atherosclerosis has undergone a critical revolution over the last three decades. The traditional view that atherosclerosis was mainly characterized by accumulation of cholesterol within the arterial wall leading to flow limiting stenoses eventually resulting in signs and symptoms of ischemia due to impaired perfusion has evolved considerably to incorporate new molecular and cellular pathways of chronic inflammation in promoting atherothrombosis [2].

Three decades ago, besides age, cholesterol and LDL concentrations were seen as invaluable risk markers for future cardiovascular events. Despite this important role of cholesterol in atherosclerosis, it became clear that many individuals who experienced a myocardial infarction have cholesterol concentrations at or below the National Cholesterol Education Program thresholds of 200 mg/dL for total cholesterol and 130 mg/dL for LDL cholesterol [3].

Currently, both dyslipidemia and inflammation are seen as partners in this vicious cycle triggering atheroma formation and proliferation. Basically, atherosclerosis is likely to start with an innate immune response involving the recruitment and activation of monocytes macrophages that respond to an excessive accumulation of modified lipids within the arterial wall, followed by an adaptive immune response involving antigen-specific T lymphocytes [2].

Even though the entire vascular endothelium is susceptible to vascular injury, the initial atherosclerotic plaque tends to occur at specific sites characterized by significant alterations in arterial flow of many middle and large arteries, especially at bifurcation sites. Specifically, at these sites regional areas of flow disturbance induce mechanical alterations of endothelial cells [2].

Normally the vascular endothelium not only provides an antithrombotic and anticoagulant balance but also tonic vasodilation that controls blood flow and pressure. Once this athero-protective phenotype is transformed, endothelial cells become an active beacon for the activation of immune responsive cells such as monocytes, macrophages, T lymphocytes, neutrophils, and mast cells as well as by resident smooth muscle and dendritic cells to form the atheromatous plaque [2].

Particularly important in this cascade of events is the action of activated T cells that enter lesions in response to the chemokine-inducible protein-10, monokine induced by interferon-γ, and interferon-inducible T cell α-chemoattractant [2]. The atherosclerotic lesion also contains cytokines that promote a T-helper 1 response known to amplify the local inflammatory activity by producing proinflammatory cytokines such as interferon-γ and CD40 ligands 40 L and 154, which contribute importantly to plaque progression [2]. Furthermore, adiponectin, a product of adipose tissue, having insulin-sensitizing, antiatherogenic, and antiinflammatory properties is also increased in the atherogenic plaque [2].

Macrophages also play important roles in the progression of atherosclerosis by exhibiting unique characteristics under the various stimuli, evolving the plaque instability, thrombus formation and remodeling [2].

Translating all this basic data into useful clinical information, results from multiple large-scale prospective studies have shown that C-reactive protein (CRP) strongly and independently predicts adverse cardiovascular events, including myocardial infarction, ischemic stroke, and sudden cardiac death [4,5]. Concentrations of high sensitive CRP (hsCRP) evaluation adds prognostic information beyond that available from the Framingham Risk Score. In contrast to several other biomarkers that also reflect biological aspects of inflammation, hypofibrinolysis, and insulin resistance, hsCRP measurement is inexpensive, standardized, widely available, and has a decade-to-decade variation similar to that of cholesterol [6].

Since there is now ample evidence linking both chronic inflammation and dyslipidemia not only in initiating but also promoting atherosclerotic injury; the goal of the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) makes perfect sense. The JUPITER population has been described as apparently healthy individuals with slight elevation in their CRP levels and the study aimed to determine whether treatment with rosuvastatin 20 mg/d would reduce the rate of first major

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cardiovascular events [7]. At the time of study closure, it was found that treatment with rosuvastatin significantly reduced the primary composite endpoint by 44% as compared with placebo. Most importantly, results of this trial clearly suggested that patients with elevated CRP stand to benefit from statin therapy, regardless of their LDL-C level [7].

It is quite evident that significant advances have occurred in our understanding of cardiovascular diseases. Nonetheless, additional breakthroughs will undoubtedly occur as we gather more data regarding alterations in inflammatory markers and how these changes cause vascular injury and accelerated atherosclerosis. Though considerable controversy still exists in how to diagnose individuals at a higher risk of developing cardiovascular disease at least based on the last publication by the American College of Cardiology/American Heart Association task force on practice guidelines it was recommended that hs-CRP might be used to inform treatment decision making if after quantitative risk assessment a treatment decision remains uncertain [8].

Therefore, we certainly await with great enthusiasm the results of the ongoing trials such as the CANTOS (Interleukin-1β inhibition using cankinumab) and CIRT (low-dose methotrexate) trials. In each of these trials an event driven protocol is using anti-inflammatory measures in an attempt to reduce cardiovascular events among stable coronary disease patients who remain at risk of another events due to a persistent pro-inflammatory response [9]. Finally, the COLCOT trial is currently evaluating if long-term use of colchicine reduces cardiovascular events in patients post myocardial infarction. The better-powered COLCOT trial is trying to replicate findings of a previous smaller study were colchicine when used with other standard secondary prevention interventions such as statins was effective in preventing cardiovascular events in patients with stable coronary artery disease [10].

Since new experimental data continue to unravel new molecular and cellular pathways of inflammation and how they are involved in the pathogenesis of atherosclerosis, such as the IL-6 pathway; continued vigilance on our part is required to follow the results of ongoing trials. These not only would allow us to determine which markers are indeed critical in identifying individuals at a higher risk of cardiovascular disease; but also which therapies might most useful in improving cardiovascular health.

Conflict of interest

None.

Sponsors

None.

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