JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Role of C-reactive protein in atherosclerosis

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CATEGORY-Original Article
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Summary

Background

C-reactive protein is one of a group of proteins called acute phase reactants that responded to inflammation .Inflammation can be caused by infection, injury or chronic disease. Cholesterol plaque accumulation in the walls of arteries caused obstruction of blood flow. Epidemiological

Studies have shown that the individuals in which cardiovascular system disease developed had elevated serum C-reactive protein levels.

Methods

1.CRP- ELISA method

2.Total cholesterol-Enzymatic method

Results

The present study specified correlation in CRP,HDL,LDL and TC as compared with control group and ASVD group based on statistical analysis. In control group CRP is >>0.41(0.17)<<& ASVD group is >>0.63(0.28)<<,HDL is >>1.69(0.48)<< in control group &>>1.31(0.36)<< in ASVD group, LDL is >>2.12(0.64)<< in control group &>>2.39(0.77)<< in ASVD group ($p<0.001$),TC is >>3.91(0.54)<< in control group & >>4.55(0.78)<< in ASVD group.

Conclusion

The present study has specified the association between CRP,HDL,LDL and TC signs of early atherosclerosis. CRP levels will rise acutely to elicit a sufficient immune response during infection, inflammation or tissue damage . In recent years, evidence has emerged linking CRP to the development and progression of chronic, auto-inflammatory diseases such as cardiovascular disease.

Abstract

C-reactive protein is a protein made by the liver. CRP is one of a group of proteins called acute phase reactants that responded to inflammation .Inflammation can be caused by infection, injury or chronic disease. Cholesterol plaque accumulation in the walls of arteries caused obstruction of blood flow. Epidemiological studies have shown that the individuals in which cardiovascular system disease developed had elevated serum C-reactive protein levels.

Key words

CRP-C-reactive protein , PC-phosphocholine , SAP-serum amyloid P component ,MACE- major adverse cardiovascular events,APO B- atherogenic apolipoprotein B, CVD-cardiovascular disease,IL- interleukin,MAC-membrane attack complex , HDL-high density lipoprotein ,LDL-low density lipoprotein,TC-total cholesterol, SNP-single nucleotide polymorphisms.

Introduction

C-reactive protein (CRP), named for its ability to bind and precipitate the pneumococcal C-polysaccharide, is the classical acute phase protein. Although it circulates at low concentrations in healthy individuals, its levels increase in response to infections, tissue injury and inflammation [1]. The role of CRP in host defence has been thought to be largely due to its ability to bind phosphocholine (PC), activate the classical complement cascade, and enhance phagocytosis [2-4].The ligand binding characteristics of CRP seem also important in understanding its role in inflammation.In addition to the recognition of microbial antigens, CRP reacts with cells at the sites of tissue injury.

Similarly to serum amyloid P component (SAP), C-reactive protein binds to nuclear antigens, damaged membranes and apoptotic cells, and is involved in the clearance of injured or apoptotic cells, as well as the material released from these damaged cells [4].

Atherosclerosis and its complications, primarily coronary artery disease (CAD) and ischemic stroke, remain the leading causes of mortality and disability worldwide. The incidence of atherosclerotic cardiovascular disease and major adverse cardiovascular events (MACE) increases with age. The probability of the clinical manifestation of atherosclerosis and the development of MACE is determined by the total plaque burden [5]. The total plaque burden is characterized by the concentration and duration of exposure to circulating atherogenic apolipoprotein B (apoB)-containing lipoproteins [6]. As plaque burden increases, the probability of atherosclerotic cardiovascular disease onset increases [5,6].

In normal, healthy individuals, baseline levels of CRP range from 1 to 5 mg/L [7]. During infection, inflammation or tissue damage, CRP levels will rise acutely to elicit a sufficient immune response over a 24–72 h period. Due to this rapid increase in serum levels of CRP, it is routinely measured as a clinical biomarker for infection or inflammation in the healthcare setting. Over recent years, evidence has emerged linking CRP to the development and progression of chronic, auto-inflammatory diseases such as cardiovascular disease [8, 9]. It has been hypothesized that CRP exerts an alternative, pro-inflammatory role in disease development, with in vitro studies demonstrating up-regulation of cell adhesion molecules, activation of endothelial cells,

deposition within atherosclerotic lesions and the increased production of inflammatory cytokines; all common features found in the pathophysiology of cardiovascular disease [7, 10-14]. This evidence has led to the development of a high sensitivity CRP assay which can accurately measure CRP levels <3 mg/L and assess an individual's risk of developing cardiovascular disease [8, 9]. Atherosclerosis is the major cause of cardiovascular disease (CVD) and is an inflammatory disease of the large and medium-sized arteries. Although CVD is uncommon in young individuals, the atherosclerotic process is initiated early in life. Arterial fatty streaks typically evolve over long time and remains asymptomatic through decades [15]. The formation of fatty streaks is associated with endothelial dysfunction and expression of adhesion molecules, followed by elevated vascular inflammation accumulation of lipids, cholesterol and calcium, foam cell formation, obstruction and finally risk for ischemic event [16, 17]. Due to the long-time progression of atherosclerosis development, the need for early biomarkers and identification of risk factors in young population is warranted.

One of the acute-phase reactants, C-reactive protein (CRP), has been pointed out as an important biomarker for atherosclerosis and acute myocardial infarction [18–20]. The CRP protein is involved in the inflammatory response and is activated by the cytokines interleukin (IL)-6 and IL-1β [21]. CRP is a member of the calcium dependent ligand-binding pentraxin family which circulates in plasma and is expressed in atherosclerotic lesions [22–24]. CRP can also activate the complement system and co-localizes with the membrane attack complex (MAC) in atherosclerotic plaques [22–24]. In addition, CRP regulates the expression of adhesion molecules in the endothelium, which suggest that CRP promotes inflammation in the atherosclerotic lesion [25]. In young healthy individuals, CRP levels are generally low. Elevated levels of CRP in the childhood are significantly associated with higher CRP levels in adults [26]. The CRP protein is encoded by the *CRP* gene, which is located on the human chromosome 1q23.2 and consists of two exons separated by one intron [27–29]. Studies have reported that plasma CRP concentration is under genetic control and in twins a heritability of CRP levels of approximately 50% have been observed [30]. Several CRP gene single nucleotide polymorphisms

(SNPs) influence the plasma CRP levels in CVDs and previous studies have aimed to elucidate the role of SNPs in the CRP locus, CRP levels and early signs of atherosclerosis [31–36].

Material and methods

Quantitative estimation of C-Reactive Protein

Principle

The CRP ELISA method is based on the principle of a solid phase enzyme linked immunosorbent assay. The assay system utilizes a unique monoclonal antibody directed against a distinct antigen on the CRP molecule. This mouse monoclonal anti-CRP antibody is used for solid phase immobilization (on the microtiter wells).A goat anti CRP antibody is in the antibody enzyme (horseradish peroxidase) conjugate solution. The test sample is allowed to react simultaneously with the two antibodies. After 45 minutes incubation at room temperature, the wells are washed with water to remove unbound labeled antibodies. A TMB reagent is added and incubated for 20 minutes resulting blue colour.

Quantitative analysis of cholesterol

Principle

Cholesterol is measured enzymatically in serum or plasma in a series of coupled reactions that hydrolyze cholesteryl esters and oxidize the 3-OH group of cholesterol. One of the reaction by products, H_2O_2 is measured quantitatively in a peroxidase catalyzed reaction that produces a colour. Absorbance is measured at 500 nm. The colour intensity is proportional to cholesterol concentration.

Results

Table 1:-

Demographic data

Mean age		Cases	Control
22.8 ± 1.9	Males	45	48
25.6 ± 4.2	Females	55	52
	Yes	80 %	20 %

Hypertensive	No	20 %	80 %
Smokers	Yes	80 %	20 %
	No	20 %	80 %

Table2:-

Subject	No.of patients	CRP (mg/dL)	HDL (mmol/L)	LDL (mmol/L)	TC (mmol/L)	P value
Control	100	0.41 ± 0.17	1.69 ± 0.48	2.12± 0.64	3.91±0.54	p<0.001
ASVD	100	0.63 ± 0.28	1.31 ± 0.36	2.39± 0.77	4.55±0.78	p<0.001

In the present study,control group and study group biochemical parameters included .The baseline measure of the studied groups are represented in table 2. The mean values sharing the significantly at 0.001 level. Both groups include total number of 200 patients. Mean values of CRP, were significantly increased as compared to control group (p<0.001),HDL decreased as compared to control group (p<0.001),LDL increased as compared to control group and TC level increased significantly in ASVD group (p<0.001) as compared to control group.

Discussion

Elevated level in CRP has been suggested as a strong predictor of cardiovascular disease and genetic variations in SNPs in the CRP gene in different studies has been associated

with higher or lower CRP levels [37, 38, 43–47].One of the aim in the present study was to elucidate the relationship between CRP genotype and signs of early atherosclerosis in the Swedish Lifestyle, Biomarkers and Atherosclerosis (LBA) cohort, which consists of young, healthy non-smoking individuals. Elevated cIMT is an indicator of hypertrophy in the intima and media layers of the vessel wall and cIMT is generally considered to be a sensitive and reproducible measurement for the quantification of early atherosclerosis [48].

CRP levels rise manifold in response to infection or tissue damage: from 5–10 mg/L

in mild cases to 320–550 mg/L in the most severe cases [49,50]. However, in atherosclerosisCRP levels are usually below 5 mg/L. A high-sensitivity assay with a threshold of0.28 mg/L was developed to measure CRP

below this level [51]. Large prospective observationalstudies have demonstrated that in surveyed populations, CRP levels were withintertiles of less than 1.0 mg/L, 1–3 mg/L, and more than 3.0 mg/L. In meta-analyses, the odds ratio for MACE between the lower and upper tertiles was between 1.58 and 2.0 [52,53].The PROVE IT-TIMI 22 trial demonstrated that, in patients on aggressive statin therapy, themedian CRP level was 2.0 mg/L. Patients with a CRP level of 2.0 mg/L or more had a 30%higher relative risk of MACE [56]. Similar CRP-level medians and cardiovascular risk ratioswere observed in subsequent large clinical trials of statin therapy [57,58]. Currently, a CRPlevel 2.0 mg/L or more is suggested by the American College of Cardiology/American Heart Association guidelines on cardiovascular disease prevention as a cardiovascular riskfactor [59].The association between the CRP level and MACE rate has been examined in largeobservational studies in postmenopausal women [56], healthy volunteers in the Physicians'Health Study [51], and MRFIT [52]. A meta-analysis of 52 prospective studies that included246,669 individuals without cardiovascular disease showed that increased CRP levelsworsened the 10-year prognosis of cardiovascular risk [53]. In addition, a meta-analysisof the East Asian population showed an association between elevated CRP and highercardiovascular risk [58]. Furthermore, the USPSTF meta-analysis that explored studiespublished from 1966 to 2007 demonstrated that relative cardiovascular risk is 1.58-foldhigher in individuals with a CRP level more than 3.0 mg/L than in those with a CRP levelless than 1.0 mg/L [57]. The problem of mCRP deposition into atherosclerotic plaques has been addressed in several immunohistochemical studies. Herein, we discuss studies of human tissues. mCRP deposits have been detected in atherosclerotic plaques of the aorta [45], carotid [50,51,56], coronary [64,65], and femoral arteries [66], as well as diseased coronary artery venous bypass grafts [67]. Furthermore, mCRP deposits have been found in inflamed humanstriated muscles and infarcted myocardium [51]. CRP colocalized with leukocytes in thromboticmasses. CRP deposits in atheromatous tissues were larger in patients with increasedCRP levels in blood plasma [64].In the present study increased level of CRP effected the levels of HDL,LDL & TC which are the factors investigated in atherosclerosis.

Conclusion

Elevated level of CRP is a strong predictor of cardiovascular disease along with HDL,LDL and TC levels. The present study has specified the association between CRP,HDL,LDL and TC signs of early atherosclerosis. CRP levels will rise acutely to elicit a sufficient immune response during infection, inflammation or tissue damage . In recent years, evidence has emerged linking CRP to the development and progression of chronic, auto-inflammatory diseases such as cardiovascular disease.

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