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Inflammatory Markers in Coronary Artery Disease: is C- Reactive Protein Losing the Game?

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Abstract

Coronary artery disease has been accepted as an inflammatory condition due to the presence of pro-inflammatory biomarkers. Previous observational studies regarding the association between inflammatory markers and CAD are inconsistent and suggest that the association may be biased and confounded. Alternatively, a potentially powerful approach “Mendelian randomization” has been established which avoids the residual confounding and reverse causations observed in conventional observations. These studies strengthen the cause-and-effect relationship between some inflammatory cytokine and the development of CAD, while weakened the case of C-reactive protein. Most of the current studies based on randomized trial are carried out in the population with European ancestry and therefore, it would be impressive to replicate these findings from other ethnic groups including high risk South Asian population.

Keywords: Inflammation; Coronary Artery Disease; Risk Factors.

1. Introduction

Coronary artery disease (CAD) is a multifactorial disease reflecting one or more classical risk factors like smoking, elevated cholesterol, and increased LDL, low HDL and hypertension, which are present in $\leq 50\%$ of CAD patients.

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Inflammation is a complex and an essential part of immune response to infections and damages in tissues. Significant link of inflammation to coronary atherosclerosis dates back to 1999 with the statement that coronary atherosclerosis is a chronic inflammatory health condition [1]. It is now well established that inflammation can exert its diverse effects on lipoprotein metabolism and vascular biology through the involvement of numerous cellular and molecular components [1]. Experimental studies in cell biology and pathology indicate that inflammation, importantly; the chronic inflammation is recognized as a major governing factor in atherosclerosis from plaque initiation to eventual rupture of unstable plaque, thereby causing myocardial infarction [2]. Large numbers of inflammatory cells are shown to be widely present in atherosclerotic plaque [2]. TNF-alpha, IL-6 and C-reactive protein (CRP) are mainly synthesized in liver, and are involved in acute phase reaction. Adipose tissue is a secondary source of the inflammatory cytokines [3] which secrete an additional inflammatory mediators and are considered to be strong predictors of inflammation in cardiovascular events. Recent literature of modern randomized studies showed a contradiction in regard of casual role of CRP in CAD as widely established in larger case-control studies. However, the clear role of CRP in CAD is still under debate and scientists are in the active pursuit of identifying a cause-effect of CRP that may influence the disease pathology.

Several approaches of clinical studies are being used to evaluate the role of inflammatory markers that may predispose individuals to CAD events. Thus, the current review was designed to critically discuss the importance of inflammatory cytokines in CAD pathogenesis. Here, a brief debate has been presented in regards of the transition stage of experimental studies designs in comparison from ethnic populations.

2. Materials and methods

The current study was conducted in Biosciences Department of COMSATS Institute of Information Technology from January- July, 2014. The literature review for the current analysis was collected from the search engine including National Centre for Biotechnology Information, ScienceDirect, and Google search engine. The phrases “coronary artery disease, CRP, case-control studies, randomized control studies, and inflammation were used to search the materials for critical review. The current study was approved from the institutional review board of COMSATS Institute of Information Technology, Islamabad Pakistan.

3. Results and Discussion

CRP is a risk marker of systemic inflammation in response to inflammatory stimuli [4]. Initially, CRP is produced in liver and is regulated by another pro-inflammatory cytokine IL-6, which in turn is regulated by TNF-alpha, and IL-1 [4]. In addition, some studies have reported that arterial tissues can also synthesize CRP [4]. The underlying mechanism of CRP in the pathogenesis of CAD is not well understood [5]. CRP is a risk marker or a risk factor in the development of atherosclerosis is yet controversial [3]. There are two mechanisms which explain the pathogenic role of elevated CRP in coronary atherosclerosis. One could be the ongoing inflammation stimulated by modified ox-LDL which leads to the production of cytokines that might induce acute-phase proteins. Alternatively, traditional risk factors of CAD like aging, smoking, obesity, hypertension, diabetes, and hyperlipidemia can also stimulate the production of acute phase proteins like CRP [3].

In the last two decades, observational studies showed that increased CRP concentrations were also associated with increased concentrations of total cholesterol, TG, HDL-cholesterol, fibrinogen, and glucose [6]. A significant link between high CRP levels and the risk of CAD events has been established in large epidemiological studies which lead to the suggestion that CRP might be a useful risk marker of coronary atherosclerosis [6]. In support of this, Ridker and colleagues in an 8 years follow up study showed that despite elevated baseline markers increased circulating CRP was a strong predictor for the future CAD events [7]. In another 8 years follow up study in women, increased CRP appeared as a strong predictor of MI, coronary revascularization, and ischemic stroke [8]. Consistently, yet another investigation found a significant association between high circulating CRP and initial major CAD events [9].

Despite strong evidence associating inflammation with atherosclerosis, a causal role for inflammatory markers in atherogenesis has remained highly controversial, especially since inflammation is linked with other conditions (i.e., obesity, hypertension, dyslipidemia, diabetes, and smoking) that are known to increase cardiovascular risk. In the observational studies, a significant link of CRP with development of CAD has been contradicted by recent studies based on randomized trials. Mendelian randomization is becoming a commonly used technique to make assessment of causality possible from observational data [10]. This approach has focused on single variants as instruments, but combination of variants into a score represents a potential improvement of the technique. It has recently strengthened the case for a causal role in coronary heart disease of lipoprotein-a [11], and weakened the case of C-reactive protein [12]. Two large new meta-analyses published in the Lancet provide the first strong evidence demonstrating a cause-and-effect relationship between a specific inflammatory protein and the development of coronary heart disease [13-14]. These studies illuminate the role of interleukin-6 receptor (IL6R) by focusing on the common Asp 358Ala variant of the IL6R gene [14]. The variant is known to dampen the inflammatory effect of IL6R. One study, conducted by IL6R Genetics Consortium Emerging Risk Factors Collaboration found that Asp358Ala was present in 39% of the population, and was not significantly related to other risk factors. 358Ala increased concentrations of IL6R and interleukin 6 and decreased concentrations of CRP and fibrinogen. Importantly, each copy of 358Ala was associated with a 3.4% reduction in the risk of CHD [14]. In another study, Interleukin-6 Receptor Mendelian Randomization Analysis (IL6R MR) Consortium performed a Mendelian randomization to analyze the impact on CHD of tocilizumab, an anti-inflammatory monoclonal antibody that blocks IL6R, in patients with rheumatoid arthritis (RA). They found that the effect of the 358Ala variant was similar to the effect of tocilizumab in RA trials and resulted in increased levels of IL-6 and decreased levels of CRP and fibrinogen. The investigators also observed a significant reduction in the risk of CHD in a second analysis of more than 25,000 subjects with CHD and 100,000 controls. They concluded that IL6R signaling appears to “have a causal role in development” of CHD and that “IL6R blockade could provide a novel therapeutic approach to prevention” of CHD [13]. Moreover, studies indicated that genetic variants underlying lipoprotein-a [15] and triglycerides are likely to be causal [16], whereas those in C-reactive protein are not [12].

4. Conclusion

it is unclear whether the inflammatory mediators are casually related to CAD. Previous evidence from observational studies is inconsistent and showed that the association may be biased or confounded. However,

significant advances have been made in the field of molecular genetics related to the role of inflammatory cytokines in the development of CAD. Various SNPs in inflammatory cytokines appear to contribute to the disease pathology. According to the Mendelian randomization approach, the genetic variants in the inflammatory genes may represent good instruments for cytokine levels that are largely free from reverse causation bias and confounding. Recent randomized control studies indicated that some inflammatory mediators have casual effect in the development of CAD. As the research area matures, a consensus for methodology and reporting will be important, particularly when the potentially powerful, but also complex, genetic risk score approach is used. Taken together with adequately powered studies, Mendelian randomization is likely to yield insights that can both guide public health policy and potential therapeutic targets for better treatments of CAD. It would be impressive to replicate the observed cause-and-effect relationship of some inflammatory mediators and pathogenesis of CAD from other ethnic population as most of the randomized studies have been reported from Europe. The current review showed a gap of observations between Europe and Asians, however, these types of larger studies are warranted to elucidate this cause-and-effect from Asian population.

Conflict of interest: none declared

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