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Value of CRP in Ischemic Heart Disease

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Abstract
It is unknown whether CRP is a direct cause or a marker of coronary artery disease (CAD), despite the fact that plasma levels of C-reactive protein (CRP) are independently linked to an elevated risk of CAD. Initial stages of atherosclerosis Coronary artery disease (CAD) is recognized to be triggered by inflammation, and the inflammatory cascade is essential for the growth of atherosclerosis. Given the significant role inflammatory processes play in coronary artery disease, recent research has looked into whether inflammatory biomarkers can help with risk stratification and identify patient groups likely to benefit from intervention. C-reactive protein (CRP) has become one of the most significant novel markers of inflammation among these biomarkers. CRP is a powerful independent predictor of adverse cardiovascular events such as myocardial infarction, ischemic stroke, and sudden cardiac death in people with or without overt coronary artery disease, according to several sizable prospective investigations. The main roles of CRP in angiogenesis include activation of the complement system, lipid uptake by macrophages, production of proinflammatory cytokines, increased expression of tissue factors in monocytes, promotion of endothelial dysfunction, and avoidance of oxidant formation.

Keywords: CRP, ischemic heart disease, inflammation, coronary artery disease

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I. Introduction

The lifetime process of angiogenesis, an acute vascular disease resulting in ischemia necrosis in acute myocardial infarction (MI), and ischemic myocardial damage are all hypothesized to be affected by inflammation at various stages in the etiology of coronary artery disease (CAD). According to Liet al. (2018), the most thoroughly researched indicator of systemic inflammation is C-reactive protein (CRP), a typical acute phase protein. The initial CRP study showed for the first time a link between minor increases in circulating CRP and eventual cardiovascular events in patients with unstable angina, which is the reason this is the focus of the intensive investigation.

The baseline CRP and coronary risk have been found to gradually increase in several prospective population-based investigations of coronary artery disease defined in this research as fatal myocardial infarction or coronary artery disease. It has been established by Isola et al. (2018) that CRP prevents atherosclerosis and has been connected to LDL for more than 25 years. Together, these findings suggest that CRP might directly cause coronary artery disease (and thus represent a significant therapeutic target), even though there is disagreement about how to interpret the epidemiological data from the two investigations. The question of the effectiveness of the CRP measurement in foretelling long-term cardiovascular consequences is a special one that is related to uncertainty. One definite possibility claimed by Tayefi et al. (2017) is that injury severity and outcome may be significantly impacted by myocardial infarction-induced big CRP response in the acute phase, as opposed to long-term relative variations in baseline CRP levels. This article's goal is to critically evaluate the information that currently exists regarding the link between CRP and coronary heart disease and to propose new techniques that can assist in removing the doubts mentioned above.

II. Literature Review

Building of CRP C-reactive protein is a non-glycosylated plasma protein that, together with the serum component amyloid protein-P (SAP), belongs to the lectin pentraxin family. Five identical non-covalent subunits make up each pentraxin, which is organized in the shape of a disc with cyclic pentameric symmetry and distinctive calcium-dependent binding to certain ligands. The flat-galectin fold of each CRP element has a pocket on the B or binding side that contains two calcium ions that bind only 4 apart, one coordinated to the CRP side chains of proteins that are carboxylate and amide with a loop on one side of the core component (Serkova et al., 2017). All physiological CRP ligands should bind to these calcium atoms in order for the native pentamer to maintain its fundamental structure and integrity.

It has been suggested by Ju et al. (2017) naturally; calcium is always present in the extracellular milieu that contains CRP in vivo. As a result, manipulating CRP in vitro investigations can provide wrong

results due to calcium insufficiency. Even at physiological pH and ionic strength without calcium, CRP rapidly aggregates, loses physiological ligand binding and typical side effects, and dissociates into easily foldable and cleavable components. Proteolytic CRP, on the other hand, is extremely stable in physiological calcium, pH, and ionic strength circumstances. It has been suggested by Nortamo et al. (2017) Even though severe mixing can cause isolated pure CRP material to clump, it is exceedingly stable, unaffected by repeated freezing and thawing, maintains its typical pentameric shape, and is extremely proteolysis resistant (Held et al., 2017). It will not disintegrate into its constituent parts, even in the presence of very strong sodium lauryl sulphate anionic detergent. CRP's usefulness as a clinical measure is significantly increased by the fact that it is stable in serum. Given these compelling results, it is doubtful that denatured CRP subunits, proteolytic cleavage fragments of CRP, or changed CRP will have any physiological or pathological effects.

Recent studies such as Khandaker et al. (2020) putative binding relationship between CRP and accessory protein factor H amplified the significance of managing CRP properly (fH). A very significant risk factor for age-related macular degeneration is one of the two primary polymorphisms of fH, and the amino acid substitution (Y402H) is situated in the seventh short repeat, the area of fH that binds CRP. Recent reports of connections between PCR and fH are based on solid-phase tests, in which the CRP is suspended—typically in calcium-free solutions—and then terminated by non-specific binding to plastic surfaces under circumstances where these immobilized proteins areunavoidable (Çağdaş et al., 2019). These experiments were repeated with CRP present, but there was no interaction with fH. There was no discernible interaction between fH and native CRP in the solution or solid phase, according to several investigations using liquid phase proteins and various CRP or fHimmobilization configurations and techniques.

CRP is a very small amount of plasma protein found in healthy people. The fact has been stated in various medical articles and reports, such as Omland and White (2017), the median is about 0.8 mg L-1 between the ages of 18 and 63. The distribution ranged between the 90th percentile of 3 mg L-1 and the 99th percentile of 10 mg L-1. Similar distributions have been noted in the general adult populations of the US and Northern Europe, despite the fact that in these unselected populations, levels are a little higher, elevations are more severe, and concentrations tend to climb a little over the course of a century. The distribution of registry-normalized CRP levels is frequently quite skewed. In the US, 33% of persons have a baseline CRP between 3 and 10 mg L-1, and 50% of people have a baseline CRP greater than 2 mg L-1 (Wirtz and von 2017). Afro-Caribbeans living in North America were found to have greater CRP levels than Northern Europeans, while Japanese or Chinese individuals had lower levels. CRP levels are roughly one-tenth those of people of European descent in Japanese ethnic groupings. However, it is unclear why this discrepancy exists. The majority of CRP levels in healthy participants evaluated by monthly serial sampling were normally between 0.1 and 3 mg L-1, although sporadic elevations were not clearly related to clinical pathology. Baseline CRP levels vary between individuals with non-coding variants in the CRP gene accounting for the majority of this genetic variation. The degree of obesity, particularly central abdominal obesity, is another important factor that is independent of genetic factors. This suggests that proinflammatory cytokines are produced by macrophages associated with this adipose tissue. It has been further supported byWirtz and von (2017) adipocytes are the source of CRP. In the healthy adult cohorts, the annual intersubjective variability of CRP at baseline was comparable to that of blood pressure or serum cholesterol levels, as well as many other markers of circulating inflammation, such as fibrinogen and white blood cell count. The infraclass correlation coefficient for CRP levels has been roughly 0.6 in recent years.

Recently, the abbreviation "hs-CRP," which stands for "highly sensitive" or "extremely sensitive" PCR, has appeared in the literature. Rather than utilizing older, less sensitive assays with detection limits between 2 and 10 mg L-one, immunoassay methods with appropriate sensitivity to quantify CRP within the normal range are used to measure CRP in blood or plasma samples and found to be superior to baseline values for assessing the acute PCR reaction (Peikert et al., 2020). It is crucial to remember that the analyte known as hs-CRP is simply CRP, nothing unique or different, and most definitely not a brand-new molecule that is unmistakably linked to cardiovascular disease. Due to CRP's vast research and over 75 years of clinical usage, it is the only extremely sensitive and entirely non-specific systemic indicator of infection, inflammation, tissue damage, and/or almost any undesired non-physiological stress. It is inappropriate to warn someone with a baseline CRP of 7 mgL-1 about an increased risk of cardiovascular disease or to suggest appropriate lifestyle changes if CRP expression may be elevated (Peikert et al., 2020). A very broad spectrum of further severe illnesses is still undiscovered, including Hodgkin's disease or kidney cancer, or additional illnesses that frequently go undetected for some time before becoming clinically present.

In recent years, there has been a lot of research on the relationship between C-reactive protein (CRP) and ischemic heart disease. Although genetic studies have demonstrated that polymorphisms linked to high levels of CRP do not raise the risk of ischemic vascular disease, epidemiological research has linked relatively high levels of CRP with coronary artery disease, indicating that CRP is a secondary rather than primary progressing atherosclerosis factor. Experimental investigations are being conducted in an effort to demonstrate

the involvement of CRP in the development of arteriosclerosis in addition to all these epidemiological and genetic studies. The complex results of genetic, epidemiological, and experimental investigations on CRP are highlighted in this review, along with the reasons why additional research may be required to fully understand the connection between CRP and atherosclerosis.

For almost thirty years, CRP has been the focus of the experimental investigation. CRP's antithrombotic, anti-inflammatory, and anti-pathogenic capabilities have been shown in reports to work in vivo. In general, CRP has anti-inflammatory characteristics since it has been demonstrated to activate the traditional complement cascade (Omland and White 2017). This would completely explain the findings of epidemiological research because CRP has been linked to atherosclerosis. The original findings were most likely a result of the commercialization of CRP with hazardous sodium acid or the presence of bacterial endotoxin (lipopolysaccharide) created by recombinant Escherichia coli in CRP, as additional research has not always been able to replicate the aforementioned symptoms.

Animal models that seek to address the query of the antithrombotic effects of CRP provide far less information. With one exception, these investigations failed to detect a link between human CRP and the development of atherosclerosis, suggesting that CRP is more of a control than a cause. Although atherosclerosis can also develop in the gastrointestinal system, mice were utilized in almost all of these investigations as an animal model of the condition. Regarding ligand binding, associated side effects, complement activation, and function as an assault substrate, there are significant species differences in CRP. The possibility of tissue damage caused by CRP inhibitors in humans after myocardial infarction was examined in 2006 using a rat reperfusion model.

Although it has been demonstrated that human CRP can activate the classical complement cascade in both humans and rats, these findings from the injection of human CRP in other species cannot be used to explain a pathogenic mechanism for the frequently observed clinical finding of elevated CRP levels in post-MI and MI declared unfavourable outcomes.

The introduction of the hypothesis that monomeric forms of CRP may exist after pentameric CRP binds to one of its ligands, leading to dissociation and subsequent functional activation, provided an elegant explanation to the contradicting CRP data in light of these observations (Çağdaş et al., 2017). Neoepitopes express different antigens from native CRP epitopes because monomeric CRP has long been known to be a tissue-insoluble protein rather than a soluble plasma protein. The inflammatory features of this monomeric CRP differ from those of pentameric CRP in that it binds to C1q, which increases neutrophil-endothelial cell adhesion, platelet activation thrombosis, and monocyte cancer, to mention a few. Different outcomes could be brought on by contaminated CRP (with hazardous sodium acid or bacterial endotoxin) or another CRP product.

Studies have specifically demonstrated that, in contrast to normal CRP, the monomeric form of CRP is localized in additional necrotic areas. The potential significance of monomeric CRP in the pathophysiology of "active" CAD must be taken into consideration because Khandaker et al. (2022) demonstrated that monomeric but not pentameric CRP has prothrombotic activity, enhancing both platelet aggregation and thrombosis under arterial perfusion circumstances. Held et al. (2017) found that healthy arteries did not accumulate monomeric CRP, whereas the human aorta and carotid atherosclerosis show different results. There was no evidence of the pentameric isoform in healthy or damaged blood arteries. In a 2017 study, Ju et al. (2017)found that while insoluble monomeric CRP can be found in microparticles from acute myocardial infarction patients, healthy controls and stable CAD patients have substantially lower levels of monomeric CRP. There is no way to know the intricate role that CRP plays.

The most precise study designs are occasionally used in epidemiological studies that demonstrate a link betweenCRP exposure and ischemic disease. An approach is used in genetic investigations with random Mendelian samples to assess the causal connections between exposures and prevent inverse association bias. It was only a matter of time before significant genetic studies were conducted to examine the relationship between high CRP levels and an increased risk of coronary heart disease because numerous studies have demonstrated that a number of single nucleotide polymorphisms in the CRP gene are associated with elevated baseline CRP levels.

III. Conclusion

When attempting to harmonies the findings of genetic, epidemiological, and experimental investigations, the results of PCR appear to be more inconclusive and extensive. It seems doubtful that increased CRP is a direct cause of ischemic diseases. However, this is in line with experimental findings that demonstrate that circulating CRP has neither antithrombotic nor anti-inflammatory characteristics. Commercial CRP contamination with hazardous sodium acid, monomeric PCR, or bacterial endotoxin is expected to have anti-inflammatory and antithrombotic effects. After MI, CRP is anticipated to bind to apoptotic cells by complement and then dissociate into monomeric CRP, which may have inflammatory qualities.

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