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EDITORIAL

From Inflammation to Acute Cardiovascular Events – a Complex Journey

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Inflammation is a major factor in the onset and progression of atherosclerosis, which is currently considered a chronic inflammatory disease. At endothelial level, inflammation leads to increased permeability to lipoproteins and their subendothelial accumulation, inducing endothelial dysfunction. The balance between pro- and anti-inflammatory properties determines the atheroma progression.[1] The link between long-term inflammation and cardiovascular disease is well-known, and it has been demonstrated that inflammation can lead to plaque vulnerabilization, triggering an acute coronary event. Moreover, increased systemic inflammation, such as the one seen in periodontal disease or COVID-19, is correlated with atheromatous plaque progression, favoring plaque rupture or coronary thrombosis.[2] Diabetes mellitus is also associated with an inflammatory condition, being one of the strongest independent risk factors for cardiovascular diseases (CVDs). Atherosclerosis progression is more accelerated in diabetic patients, increasing the risk for late complications.

It has been clearly demonstrated that statin therapy considerably lowers inflammation, with the highest impact particularly in high-risk patients and in those with already established CVD. Interestingly, statin therapy has been demonstrated to reduce the neointimal proliferation that leads to in-stent restenosis, via an inflammatory pathway.[3] Since persistent low-grade inflammation is associated with high levels of low-density lipoprotein cholesterol (LDL), the benefits of statin therapy on cardiovascular mortality are linked with both LDL-cholesterol reduction and anti-inflammatory effects.[4] Statins decrease inflammatory cell adhesion, platelet activation, foam cell generation, and matrix remodeling, reducing C-reactive protein levels by 25–50%. At the same time, it has been shown that the anti-inflammatory properties of statins are associated with their potential to reduce the level of pro-inflammatory cytokines in individuals with hypercholesterolemia, diabetes, or metabolic syndrome.[5]

Perhaps the disease that best illustrates the impact of inflammation on CVD is COVID-19. This pandemic triggered an unprecedented rise in cardiovascular mortality that translated into life losses around the world. The World Health Organization provided a case definition for post-COVID-19 condition, a term used to describe the persistence of symptoms for over 3 months following a SARS-CoV-2 infection, with these symptoms lasting at least 2 months and not being attributable to any other illness, a situation which has now commonly become known as 'long COVID'.[6] While the short-term impacts of COVID-19 on mortality continue to emerge, the virus also has long-term effects on mortality that may become apparent over time.[7] Adults with post–COVID-19 condition have elevated rates of adverse health outcomes and mortality during follow-up.[8] Although the true burden of cardiovascular pathology post-acute COVID-19 remains elusive, the prevalence of cardiac symptoms in this phase appears high. Nevertheless, the reported long-term medical problems are not necessarily the same symptoms as for the acute infection, and there is evidence that COVID-19 can cause lasting damage to the kidneys, lungs, heart, and

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brain, which could potentially lead to increased mortality risk.[9] Therefore, continuous monitoring of the 'long COVID' population is considered nowadays crucial for improving quality of life among these patients.

A major factor in the acute pathophysiology of COVID-19 is thromboinflammation caused by the elevated systemic inflammatory response.[10] This is linked to an increased prothrombotic state, including a rise in the activation of the coagulation cascade and clot formation, as evidenced by significantly elevated D-dimer levels and a high incidence of thrombotic events, particularly in hospitalized and immobilized patients.[11] Patients who survived severe and moderate COVID-19 were reported to have post-discharge ischemic heart failure, stroke, and thrombotic events. A recent study found that hospitalized survivors of COVID-19 had a higher risk of deep vein thrombosis and pulmonary embolism than the general population. This suggests that the thromboinflammatory state persists even after the infection has been resolved.[12] In a population of nearly 500,000 patients, COVID-19 was linked to an increase in deep venous thrombosis rates of nearly 50%.[13] Results from the START-COVID-19 registry indicated that thromboprophylaxis was administered to up to 70% of patients, and those with thrombotic complications had higher median D-dimer levels, which confirmed the presence of COVID-19-associated coagulopathy.[14]

Prolonged immobilization, fractures, and surgical interventions, especially orthopedic ones, are well-known risk factors for thromboembolic events.[15–17] Therefore, it is not surprising that during the acute phase of COVID-19, the risk of thromboembolic events was even higher in these patient categories, highlighting once again the link between COVID-19 and thromboinflammation. The incidence of venous thromboembolism was 8% in a retrospective study that included patients who had total joint replacement surgery during the COVID-19 pandemic, with women and obese individuals having a higher risk.[18]

A major tool to reduce the burden of acute inflammation on cardiovascular system is represented by vaccination, which reduces the risk of infections that can exacerbate underlying heart conditions. Patients with CVDs are vulnerable patients, at an increased risk for complications from infectious diseases, making vaccination an essential public health protection against infections.[19] Respiratory infections, particularly influenza and pneumococcal infections can exacerbate cardiovascular diseases leading to severe outcomes.[20] Consequently, vaccination in this patient population is essential for reducing hospitalizations and mortality.

According to the guidelines of the European Society of Cardiology, vaccination against influenza, pneumococcus, and COVID-19 should be considered for patients with heart failure.[21] Annual influenza vaccination is strongly recommended for all patients above 65 years with CVD, including those with coronary artery disease and heart failure.[22] Research indicates that pneumococcal vaccination reduces the incidence of pneumonia by approximately 45–75% and pneumococcus-related cardiovascular complications by up to 50%, thereby improving overall survival rates.[23] After the pandemic, COVID-19 vaccination became widely available and is recommended not only for preventing severe SARS-CoV-2 infections, but also for reducing the overall risk of cardiovascular complications among patients with CVD.[24]

From inflammation to thromboinflammation, from infections to cardiovascular diseases via inflammatory pathways, these journeys illustrate a pathophysiological mechanism in which inflammation plays a major role. This should be the focus of cardiovascular research in the forthcoming years, to identify useful tools for fighting CVDs in the post-COVID era.

CONFLICT OF INTEREST

Nothing to declare.

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