ISSN 2231-2218

ASIAN JOURNAL OF PHARMACEUTICAL AND BIOLOGICAL RESEARCH

AJPBR

Indexed by:

ROAD Crossref Universal Impact Factor IMPACT FACTOR SEARCH

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 3
SEP-DEC. 2023

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 3
SEP-DEC. 2023

C-REACTIVE PROTEIN AS A PREDICTOR OF CARDIOVASCULAR DISEASES

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Abstract: The inflammatory marker, high-sensitivity C-reactive protein (hsCRP), plays an important role in predicting various cardiovascular diseases. It can predict myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death in both healthy individuals and patients with coronary syndrome. The hsCRP provides additional information about prognosis in the presence of other risk factors such as cholesterol levels, coronary risk scale, metabolic syndrome, and blood pressure. It is also a useful tool for assessing patients with atherosclerosis. An hsCRP level below 1 mg/L indicates a low risk of cardiovascular disease. Values between 1 and 3 mg/L indicate moderate risk, and values greater than 3 mg/L are associated with high cardiovascular risk. The significance of determining hsCRP levels is that it helps in early detection of patients susceptible to cardiac problems. This allows the initiation of preventive measures and timely treatment, which helps to improve their prognosis and prevent recurrence and death due to heart disease. This article summarizes the epidemiological evidence on the association between CRP and atherothrombotic disease and provides clinical guidelines for hsCRP screening for cardiovascular risk assessment.

Key words: C-reactive protein (CRP), hsCRP, acute phase of inflammation, low-density lipoproteins (LDL), risks of vascular pathologies, atherosclerosis, atherothrombosis, proinflammatory cytokines, myocardial infarction, ischemic stroke.

A new risk factor for determining the threat of CVD

Meanwhile, as blood lipids are important in coronary heart disease (CHD), 50% of all MI are registered among people without obvious hyperlipidemia. For

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Volume 12 Issue 3
SEP-DEC. 2023
example, as a result of the Women's Health Study, which involved 28,000 healthy middle—aged women in the United States with biochemical blood parameters, 77% of all future heart attacks occurred among subjects with LDL cholesterol below 160 mg/dl, and 46% in patients with LDL cholesterol below 130 mg/dl [1]. Despite the fact that the use of global forecasting algorithms, such as those obtained from the Framingham Heart Study [2], significantly improve the definition of the threat of cardiovascular diseases, about 20% of all coronary cases are detected in the absence of certain classical risk factors for vascular diseases.

Therefore, today the main problems related to national screening programs for the identification of the risk of cardiovascular diseases and their prevention are being considered, and this fact has been subjected to a lot of controversy from many representatives of the medical community. Nevertheless, more and more diagnostic cases are being identified, showing the inaccuracy of using only classical risk factors. Recently, in an analysis of more than 120,000 patients with coronary heart disease, 15% of men and 19% of women were not diagnosed with hyperlipidemia, hypertension, diabetes or smoking, and more than 50% had only 1 of these common risk factors [3]. In another large analysis, 85% to 95% of participants with coronary heart disease had at least 1 common risk factor, but the same can be said for participants without coronary heart disease, despite being followed for 30 years.4 Thus, due to the significant need to improve the detection of vascular risk, many studies over the past decades have focused on identifying and evaluating new risk factors for atherosclerotic growth [5, 6].

- When evaluating a new biomarker as a potential screening tool, clinicians should consider the following criteria:
- Is there a standardized, reproducible, and cost-effective biomarker analysis;
- Does the assumed data demonstrate that the biomarker predicts future risk;
- Does the use of a biomarker in combination with lipid screening or existing

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SJIF 2022: 4.465
Volume 12 Issue 3
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algorithms for predicting global risk, such as the Framingham scale, significantly improve predictive ability?

The application of these basic epidemiological requirements to a number of new risk factors, including highly sensitive C-reactive protein (hsCRP) and other markers of inflammation, lipoprotein(a), homocysteine and markers of fibrinolytic and hemostatic function such as fibrinogen, D-dimer, tissue plasminogen activator and plasminogen activator-1 inhibitor antigen, indicates that It is shown that today hsCRP is the most promising of these biomarkers from the point of view of clinical application [7, 9]. For example, when directly comparing the relative ability of various biomarkers, including lipid fractions, to predict future cardiovascular diseases (CVD; combined endpoint of death from coronary heart disease, nonfatal myocardial infarction, stroke, and coronary revascularization) in the Women's Health Study, hsCRP proved to be the most powerful predictor of cardiovascular risk [10]. The same result was observed with respect to the outcomes of peripheral artery diseases [11]. Moreover, the prediction models that included hsCRP in addition to the lipid profile were significantly better than the lipid-only models. Although other markers of inflammation, including cytokines such as interleukin-6 [12] and tumor necrosis factor-α; [13] cell adhesion molecules such as soluble intercellular adhesion molecule-1 [14, 15], P-selectin [16], and soluble CD40 ligand [17]; macrophage inhibitory cytokine 1 [18]; lipoprotein-associated phospholipase A2 [19]; and the number of leukocytes [20] have also shown promising results as markers of vascular risk, and all of them have analytical deficiencies that need to be eliminated before they can be used in clinical practice. For example, the half-life of some of these markers is too short for clinical diagnostic testing, while the ability of other risk predictions in the general population after adjustment for traditional risk factors was negligible [21, 22].

CRP is the main marker of the acute phase

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In the acute phase of inflammation, the immune system is activated, which causes an increase in body temperature. This phenomenon is known as fever. An increase in temperature helps to accelerate metabolic processes, activate the body's defense mechanisms and destroy inflammatory pathogens. In addition, a change in vascular permeability allows leukocytes and other immune cells to penetrate into the focus of inflammation and have a protective effect. The inflammatory process also affects the biosynthetic and metabolic profile of organs. It can cause changes in organ functions, as well as a decrease in the synthesis of certain substances necessary for the normal functioning of the body. The immune system plays a key role in the acute phase of inflammation. It activates various groups of cells, such as leukocytes, macrophages and phagocytes, which are involved in the destruction of pathogens and the restoration of damaged tissues. The central nervous system controls the inflammatory process and participates in its regulation. It transmits information from immune cells to peripheral organs and back, which allows the body to respond effectively to inflammation. The endocrine system also plays an important role in the acute phase of inflammation. It controls the production of hormones that regulate the body's immune and inflammatory responses. For example, the hormone progesterone can reduce inflammation, and stress hormones such as cortisol can reduce immune responses. The cardiovascular system is also activated in the acute phase of inflammation. Vasodilation, increased capillary permeability and increased blood flow rate contribute to the delivery of immune cells and nutrients to the site of inflammation. However, in some cases, inflammation can cause damage to the vascular wall and lead to complications. Thus, the acute phase of inflammation is a complex process in which many body systems interact and perform their functions to quickly and effectively resist inflammation. Determining the level of CRP in the blood allows not only to diagnose the presence of an inflammatory process, but also to assess its activity. An increase in CRP indicates the development or exacerbation

of inflammation, as well as tissue necrosis. A decrease in the level of CRP may indicate the effectiveness of the treatment. It is very important to note that CRP is only a general indicator of inflammation, and other clinical data must be taken into account for its interpretation. Just like any other laboratory indicator, the results of determining CRP can be falsely positive or falsely negative, so an integrated approach is required when interpreting the data obtained. In general, measuring the concentration of CRP is an important tool in clinical practice and helps to determine the effectiveness of treatment and the dynamics of changes in inflammatory processes.

Changes in the base concentrations of hscrp in CVD

Inflammatory processes in the walls of blood vessels play an important role in the occurrence of atherosclerosis. Recent studies have shown that sluggish inflammation is a key factor that leads to the formation of chronic inflammation inside the vessels. This inflammation is associated with increased levels of highly sensitive C-reactive protein (hsCRP) in the blood. High levels of hsCRP are a predictor of the risk of developing cardiovascular diseases such as myocardial infarction, cerebral stroke and sudden cardiac death. These diseases can occur even in people who have not previously had cardiovascular problems. This discovery is a significant step in understanding the mechanism of atherosclerosis and its connection with inflammatory processes. Now it is possible to develop new methods of prevention and treatment that will be aimed at suppressing sluggish inflammation and reducing hsCRP levels in the body. It is important to emphasize that controlling levels of inflammation and hsCRP is not only a prevention of cardiovascular diseases, but also a way to prevent their occurrence in people who are not at risk due to heredity or lifestyle. Thus, sluggish inflammation and elevated hsCRP levels play an important role in the development of atherosclerosis and cardiovascular diseases.

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Regular monitoring and reduction of these indicators can help in preventing acute forms of such diseases and maintaining the health of the cardiovascular system.

hsCRP and atherothrombosis: biological factors

Inflammation characterizes all phases of atherothrombosis and provides the most important pathophysiological link between early lesion formation and plaque rupture, leading to occlusion and infarction [23, 24]. Primary pro-inflammatory cytokines such as interleukin-l and tumor necrosis factor-α potentiate the expression of adhesion molecules on vascular endothelial cells, which leads to the recruitment of leukocytes into the arterial wall in the early stages of atheromatous lesion development. Primary cytokines also activate chemokines that promote the subsequent migration of monocytes into the subendothelial space. The mononuclear cells in this initial infiltration, together with the internal vascular cells, subsequently release growth factors that stimulate the proliferation of smooth muscle cells and lead to the progression of plaques. Other pro-inflammatory mediators, such as the CD40 ligand, induce the expression of tissue factor and thus contribute to the formation of blood clots. Primary proinflammatory cytokines also stimulate the expression of matrix cytokines such as interleukin-6, which act remotely, creating a systemic enhancement of the inflammatory response, a component of which is the production of CRP.

As the scientific understanding of atherothrombosis as an inflammatory disease has developed, evidence has emerged of the direct role of CRP at all stages of the atherosclerotic process. CRP, consisting of 5 23-kDa subunits, is a member of the family of pentraxin proteins of the innate immune response. Although it was initially thought that it was synthesized only by the liver in response to interleukin-6, recent data indicate that CRP is also produced in smooth muscle cells of human coronary arteries and is expressed mainly in affected vessels [25, 26]. In one report, it was found that the levels of CRP mRNA in atherosclerotic plaques were 7 and 10

times higher than in the liver and normal blood vessels, respectively [27]. Despite the fact that CRP is traditionally considered a passive marker of the inflammatory process, laboratory studies have shown that it directly affects vascular vulnerability through various mechanisms, including enhanced expression of molecules of local adhesion of the surface of endothelial cells [28], monocytic chemoattractant protein -1 [28, 29], endothelin-1 [30], and endothelial inhibitor-activator of plasminogen – 1 [31]; reduces the bioactivity of endothelial nitric oxide [30, 32, 33]; increases the induction of tissue factor in monocytes [34]; increases the absorption of LDL by macrophages [35]; and colocalization with a complement membrane attack complex within atherosclerotic lesions [36]. Recent data also show that the expression of human CRP in CRP-transgenic mice directly enhances intravascular thrombosis in arterial damage and models of photochemical damage to the endothelium [37].

Despite these findings, the question of whether these potentially atherogenic effects of CRP have direct clinical significance remains controversial. Plasma or serum concentrations of hsCRP, which are most useful for predicting cardiovascular risk in primary prevention clinical settings, are lower than concentrations of CRP in tissues that cause atherogenic reactions in laboratory studies. While the hsCRP ranges that differentiate low-, medium-, and high-risk individuals in epidemiological studies are less than 1, 1-3, and more than 3 mg/l, CRP levels that have been implicated in proinflammatory reactions at the cellular level typically range from 5 to 900 mg/L, although there are exceptions (for example, concentrations of CRP up to 5 mg/l were associated with a decrease in nitric oxide production). It is possible that the levels of CRP in plasma only poorly reflect the concentration in tissues and that the local concentration of CRP is present in sufficient quantities to promote atherogenesis in individuals with clinically elevated circulating blood levels (i.e.≥1 mg/l). Moreover, recent clinical data suggest that the range of hsCRP concentrations useful for predicting CVD is wider than originally thought.; very low concentrations

of hsCRP (<0.5 mg/l) are almost never associated with the future development of vascular diseases, while concentrations exceeding 10 mg/l represent patients at very high risk [38, 39].

The trigger of the initial arterial inflammatory reaction remains unclear, although excess LDL cholesterol, smoking, obesity, hypertension and metabolic abnormalities probably contribute to this. Given the primacy of infection in inducing an inflammatory response, it has been suggested that infectious sources such as Helicobacter pylori, leading to an increase in circulating cytokines, or local infectious sources of intracellular organisms inside plaques, such as Chlamydia pneumoniae or cytomegalovirus, are responsible. However, the presence of antibodies to these and other infectious agents does not allow consistent prediction of CVD cases in prospective epidemiological studies [7].

Conclusion

C-reactive protein (CRP) is a substance produced by our body in response to inflammatory processes. And although it is not yet clear exactly what role it has in the physiology of our body, its prognostic value has already been proven in cardiology and other medical fields. Many studies have shown that the concentration of CRP can predict the risk of developing cardiovascular diseases in different groups of patients - both in healthy people and in patients with heart attacks, angina pectoris, diabetes, kidney disease and others. Therefore, it is important to include the measurement of CRP concentration in the standard practice of laboratory diagnostics. This will significantly expand opportunities in the field of cardiology, nephrology, endocrinology and other medical industries. Thanks to this simple test, doctors will be able to more accurately predict the risk of cardiovascular problems and take appropriate measures to prevent or treat them. The introduction of this method will help improve the health of patients and reduce mortality from cardiovascular diseases.

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