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Review

Clinical relevance of high sensitivity C-reactive protein in cardiology

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ABSTRACT

Coping with cardiovascular diseases (CVD), which are of the main causes of death worldwide, has influenced investigation of high sensitivity CRP (hsCRP) and its role in pathogenesis, prognosis and prevention of CVD. hsCRP can be synthesized in vascular endothelium, atherosclerotic plaques, and theory of inflammatory origin of atherosclerosis is being more widely debated, raising questions, whether higher hsCRP plasma concentration might be the cause or the consequence. Summing up controversial data from multiple studies, guidelines recommend hsCRP testing for both, primary (stratifying CVD risk groups, selecting patients for statin therapy) and secondary CVD prevention (prognosis of CVD and its treatment complications, evaluation of treatment efficacy in moderate CVD risk group). hsCRP testing also has role in heart failure, atrial fibrillation, arterial hypertension, valve pathology and prognosis of coronary stent thrombosis or restenosis. Medications (the well-known and the new specific – CRP binding) affecting its concentration are being investigated as well.

1. Introduction

Cardiovascular diseases remain the leading cause of death worldwide [1], making it essential to realize the causes, pathogenesis of these diseases and improve their diagnostic and treatment capabilities as well as prophylactic programs.

Inflammation is thought to be the key mechanism in the pathogenesis of atherosclerosis, from the formation and progression of the plaque till its rupture, and stent restenosis

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[2–5]. The process of inflammation is also significant in development of arterial hypertension, heart failure, valvular disease and atrial fibrillation [6–8].

Since vascular inflammatory changes can hardly be evaluated using cardiac imaging methods, the role of inflammation biomarkers testing in peripheral blood is increasing, with the hsCRP being the most profoundly studied in cardiovascular diseases [1,3]. It remains stable in samples over long periods of time and can be quite simply, rapidly and cheaply tested [1].

Multiple prospective cohort studies have shown the association between increased CRP levels and increased CVD event risk in patients with established disease, and the incidence of first cardiovascular events in individuals at risk for atherosclerosis [9]. It makes hsCRP testing valuable in both, primary and secondary CVD prophylaxis. And for those, who already suffer from CVD, this test is useful in evaluation of disease severity, treatment efficacy and outcome prognosis [1,10,11].

What is more, a number of drugs used in the treatment of CVD reduce serum CRP, therefore possibly contributing to its therapeutic effects [12–14]; the issue is being discussed in the article as well.

1.1. *CRP qualities, detection*

CRP belongs to the pentraxin protein family and is synthesized in hepatocytes and some extrahepatic tissues, such as vascular smooth muscle, atherosclerotic plaques, intracardial tissues [1–3,12]. The idea about CRP being synthesized intracardially is confirmed by measuring CRP concentration gradient in the sinus venosus, peripheral blood and coronary arteries (proximally and distally to the atherosclerotic plaque) after percutaneous angioplasty [3]. There are two CRP types with different qualities: pCRP (pentamer) and mCRP (monomer). mCRP evolves when the pentamer is dissociated and is synthesized by the cells which are activated by the pathological process (tissue necrosis, trauma, infection and related mediators: interleukins IL-1, IL-2, IL-17 and tumor necrosis factor alpha [TNFα]). mCRP has proinflammatory and prothrombotic qualities [12]. Metabolism among the healthy and the diseased does not differ and the rate of synthesis depends on the intensity of pathological process. The half-life is ~19 h and the majority is eliminated through liver. CRP concentration in blood serum in healthy individuals usually does not exceed 10 mg/L (mean 0.8 mg/L) [1,3,12]. If stimulated, synthesis can increase over 1000 times. The concentration doubles every 8 h and reaches its maximum in 36–50 h [1,2,4]. The basal CRP concentration depends on the following factors: patient's age, sex, ethnicity, race, hormonal condition, smoking status, obesity, alcohol consumption, eating habits, infectious agent, duration of the disease, co morbidities, drugs, genetic polymorphism; therefore, the average of two measurements should be used [1,2,12]. Blood plasma concentration is estimated using qualitative, semi-qualitative latex agglutination and quantitative methods (immunoenzyme, immunoluminometric, immunoturbidimetric, nephelometric), the latest being the most popular [1]. CRP values lesser than 0.8 mg/L are hard to accurately access using regular methods that is why a more accurate (less than 0.3 mg/L), cheaper and faster (15–30 min) method has evolved, i.e., high sensitivity CRP, which is used in experimental cardiology [1–3].

1.2. *CRP in CVD pathogenesis*

Inflammation is considered to be an essential factor in atherosclerosis and acute coronary syndromes (ACS) development by stimulating atheroma formation, destabilization of damaged atherosclerotic plaques and formation of occlusive thrombi [3,4].

In case of chronic low-intensity inflammation CRP damages the glycocalyx of vascular endothelium, causing its dysfunction and making it more susceptible to proatherogenic factors [4]. Moreover, the processes of endothelium-dependent vasodilatation, endothelial stem cell migration and adhesion are disturbed and apoptosis is induced [4]. Infiltration of vascular wall with inflammatory cells, neutral lipid deposition in arterial intima is stimulated and macrophages use up plasma low-density lipoproteins (LDL) easier, forming foam cells [1,4,6]. Vascular smooth muscle cells proliferate faster, migrate to the intima and synthesize more extracellular matrix. Inflammatory cells boost up metabolic activity in vascular walls making the medium more acidic, which in turn promotes faster smooth muscle cell apoptosis [1,4,6,15]. By activating the angiotensin-aldosterone system, angiotensin-1 and angiotensin-2 receptors, CRP promotes proatherogenic activity of angiotensin, directly and indirectly stimulates structural and functional modification of arterial walls, heart and vascular remodeling, vascular stiffening, increment of peripheral vascular resistance, interferes with arterial blood pressure (ABP) regulation mechanisms [4]. CRP induces activation of metalloproteinases (MMP) (which cause collagen destruction) in endothelial cells and macrophages and suppresses tissue MMP inhibitors. All of it increases the probability of atherosclerotic plaque remodeling, destabilization and rupture [15]. Prothrombotic status can be described as activation of the complement system, formation of thrombin, release of tissue factor from the endothelium, mononuclear cells and smooth muscle cells; endothelium is covered with more adhesion molecules which then prompt thrombocyte adhesion. Fibrinolysis is diminished, because CRP stimulates plasminogen activator inhibitor-1, which in turn decreases the fibrinolytic abilities of plasminogen activator [1,4,6]. Oxidative stress takes place since CRP stimulates certain vascular cells to synthesize reactive oxygen radicals more rapidly [15]. Vicious circle develops: foam cells create and maintain proinflammatory medium in the subintima layer of atherosclerotic vessels, therefore stimulating cytokine and CRP synthesis and production, whereas CRP itself maintains inflammation by stimulating the release of various cytokines (IL-1, IL-2, TNFα) from macrophages and foam cells and promoting self-production [6]. CRP pathogenesis is depicted in Figure.

However it remains unclear, whether CRP is truly related to vascular damage, since the majority of proof comes from research done in vitro and with animals, where CRP is obtained from *Escherichia coli* and can possibly be polluted with bacterial lipopolysaccharide remains and sodium azide (which is used as a preservative). What is more, the pathogenetic relation between proatherogenic, proinflammatory and prothrombotic effects of CRP and CVD development was not confirmed by