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Derleme Makalesi

C-Reaktif Proteinin Kardiyovasküler Hastalıklarla İlişkisi

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Ö Z E T

C reaktif protein akut faz proteini olup, enflamasyon olayları sırasında karaciğerden salınımı uyarılır. Enfeksiyonların teşhisinde ve hastalığın seyrinin takibinde uzun zamandır kullanılmaktadır. Kardiyovasküler sistem ve enflamasyon arasındaki ilişkinin gösterilmesi enflamatuvar belirteçlerin önemini artırmıştır. CRP düzeyinin bakteriyel, viral enfeksiyonlar ve romatizmal hastalıkların yanısıra ateroskleroz gibi kardiyovasküler olaylarda da artığı görülmüştür. CRP düzeylerinin saptanmasıyla hastalığın takibi sağlanabilir ve sağlıklı bireyler için kardiyovasküler hastalık riski önceden saptanabilir. Yapılan pek çok çalışmada, aterosklerozlu, myokard enfarktüslü, aritmili, diabetes mellituslu ve hipertansiyonlu hastalarda CRP düzeylerinde anlamlı artış bulunmuştur. Kardiyovasküler hastalıklarla CRP arasındaki ilişkinin altında yatan mekanizmaların anlaşılması için daha fazla çalışmaya ihtiyaç vardır.

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Review Article

An Association Between C-reactive Protein and Cardiovascular Diseases

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A B S T R A C T

C reactive protein is an acute phase protein and is known to be stimulated by liver during inflammatory processes. It has been in use for the diagnosis of infections and for monitoring the course of a disease for a long period of time. The demonstration of a relationship between cardiovascular system and inflammation enhanced the importance of inflammatory markers. Besides bacterial infections, viral infections and rheumatic diseases, CRP levels were also found to be elevated in cardiovascular events such as atherosclerosis. By detecting CRP levels, disease monitoring can be achieved and the risk of cardiovascular diseases for healthy individuals can be determined beforehand. In several studies performed, CRP levels were found significantly high in patients with atherosclerosis, myocardial infarction, arrhythmia, diabetes mellitus and hypertension. More studies are needed to be performed to understand the mechanisms lying between cardiovascular diseases and CRP.

1. Introduction

Cardiovascular diseases (CVD) are the most common causes of death worldwide. Although the average life span was around 46 years in 1950s, in 2000s it is 70 years of age (1,2). The prolongation of life period elevated the incidence of cardiovascular diseases. This caused by an increase in the awareness of cardiovascular diseases which then resulted in a progress in treatment methods. In most European countries, a decrease in the cardiovascular mortality rates has been displayed, even though this did not change the idea that it is the most vital cause of death (3).

In Turkey, a study known as "TEKHARF" (Turkish Adult Risk Factor Study) has involved cardiovascular patients between the ages of 45-74. After 12 years of follow-up period, death rates related to cardiovascular diseases were found to be 3.84 in thousand for women and 7.64 in thousand for men. These incidence rates were found to be the highest among all other European countries (4).

It is important not only to develop new strategies for treatment but also to determine risk factors for CVD and to prevent the progress of these factors.

Several risk factors have been defined for CVD by several researchers. Among all these risk factors, atherosclerosis, an inflammation induced mechanism, is found to be a remarkable cause of CVD (5). This review aims to present a relationship between the cardiovascular diseases and C reactive protein (CRP), an inflammation marker.

Cardiovascular Diseases

CVD involve several vascular system diseases such as coronary heart disease, stroke and aortic aneurysm. Typical risk factors for cardiovascular diseases are known as age, sex, genetics, smoking habits, abdominal obesity, dyslipidemia, hypertension, diabetes mellitus, lack of physical activity and unhealthy diet. All these factors are usually found to be together in most patients. Therefore, it is hard to evaluate each factor separately (6). A study known as "Nurses' Health Study" demonstrated an 84% decrease in the rate of incidence in cardiovascular heart diseases in women who ate healthy food, exercised regularly, stopped smoking and had ideal weights (7).

Cardiovascular Risk Factors

Smoking

The daily consumption rates of cigarette have a high influence on hazardous effects of smoking on CVD. A synergistic effect of smoking on the risk of cardiovascular diseases have been previously displayed (8). Passive smoking were also found to elevate the risk of coronary heart disease (9). A period of 10 years were suggested to be necessary for people to reach the same risk level as nonsmokers in terms of CVD (10).

Dyslipidemia

An elevation in LDL cholesterol levels causes an important increase in cardiovascular morbidity and mortality risks. LDL levels can be reduced by healthy diet and an increase in physical activities. In necessary cases, drug usage may help to reduce LDL cholesterol levels. Statins are the most common drugs that have been in use for this purpose. In a study named as "Heart Protection Study" vitamins were used as a placebo and found to reduce the risk of CVD mildly, whereas statins caused a significant decrease (11). Anti-inflammatory and antithrombotic effects of statins also help to reduce the coronary events. In patients who were treated with statins, CRP levels were found to be reduced (12, 13).

Diet

Eating habits have an important role on LDL-cholesterol levels. While the consumption of saturated fat increases LDL/HDL ratio and increases the risk of CVD, the consumption of unsaturated fat increases only HDL levels and reduces both LDL and total cholesterol levels and presents a protective role on CV system (14). According to "Nurses' Health Study" reveals a reduction in cardiovascular risk by taking unsaturated fats (15).

Physical Activity Rate

Inactive life style has been accepted as one of the risk factors that causes an elevation in CVDs. A physical activity performed 4-5 days a week for minimum 30 minutes helps cardiovascular system to act properly. Regular exercise lowers LDL-cholesterol and triglyceride levels. It also helps to lose weight for individuals who are under the risk of CVDs due to overweight (16).

Diabetes Mellitus

Diabetes Mellitus (DM) increases CV morbidity rates 2 to 3 times more as it is an independent risk factor for atherosclerosis (17). Atherosclerosis is an inflammatory disease and has been reported that DM induces the formation of inflammation (18). This is due to hyperglycemia that causes oxidative stress which then damages vascular endothelial cells. An enhancement in endothelin-1 levels destroys vessel permeability and therefore, proinflammatory substances such as leukocytes, pass through the vessels. Their accumulation causes the formation of atherosclerotic plaques. CRP has been considered as an independent marker for type 2 diabetes (19, 20). A significantly higher CRP levels were detected in healthy women who are non-smokers and non-diabetic, but having a family history of DM (21).

High Blood Pressure

Arterial blood pressure is normal at a level of 130/85 mmHg. Hypertension occurs in cases with higher levels of blood pressure. It is a vital risk factor for CVDs as it causes stroke, heart failure, kidney failure and peripheral vascular system dysfunctions (22, 23).

In Framingham Heart Study, it was reported that the risk of people with high blood pressure (130-139/85-89 mmHg) are twice more than that of ones with normal levels of blood pressure (120/80 mmHg) for CVDs (24). In a study performed by Jimenez et al., total stroke risk was found to be significantly higher among hypertensive men with elevated hsCRP compared with normotensive men with low hsCRP (25).

Homocysteinemia

Homocysteinemia results from an inherited metabolic defect that leads to very high levels of the homocysteine produced via demethylation of dietary methionine, which is abundant in animal protein. Hyperhomocysteinemia may arise from genetic defects of enzymes involved in homocysteine metabolism. The enzymes involved are 5, 10-methylene tetrahydrofolate reductase (MTHFR), methionine synthase, and cystathionine-β-synthase. Hyperhomocysteinemia can also arise from nutritional deficiencies of folate (vitamin B9), vitamin B6, and vitamin B12 that are the coenzymes used in homocysteine metabolism (26).

Homocysteine can mediate the formation of cardiovascular disease by several different mechanisms such as its adverse effects on smooth muscle cells and vascular endothelium which results in alterations in subclinical arterial structure and function. Some of the possible mechanisms of these effects include an increase in oxidative damage, proliferation of vascular smooth muscle cells, endothelial dysfunction, an increase in the synthesis of collagen and deterioration of arterial wall elastic material. Examination of the effect of homocysteine on CRP, revealed that homocysteine significantly induced mRNA and protein expressions of CRP in vascular smooth muscle cells (VSMCs). This study demonstrated that homocysteine is capable of initiating an inflammatory response in vascular smooth muscle cells. The effect of homocysteine is produced by stimulating CRP production, which is mediated through NMDAr-ROS-ERK1/2/p38-NF-κB signal pathway. These findings provided new evidence for a role of homocysteine in pathogenesis of atherosclerosis (27).

C-Reactive Protein (CRP)

CRP is structured by five protomers non-covalently bound to each other, placed around the nucleus and has a molecular weight of 118 kDa. The molecule is named as CRP as it was found to be entrapped to the C polysaccharide of pneumococcus species. CRP is an acute phase protein and its level increases during inflammatory events and tissue damage. Therefore, CRP can be used as a marker for the diagnosis and follow-up of inflammatory diseases (28).

CRP has two major roles: Increasing phagocytosis and prompting the classical complement cascade (29-32). CRP can form a complex structure by binding capsular polysaccharides, phosphatidylcholine, apoptotic cells and fibronectin via calcium. This complex structure prompts the classical complement cascade (33, 34).

The stimulation of proinflammatory cytokines such as Interleukin-6 (IL-6), Interleukin-1 Beta (IL-1β) and tumor necrosis factor alpha (TNFα) enhances CRP release from the liver. CRP release causes the enhancement of monocytes, activation of endothelial cells, elevation of tissue factor and TNF and the release of adhesion molecules then the atherosclerosis occurs. CRP can also be produced in the heart, kidney, adipocytes, arteries and atherosclerotic plaques (35). Therefore, CRP has been considered as not only an inflammatory marker, but also, a determinant risk factor for cardiovascular diseases.

Factors Increasing CRP Levels

CRP is synthesized by the liver and its half-life is eighteen hours. Its elimination time is independent from its dose. Therefore, its rate of synthesis detects the concentration of CRP in the circulatory system (36). As well as inflammatory events, factors which cause tissue damage also elevate CRP levels. It has been reported that smoking enhances CRP levels (37, 38).

Another crucial factor is body mass index (BMI). Obesity occurs when BMI is over 30 kg/m2 (39). A positive association was detected between the CRP levels and lipid amounts within the whole body (40, 41). In case of obesity the secretion of high amounts of IL-6 from the adipose tissue elevates CRP levels as well as the risk of CVDs (42, 43).

It is also reported that the usage of oral contraceptives increase CRP levels (44). Other factors affecting CRP levels involve blood pressure, diabetes mellitus, low HDL and high triglyceride levels, tissue damage, hormone replacement therapy.

CRP and Cardiovascular Diseases

Prior studies demonstrated that CRP is a vital agent to detect the risk of CVDs and therefore, plays an important role in the follow-up of a disease. Several investigators reported a relationship between CVDs and high levels of CRP. According to the reports of Centers for Disease Control and Prevention (CDC) and American Heart Association (AHA) and several other investigators, CRP can be used as a marker to demonstrate the relationship between CVDs and inflammation (45-49).

Ridker et al. followed up twenty seven thousand healthy women in Women Health Study and measured LDL and CRP levels. After the follow-up period sudden deaths related to CVDs were compared with CRP and LDL levels and finally CRP was reported as a more important marker than LDL to detect CVD risks (50). In a study performed by Morrow et al. troponin T and CRP levels of the patients were measured and it was found that patients with CRP levels above 7.21 mg/dL die within 14 days. Death rate of individuals with CRP levels above 1.55 mg/dL were found to be higher than the ones with CRP levels below 1.55 mg/dL (51).

The risk of CVDs increase with the increasing levels of blood CRP levels. This is classified as; <1 mg/L: low risk, 1-3 mg/L: medium risk, >3 mg/L: high risk (47-48). In 1999, WHO reported that blood CRP levels above 1 mg/L can be considered as a risk factor for CVDs (50).

CRP and Atherosclerosis

Steinberg and his colleagues in 1989, first proposed the LDL oxidation hypothesis for atherosclerosis. Since then, the evidence has been occurred supporting the hypothesis that oxidative modification of LDL has the key role for the progression of atherosclerosis (52-53). Oxidation of LDL in the arterial wall occurs as a result of its exposure to reactive oxygen species (ROS) like nitric oxide, OH, O2- (free radicals), macrophages, and some enzymes such as lipoxygenase. Free radicals and other reactive species (H2O2, HOCl) also occur during macrophage activation. There is evidence supporting the idea that common risk factors for atherosclerosis increase the risk of ROS production not only from the endothelial cells, but also from the smooth muscle cells and the adventitial cells. Therefore conditions such as, diabetes mellitus, arterial hypertension, hypercholesterolemia, aging, smoking, and nitrate intolerance increase the production of free ROS (54).

Oxidized LDL is involved in foam cell formation, stimulates endothelial cells to produce inflammatory markers. It has cytotoxic effects on endothelial cells, inhibits nitric oxide-induced vasodilatation and the motility of tissue macrophages. The oxidation of LDL lipids and apolipoprotein B 100 renders LDL pro-atherogenic (55). Now, it is generally accepted that the macrophage uptake of oxidatively modified LDL and then the formation of cholesterol laden foam cells is important to initialize the event of atherosclerosis leading to vascular diseases.

Finally the damage occurred in vascular endothelial cells via toxic, mechanical, immunological, metabolical agents such as smoking, viral/microbial infection, physical injury or stress, hyperlipidemia (high levels of LDL, VLDL), homocysteinemia, hypertension and diabetes mellitus deteriorates endothelial permeability. As a result, blood lipoproteins (especially LDL) migrate within the blood vessel and starts to accumulate. These events trigger several immunological reactions. These cause the mounting up of smooth muscle cells and the formation of fatty fibrous atheroma plaques. During the immunological reactions the stimulation of proinflammatory cytokines, such as IL-6 stimulates CRP release. It has also been suggested that CRP triggers inflammation as it is shown to be secreted after

endothelial damage. Even in the early stages of atherosclerotic plaque formation, the presence of CRP was reported in the vessel wall (56). Hatanaka et al. suggested that atherosclerosis could be triggered by CRP via an elevation of vascular access of lipid complexes through the endothelium layer by macrophages accumulating in atherosclerotic lesions (57). CRP also stimulates the secretion of adhesion molecules such as VCAM1 (Vascular-Cell-Adhesion Molecule-1), ICAM1 (Intracellular-Adhesion Molecule-1) as well as selectins and chemokines like Monocyte Chemotactic Protein-1 (MCP-1) and Monocyte Colony Stimulating Factor (mCSF) from the endothelial cells. Therefore, CRP is considered as a proatherogenic molecule (58).

There are several studies demonstrating an association between coronary artery disease and CRP. Hs-CRP, IL-1β, IL-6 and TNF-α levels of patients with coronary artery disease were found significantly higher than healthy individuals (59).

CRP and Myocard Infarction

Myocardial infarction is defined as the tissue necrosis caused by a blood clot. The secretion of CRP and some proinflammatory cytokines are being stimulated to restore this damage. However due to overstimulation of these substances more tissue damage occurs and this worsens the clinical picture. Successful thrombolytic treatment may make an important contribution to the survival benefit of acute myocardial infarction (60). Magadle et al reported high CRP levels in STEMI patients and concluded that CRP could be a good diagnostic marker for early complications (61). Dibra et al reported high myocardial damage in STEMI patients with high CRP levels (62). In a study named as OPUS TIMI 16, patients with high levels of hs-CRP had elevated levels of mortality and cardiac failure. Mortality risk was noted in patients with hs-CRP levels above 10 mg/L (63). A relationship between CRP levels and the number of complex coronary lesions in patients with acute myocardial infarction was also reported (64).

CRP and Arythmia

A positive relation between CRP levels and the risk of atrial fibrillation development was detected (65). In "Cardiovascular Health Study", 5806 patients above 65 years of age were followed and CRP levels in patients with atrial fibrillation was found as higher than the ones without atrial fibrillation. In addition, patients without atrial fibrillation but with high levels of CRP demonstrated atrial fibrillation progress (66, 67). In an experimental study Kumagai et al. reported a decrease in CRP levels after atorvastatin treatment to reduce the progress of inflammation (68).

CRP and Hypertension

Hypertension is an important risk factor for atherosclerosis. Pietri et al found a relation between essential hypertension and mild chronic inflammation (69). There are also studies who reported elevated levels of CRP in patients with primary hypertension and prehypertension (70, 71). However, it is not known whether inflammation induces hypertension or hypertension induces inflammation. According to another study performed by Blake et al., CRP is being released in response to inflammation and causes an increase in endothelin-1 levels which then reduces NO levels and elevates blood pressure (72). Endothelial dysfunction occurs due to an imbalance between the substances produced from the endothelial cells and the substances that change blood pressure. This deteriorates the permeability of vessel walls. The increased permeability of proinflammatory molecules to the tissue cause the formation of atherosclerotic plaques (73-75).

Conclusion

Cardiovascular diseases are the leading causes of death worldwide. It is widely accepted that atherosclerosis is an inflammatory process and induces cardiovascular diseases. Several cardiovascular risk factors such as smoking, obesity, diabetes mellitus, hypertension, age, sex, unhealthy diet and dyslipidemia have been determined. However, due to a relation between inflammation and atherosclerosis, inflammatory markers, especially, C-reactive protein (CRP), were assumed as a reliable cardiovascular marker in some studies whereas other studies suggested no additional role for CRP and suggested that its elevation is due to its interaction with cardiovascular risk factors (76). Therefore, its usage alone could not be considered as reliable.

Conflict of Interest: The authors declare that confirm that there is no conflict of interest regarding the publication of this article.

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