Review Article

High Sensitivity C-Reactive Protein (hsCRP): A Predictive Inflammatory Biomarker of Vascular Diseases

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Abstract

The role of inflammation in the pathogenesis of atherosclerosis has been firmly established in the past two decades. C-reactive protein (CRP) is an acute phase reactant synthesized mainly by the liver. It is a member of pentraxin family of proteins. Serum CRP levels are elevated in response to acute infections, inflammatory conditions and trauma. CRP is believed to be involved throughout the atherogenic process and is now considered as an ideal biomarker for global cardiovascular disease risk prediction. Recent advancement suggests that high sensitivity CRP (hsCRP) has more accurate value than conventional CRP. Numerous studies have shown an association of CRP with incidental hypertension, metabolic syndrome, coronary artery disease, acute coronary syndrome, peripheral artery disease, stroke and recurrent coronary and cerebrovascular events.

Keywords: Serum hsCRP, Inflammation, Cardiovascular diseases

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Introduction

Despite substantial differences in ethnicities, habits and cultures, the prevalence of cardiovascular risk factors and atherosclerosis remains the major cause of death in developing and developed countries[1,2]. The traditional Framingham risk factors (dyslipidemia, blood pressure, diabetes, obesity and cigarette smoking) have been used as the starting point for evaluating individual risk to vascular disease and each factor is strongly associated with increased risk to cardiovascular disease (CVD) in adults and in children, associated with family history of CVD[1-4]. It has been estimated that the traditional CVD risk factors may explain about 50% of CVD morbidity and mortality[4], eliciting efforts to identify additional predictive factors like C-reactive protein (CRP)[5].

CRP was first discovered in 1930 by William Tillet and Thomas Francis at the Rockefeller Institute for Medical Research in New York[6]. Blood samples from the patients of acute Streptococcus Pneumonie infection found that the sera of these patients formed a precipitin with an extract from the streptococcal bacterium. The extract was originally labelled Fraction C and was later confirmed as a polysaccharide. As a result of its reactivity with the C polysaccharide of the Streptococcus cell wall, the 'substance' in the sera was named CRP[6,7]. A decade later, Oswald Avery and Maclyn McCarty with their research team described CRP as an 'acute-phase reactant' that was increased in serum of patients suffering from a spectrum of inflammatory stimuli and inflammation[8-10].

Results of recent studies suggest that, CRP also directly participates in the pathogenesis of CVD[11]. In addition, increased CRP is associated with multiple risk factors for CVD, including obesity, insulin resistance and hypertension and has demonstrated significant predictive value for risk of metabolic syndrome[12]. In apparently healthy individual's plasma CRP concentrations are widely distributed, reflecting substantial inter-individual variability driven by multiple environmental, sociodemographic, behavioral and lifestyle factors[13-14].

Structure of CRP

CRP is a 206-amino acid member of the short pentraxin family, alongside serum amyloid P component (SAP), with high phylogenetic conservation[15]. Pentraxins share a characteristic structure: five identical non-glycosylated globular subunits - each of which is constituted by two β-pleated sheets - which are noncovalently associated and arranged in a symmetric cyclic pattern around a central pore, determining a pentameric, discoidal and flattened configuration[16]. The molecular weight of CRP is 115 kDa. Each CRP protomer has the flattened beta-jellyroll lectin fold and bears on one

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face, the B or binding face, a pocket which contains two calcium ions bound just 4 A° apart by coordination with protein carboxylate and amide side chains derived from loops that congregate on one face of the protomer core. These calcium atoms are essential for all physiological ligand binding by CRP and also markedly stabilize both the structure of the protomer and the integrity of the native pentamer[17]. Although CRP is secreted by hepatocytes in the form of pentameric molecules (p CRP), it is susceptible to modifications both in vitro and in vivo. In vitro, while stored under non-physiological conditions such as in the absence of calcium, the monomers in CRP are slowly dissociated by a nonproteolytic and irreversible process and release the monomeric form of CRP (m CRP)[18,19]. In the absence of calcium, both pCRP and mCRP are susceptible to proteolytic degradation[20]. mCRP is associated with enhanced complement fixation. This molecule rapidly detaches from cell membrane and finally dissociates in solution of m CRPs, the final and most important form of m CRP. This second stage is associated with more powerful atherogenic properties[21,22].

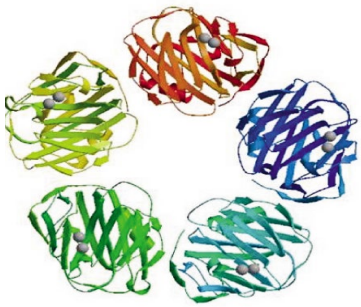

Figure-1: Molecular structure and morphology of human CRP[17]

Synthesis of CRP

CRP is predominantly synthesized in the liver with the gene location on chromosome 1q23.2, typically within the transcriptional phase of the response to proinflammatory cytokines[23]. IL-6 appears to be the main regulator, by promoting de novo synthesis of CRP via upregulation of C/EBPβ and C/EBPδ, key transcription factors in this process[24]. In addition, IL-6 signaling may be reinforced by IL-1β and TNF, both of which increase transcription rate of CRP[25].

Following synthesis and release into circulation, serum CRP level tends to increase significantly 6-8 hours after initial stimulation, peaking at 24-48 hours, with a half-life of approximately 19 hours. CRP concentration in circulation is primarily determined by its synthesis rate[26]. Although the liver is the main site for production and release of CRP, its mRNA also has been found in extrahepatic sites, including adipose tissue[27], lungs[28], epithelial cells of renal cortical tubules[29], lymphocytes and atherosclerotic lesions in both macrophages and smooth muscle cells[30,31].

High Sensitivity C-Reactive Protein (hsCRP)

Although, CRP is an efficient marker for inflammation, it is not detectable at a very low level (<3 mg/L) by routine lab methods. However, recent high-sensitivity assay techniques such as immunonephelometric, immunoturbidimetry, high-sensitivity enzyme-linked immunosorbent assay (ELISA) and resonant acoustic profiling (RAP) techniques can detect hsCRP at a level lower than 3 mg/L and so are more important for detection of the pro-inflammatory state at the earliest[32]. The hsCRP is more precise than standard CRP when measuring baseline concentrations. The American Heart Association and U.S. Centers for Disease Control and Prevention have defined risk groups as follows low: hsCRP level under 1.0 mg/L, average: between 1.0 and 3.0 mg/L and high: above 3.0 mg/L[33]. These high-sensitivity assays help to quantify low grades of systemic inflammation in the absence of overt systemic inflammatory or immunologic disorders & thus helps to predict a person's risk of developing CVDs. The hsCRP assays have been standardized across several commercial platforms and can be accurately measured from fresh plasma or frozen plasma[34].

CRP as an Independent Risk Factor for CVD

A number of large, prospective epidemiologic studies have indicated that CRP is a strong independent predictor of future cardiovascular events including myocardial infarction, ischemic stroke, peripheral vascular disease and sudden cardiac death among individuals without known CVD[35,36]. The association between elevated CRP and future CVD events has generally been consistent among these studies[35-37].

For example, in a cohort of 1086 apparently healthy middle-aged men in the dataset of the Physicians' Health Study, subjects with baseline levels of CRP that were in the highest quartile, had a twofold increase in risk of ischemic stroke or peripheral vascular disease (p=0.02) and a threefold increase in risk of myocardial infarction (p=0.001), relative to subjects in the lowest quartile. These effects were independent of other cardiovascular risk factors, including lipid levels and tobacco use[38].

The Honolulu Heart Program analyzed frozen serum samples to assess the relationship of CRP to the development of myocardial infarction in clinically healthy men over a follow-up period of 20 years. Overall, CRP levels in this study were associated with coronary events that occurred as many as 15 years later. As early as five years follow-up, the risk of myocardial infarction grew with increasing CRP levels[39].

At 10 to 15 years follow-up, the relative odds of myocardial infarction in the highest CRP quartile were 2.1 times that of the lowest quartile, after adjustment for risk factors such as total cholesterol, hypertension and type 2 diabetes mellitus (p=0.016). The strongest correlation between CRP and risk of myocardial infarction occurred among those men without other risk factors[39].

Nested case-control analyses of 1,21,700 women in the Nurses' Health Study and 51,529 men in the Health Professionals Follow-up study recently supported the results of the Women's Health Study, finding that CRP is a predictor of chronic heart diseases (CHD) that is independent of other cardiovascular risk factors[40].

Providing additional support for the predictive value of CRP, the Cardiovascular Health Study evaluated protein levels in an elderly population without a history of vascular disease. In this study of 3,971 men and women aged 65 years or older, a single instance of elevated CRP levels was associated with an increased 10-year risk of CHD beyond traditional risk factors, especially in moderate high-risk men and in high-risk women[41].

Elevated CRP have been shown to be a strong predictor of future cardiovascular risk in patients with established CHD with or without a previous myocardial infarction. In the Scandinavian Simvastatin Survival Study, elevated CRP levels predicted mortality in patients with stable ischemic heart disease[42]. Furthermore, Blake and Ridker have shown that elevated CRP can predict risk of cardiovascular events (including death, acute myocardial infarction and need for revascularization procedures) in patients with acute coronary syndromes (ACS)[43].

The Role of CRP in the Pathophysiology of Atherosclerosis

Inflammatory mechanisms play a central role in all phases of atherosclerosis, from the initial recruitment of circulating leukocytes to the arterial wall to the rupture of unstable plaques, which results in the clinical manifestations of the disease. CRP plays a pivotal role in atherogenesis by the following processes:

i. Complement activation: Activation of the classical pathway of the complement system is a well-known and direct biological function of CRP. Via this action, CRP directly amplifies and facilitates innate immunity, a process that has already been associated with initiation and progression of CVD for a long time[44].

ii. Interaction with cell surface receptors: CRP binds to several receptors on human monocytes; to FcRγIIa (CD32) with high affinity and to FcRγI (CD64) with lower affinity increasing phagocytosis and the release of inflammatory cytokines[45].

iii. Thrombosis: Direct actions of CRP contribute to the induction of a prothrombotic state that may enhance the procoagulant activity or reduce fibrinolysis[46].

iv. Cellular modulation, recruitment and activation: CRP may be a direct regulator of endothelial cell activation and dysfunction, by inducing the expression of intracellular adhesion molecules, vascular E-selectin and monocyte chemoattractant protein-1 (MCP-1)[47].

v. Nitric oxide (NO) synthesis: CRP may interfere with NO synthesis by inhibiting endothelial nitric oxide synthase (eNOS) activity through various pathways & all of which ultimately lead to endothelial dysfunction[48].

vi. Apoptosis: CRP is directly involved in the process of apoptosis. Apoptosis of vascular smooth muscle cells (SMC) also plays an important role in progression of atherosclerotic lesions and contributes to increased plaque vulnerability[48].

vii. Activation of metalloproteinases: CRP to augment expression of metalloproteinase-1 (MMP-1) and metalloproteinases 1, 2 and 9 responsible for remodeling the extracellular matrix (ECM)[49].

CRP and Ischemic Stroke

Stroke is an important cause of morbidity and mortality. Development of stroke is the result of longstanding vascular inflammation, plaque rupture, thrombosis and subsequent brain ischemia or infarction. Among the several markers of inflammation, serum CRP is of particular importance. Several previously published studies found an association between high serum CRP level and development of stroke[50,51].

In a prospective longitudinal study on 10456 healthy men by Jimenez et al, baseline serum hsCRP>3 mg/L was associated with increased risk of incident stroke by 40% as compared with hsCRP<1 mg/l over a 15-year follow-up period. The risk was greater in hypertensive rather than normotensive men[50]. The results of a systematic review of 12 prospective observational studies revealed an independent association of baseline CRP with excessive risk of ischemic stroke but not hemorrhagic stroke[51].

CRP and Metabolic Syndrome

Recent evidence suggests that CRP plays a major role in the physiologic processes associated with the metabolic syndrome. High levels of CRP have been shown to be an independent predictor of

cardiovascular risk for all degrees of severity of the metabolic syndrome[52]. Furthermore, elevated CRP has been correlated with abdominal obesity in men with atherogenic dyslipidemia, an important clinical characteristic of the metabolic syndrome[53]. In a study by Sridevi D found that, the CRP levels are elevated in Type 2 diabetic patients with the metabolic syndrome and hence, CRP is added as a diagnostic criterion for metabolic syndrome[54].

CRP and Hypertension

Hypertension is an important worldwide public-health challenge because of its high frequency and concomitant risks of cardiovascular and kidney disease[55]. Many recent studies showed correlation between hypertension and inflammation. New proof indicates that vascular inflammation may have a role in the initiation and/or development of hypertension[43]. This is evident from the elevated levels of inflammatory markers like Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6) and C-Reactive Protein (CRP) found in people with hypertension[56]. CRP increases the blood pressure by several mechanisms. It decreases the production of nitric oxide by endothelial cells, so indirectly inhibits vasodilatation. On the other hand, it increases leukocyte adhesion, platelet activation, oxidation and thrombosis. CRP upregulates the angiotensin type-I receptor so mediates the angiotensin-II mediated increase in blood pressure[57]. All these facts indicate that, CRP has a role in development of hypertension. Ki Chul Sung and Workers found hsCRP to be an independent risk factor for development of hypertension among Korean population[58].

CRP and Type 2 diabetes mellitus (DM)

Diabetes is a disease with chronic low-grade inflammation. Different studies have shown that inflammatory markers in blood like CRP, IL-6, Plasminogen activator inhibitor-1 (PAI-1) and fibrinogen are elevated significantly in diabetic population[59]. Twelve recent meta-analysis including 18 prospective studies demonstrated that high baseline CRP levels are associated with insulin resistance, higher HbA1c levels and future type 2 DM[60].

Gohel MG and Chacko AN in their study showed statistically significant increase in concentration of hsCRP in type 2 DM compared to healthy persons[61]. Amanullah S in his study showed significant increase of CRP in subjects with type 2 DM[62]. There may also have a significant relationship between CRP and complications of Type 2 diabetes mellitus through the acute phase response[63].

Conclusion

It is now an established fact that elevated CRP levels are associated with a worse prognosis for vascular events like myocardial infarction, stroke & unstable angina. Moreover, many epidemiological studies have shown a positive association between CRP and cardiovascular risk. So, conventional CRP or recent advance hsCRP may be considered as a potential adjunct for global risk assessment in the primary prevention of vascular disease.

Conflict of Interest

The authors declare to have no conflicts of interest.

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References

1. Kuller LH. Cardiovascular disease is preventable among women. Expert Rev Cardiovasc Ther. 2010; 8 (2): 175-87.
2. Stamler J, Neaton JD, Wentworth DN. Blood pressure (systolic and diastolic) and risk of fatal coronary heart disease. Hypertension. 1989; 13 (5): 1-12.
3. Lamon-Fava S, Wilson PW, Schaefer EJ. Impact of body mass index on coronary heart disease risk factors in men and women. The Framingham Offspring Study. Arterioscler Thromb Vasc Biol. 1996; 16 (12): 1509-15.
4. Wei M, Mitchell BD, Haffner SM, Stern MP. Effects of cigarette smoking, diabetes, high cholesterol, and hypertension on all-cause mortality and cardiovascular disease mortality in Mexican Americans. The San Antonio Heart Study. Am J Epidemiol. 1996; 144 (11): 1058-65.
5. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet. 2009; 373 (9670): 1175-82.
6. Tillett WS, Francis T. Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. J Exp Med. 1930; 52(4): 561-71.
7. Clyne B, Olshaker JS. The C-reactive protein. J Emerg Med. 1999; 17 (6): 1019-25.
8. Abernathy TJ, Avery OT. The occurrence during acute infections of a protein not normally present in the blood: I. Distribution of the reactive protein in patient's serum and the effect of calcium on the flocculation reaction with C polysaccharide of pneumococcus. J Exp Med. 1941; 73 (2): 173-82.
9. Macleod CM, Avery OT. The occurrence during acute infections of a protein not normally present in the blood: II. Isolation and properties of the reactive protein. J Exp Med. 1941; 73 (2): 183-90.
10. Stancel N, Chen CC, Ke LY, Chu CS, Lu J, Sawamura T, et al. Interplay between CRP, atherogenic LDL and LOX-1 and its potential role in the pathogenesis of atherosclerosis. Clin Chem. 2016; 62 (2): 320-7.

11. Paul A, Ko KW, Li L, Yechoor V, McCrory MA, Szalai AJ, et al. C-reactive protein accelerates the progression of atherosclerosis in apolipoprotein E-deficient mice. Circulation. 2004; 109 (5): 647-55.
12. Haffner SM. The metabolic syndrome: inflammation, diabetes mellitus and cardiovascular disease. Am J Cardiol. 2006; 97 (2A): 3A-11A.
13. Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation. 2001; 103 (13): 1813-8.
14. de Maat MP, Kluft C. Determinants of C-reactive protein concentration in blood. Ital Heart J. 2001; 2 (3): 189-95.
15. Mantovani A, Garlanda C, Doni A, Bottazzi B. Pentraxins in innate immunity: From C-reactive protein to the long pentraxin PTX3. J Clin Immunol. 2008; 28 (1): 1-13.
16. Thompson D, Pepys MB, Wood SP. The physiological structure of human C-reactive protein and its complex with phosphocholine. Structure. 1999; 7 (2): 169-77.
17. Casas JP, Shah T, Hingorani AD, Danesh J, Pepys MB. C-reactive protein and coronary heart disease: a critical review. J Int Med. 2008; 264 (4): 295-314.
18. Taylor KE, van den Berg CW. Structural and functional comparison of native pentameric, denatured monomeric and biotinylated C-reactive protein. Immunology. 2007; 120 (3): 404-11.
19. Schwedler SB, Filep JG, Galle J, Wanner C, Potempa LA. C-reactive protein: a family of proteins to regulate cardiovascular function. Am J Kidney Dis. 2006; 47 (2): 212-22.
20. Boncler M, Watała C. Regulation of cell function by isoforms of C-reactive protein: a comparative analysis. Acta Biochim Pol. 2009; 56 (1): 17-31.
21. Suresh MV, Singh SK, Agrawal A. Interaction of calcium-bound C-reactive protein with fibronectin is controlled by pH: in vivo implications. J Biol Chem. 2004; 279 (50): 52552-7.
22. Ji SR, Wu Y, Potempa LA, Liang YH, Zhao J. Effect of modified C-reactive protein on complement activation: a possible complement regulatory role of modified or monomeric C-reactive protein in atherosclerotic lesions. Arterioscler Thromb Vasc Biol. 2006; 26 (4): 935-41.
23. Álvarez FDCH, González AP, Ravelo Dopico RR, Grek OG. Proteína C reactiva y enfermedad arterial coronaria. Rev Cubana Cardiol. Cir Cardiovasc. 2011; 17 (1): 69-80.
24. Black S, Kushner I, Samols D. C-reactive Protein. J Biol Chem. 2004; 279 (47): 48487-90.
25. Nanri A, Moore MA, Kono S. Impact of C-reactive protein on disease risk and its relation to dietary factors. Asian Pac J Cancer Prev. 2007; 8 (2): 167-77.
26. Trujillo ME, Scherer PE. Adipose tissue-derived factors: impact on health and disease. Endocr Rev. 2006; 27 (7): 762-78.
27. Semple SJ. C-reactive protein - biological functions, cardiovascular disease and physical exercise. SAJSM. 2006; 18 (1): 24-8.
28. Agassandian M, Shurin GV, Ma Y, Shurin MR. C-reactive protein and lung diseases. Int J Biochem Cell Biol. 2014; 53: 77-88.
29. Jabs WJ, Lögering BA, Gerke P, Kreft B, Wolber EM, Klinger MH, et al. The kidney as a second site of human C-reactive protein formation in vivo. Eur J Immunol. 2003; 33 (1): 152-61.
30. Devaraj S, Torok N, Dasu MR, Samols D, Jialal I. Adiponectin decreases C-reactive protein synthesis and secretion from endothelial cells: evidence for an adipose tissue-vascular loop. Arterioscler Thromb Vasc Biol. 2008; 28 (7): 1368-74.
31. Calabro P, Willerson JT, Yeh ETH. Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells. Circulation. 2003; 108 (16): 1930-2.
32. Roberts WL. CDC/AHA Workshop on markers of inflammation and cardiovascular disease: Application to clinical and public health practice: laboratory tests available to assess inflammation--performance and standardization: a background paper. Circulation. 2004; 110 (25): e572-6.
33. Zangana SN. The relation of serum high-sensitive C-reactive protein to serum lipid profile, vitamin D and other variables in a group of hypertensive patients in Erbil-Iraq. IJSR. 2016; 5 (9): 444-8.
34. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation. 2003; 107 (3): 363-9.
35. Badiger RH, Dinesha V, Hosalli A, Ashwin SP. hsC-Reactive Protein as an indicator for prognosis in acute myocardial infarction. J Sci Soc. 2014; 41 (2): 118-21.
36. Lagrand WK, Visser CA, Hermens WT, Niessen HW, Verheugt FW, Wolbink GJ, et al. C-reactive protein as a cardiovascular risk factor: more than an epiphenomenon? Circulation. 1999; 100 (1): 96-102.
37. Ridker PM, Bassuk SS, Toth PP. C-reactive protein and risk of cardiovascular disease: Evidence and clinicial application. Curr Atheroscler Rep. 2003; 5 (5): 341-9.
38. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997; 336 (14): 973-9.
39. Sakkinen P, Abbott RD, Curb JD, Rodriguez BL, Yano K, Tracy RP. C reactive protein and myocardial infarction. J Clin Epidemiol. 2002; 55 (5): 445-51.
40. Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K et al. Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med. 2004; 351 (25): 2599-610.
41. Cushman M, Arnold AM, Psaty BM, Manolio TA, Kuller LH, Burke GL, et al. C-reactive protein and the 10-year incidence of coronary heart disease in older men and women. Circulation. 2005; 112 (1): 25-31.

42. Crea F, Monaco C, Lanza GA, Maggi E, Ginnetti F, Cianflone D, et al. Inflammatory predictors of mortality in the Scandinavian Simvastatin Survival Study. Clin Cardiol. 2002; 25 (10): 461-6.
43. Blake GJ, Ridker PM. C-reactive protein and other inflammatory risk markers in acute coronary syndromes. J Am Coll Cardiol. 2003; 41 (4 Suppl S): 37S-42S.
44. Torzewski J, Torzewski M, Bowyer DE, Fröhlich M, Koenig W, Waltenberger J, et al. C-reactive protein frequently colocalizes with the terminal complement complex in the intima of early atherosclerotic lesions of human coronary arteries. Arterioscler Thromb Vasc Biol. 1998; 18 (9): 1386-92.
45. Crowell RE, Du Clos TW, Montoya G, Heaphy E, Mold C. C-reactive protein receptors on the human monocytic cell line U-937. Evidence for additional binding to Fc gamma RI. J Immunol. 1991; 147 (10): 3445-51.
46. Penn MS, Topol EJ. Tissue factor-the emerging link between inflammation, thrombosis and vascular remodeling. Circ Res. 2001; 89 (1): 1-2.
47. Hattori Y, Matsumura M, Kasai K. Vascular smooth muscle cell activation by C-reactive protein. Cardiovasc Res. 2003; 58 (1): 186-95.
48. Jialal I, Verma S, Devaraj S. Inhibition of endothelial nitric oxide synthase by C-reactive protein: Clinical relevance. Clin Chem. 2009; 55 (2): 206-8.
49. Doronzo G, Russo I, Mattiello L, Trovati M, Anfossi G. C-reactive protein increases matrix metalloproteinase-2 expression and activity in cultured human vascular smooth muscle cells. J Laborat Clin Med. 2005; 146 (5): 287-98.
50. Ahmadi-Ahangar A. Predictive ability of C-reactive protein for stroke. Caspian J Intern Med. 2016; 7 (3): 151-2.
51. Zhou Y, Han W, Gong D, Man C, Fan Y. Hs-CRP in stroke: A meta-analysis. Clin Chim Acta. 2016; 453: 21-7.
52. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. Circulation. 2003; 107 (3): 391-7.
53. Lemieux I, Pascot A, Prud'homme D, Alméras N, Bogaty P, Nadeau A, et al. Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. Arterioscler Thromb Vasc Biol. 2001; 21 (6): 961-7.
54. Devaraj S, Singh U, Jialal I. Human C-reactive protein and the metabolic syndrome. Curr Opin Lipidol. 2009; 20 (3): 182-9.
55. Whelton PK. Epidemiology of hypertension. Lancet. 1994; 344 (8915): 101-6.
56. Pauleto P, Rattazzi M. Inflammation and Hypertension: the search for a link. Nephrol Dial Transplant. 2006; 21 (4): 850-3.
57. Devaraj S, Xu DY, Jialal I. C-reactive protein increases plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells; implications for the metabolic syndrome and atherothrombosis. Circulation. 2003; 107 (3): 398-404.
58. Sung KC, Suh JY, Kim BS, Kang JH, Kim H, Lee MH, et al. High sensitivity C-reactive protein as an independent risk factor for essential hypertension. Am J Hypertens. 2003; 16 (6): 429-33.
59. Kimberly MM, Cooper GR, Myers GL. An overview of inflammatory markers in type 2 diabetes from the perspective of the clinical chemist. Diabetes Technol Ther. 2006; 8 (1): 37-44.
60. Wang X, Bao W, Liu J, Ouyang YY, Wang D, Rong S, et al. Inflammatory markers and risk of type 2 diabetes: A systematic review and meta-analysis. Diabetes Care. 2013; 36 (1): 166-75.
61. Gohel MG, Chacko AN. Serum GGT activity and hsCRP level in patients with type 2 diabetes mellitus with good and poor glycemic control: An evidence linking oxidative stress, inflammation and glycemic control. J Diabetes Metab Disord. 2013; 12 (1): 56.
62. Amanullah S, Jarari A, Govindan M, Basha MI, Khatheeja S. Association of hsCRP with diabetic and non-diabetic individuals. JJBS. 2010; 3 (1): 7-12.
63. Kang ES, Kim HJ, Ahn CW, Park CW, Cha BS, Lim SK et al. Relationship of serum high sensitivity C-reactive protein to metabolic syndrome and microvascular complications in type 2 diabetes. Diabetes Res Clin Pract. 2005; 69 (2): 151-9.

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