How To Change Ceruloplasmin Levels In Heart Disease

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ABSTRACT

Ceruloplasmin (CP) is a blue serum protein found in human serum that carries approximately 95% of the total circulating copper (Cu) in healthy individuals. The relationship of CP with OS, inflammation, and DNA damage is known. Oxidative stress (OS), inflammation and DNA damage are the main underlying causes of atherosclerotic heart disease also. Many studies indicated a close association between high serum CP and several types of heart disease. However, the levels of CP were still unknown in many heart diseases. To gather the studies of CP in heart disease and prepare the ground for new studies for researchers, we designed this review.

Keywords: Ceruloplasmin, oxidative stress, heart disease.

Halp Hastalıklarında Seruloplazmin Değerleri Nasıl Değişir

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ÖZET

Kanda yaygın olarak bulunan ve mavi protein olarak adlandırılan ceruloplazmin (CP) sağlıklı kişilerde kanda bakırın % 95'ini taşır. Oksidatif stres, inflamasyon ve DNA hasarı ile ilişkisinin varlığı bilinmektedir. Oksidatif stres, inflamasyon ve DNA hasarı, başta koroner arter hastalığı olmak üzere pek çok kalp hastalığı etiyolojisinde de suçlanmaktadır. Çok sayıda çalışma kalp hastalıklarında CP'nin yerini ortaya koymuştur. Ancak çoğu kalp hastalığında halen CP seviyelerinin nasıl değiştiği bilinmemektedir. Literatürdeki CP ile yapılmış kalp hastalıklarındaki çalışmaları bir araya getirmek ve yapılacak yeni çalışmalara zemin hazırlamak için bu derlemeyi yaptık.

Anahtar Kelimeler: Seruloplazmin, oksidatif stres, kalp hastalıkları.

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I. Introduction

Ceruloplasmin (CP) is a blue serum protein found in humans that carries approximately 95% of the total circulating copper (Cu) in healthy individuals (1,2). CP has been known for a long time and was first purified from the α-2-globulin fraction of human serum by Holmberg and Laurell (3,4). CP is synthesized mainly in the hepatocyte (95%) but is also produced by other cell types, such as monocytes, astrocytes, and Sertoli cells (5). Heart disease is the leading cause of death in the world currently (6). Oxidative stress (OS), inflammation and DNA damage are the main underlying causes of atherosclerotic heart disease (AHD) (7–9). The relationship of CP with OS, inflammation, and DNA damage has been shown in previous studies (10–12). Many studies have also indicated a close association between high serum CP and several types of heart disease (13–16). However, the status of CP is still unknown in many heart diseases. The purpose of this review is to gather the studies of CP in heart disease and also to prepare the ground for new studies for researchers.

II. Structure and functions of human ceruloplasmin

CP contains seven Cu atoms per molecule, and its average concentration is about 300 μg/ml in plasma (1,2). Its best-known function is to transport Cu. In addition, CP plays a role in coagulation, angiogenesis, iron (Fe) homeostasis, defense against oxidant stress, and inactivation of biogenic amines (1–4,17–21). CP is a member of the inflammation-sensitive plasma protein (ISPPs) family that includes fibrinogen, haptoglobin, αl-antitrypsin, and orosomucoid (15,16,21–26). It facilitates Fe transport and storage by the catalyzed oxidation of Fe^{2+} to Fe^{3+} along with ferroxidase activity (1,2). As a result, CP provides Fe without generating a toxic product by binding to transferrin in the plasma (27). Because there are free ferric ions and ferritin binding sites, CP can act as an oxidant or an antioxidant (27). CP helps control membrane lipid peroxidation by providing the oxidation of the cation (28), takes place in the structure of high-density lipoprotein (HDL) (28) and also blocks the function of the oxidants by binding to it (28). CP also has the ability to bind to and transport magnesium (27,28).

A CP molecule is formed from a single polypeptide chain comprising 1046 peptides (27,28). The total carbohydrate content is 8 to 9.5% (27,28). It carries three glucosamine-linked oligosaccharide side chains (27,28). First, the peptide chain is formed (27,28). Cu is then added through the ATPase (27,28). Carbohydrate side chains are then added to the endoplasmic reticulum (27,28). In addition to transport by CP, Cu also plays a role in the formation of CP proteins (27,28).

IIIa. Heart Failure

In heart failure (HF), there have been numerous studies of CP. The main antioxidant function of CP is related to its ferroxidase I activity, which in turn influences Fe-dependent oxidative and nitrosative radical species generation (29). Peroxynitrite, whose production is increased in HF, may decrease the antioxidant function of CP by amino acid modification (29). In addition, it is believed that CP decreases the bioavailability of nitric oxide (NO) in HF.

Studies have reported that increased CP levels are related with a poorer prognosis of HF. It is believed that elevated CP levels can be a marker for hospitalization, all-cause mortality and cardiovascular event frequency, and death from HF. Hammadah et al. showed that increased serum CP levels were an independent predictor of all-cause mortality. Researchers suspect that the measurement of CP may help to identify patients with HF who have an increased mortality risk (30). A community-based study showed that CP was associated with the incidence of HF, death from HF, and cardiovascular disease (31). This previous study included 9240 individuals and followed them for a total of 10.5 years (31). As a result of 22 years of follow-up, Engström et al. showed that CP and other low-grade inflammatory markers were significantly related with a high incidence of HF (32). However, the presence of an association between serum CP levels and increased mortality has not been confirmed by peripartum cardiomyopathy (33).

High CP levels typically occur independently from HF causes, and both are correlated with a low ejection fraction (EF) and increased C-reactive protein (CRP). A previous study found increased CP levels in patients with ischemic or nonischemic cardiomyopathy and a linear correlation with CRP and left ventricular ejection fraction (34). Another study showed increased serum CP levels in patients

with idiopathic dilated cardiomyopathy compared with controls (35). There are also studies that have reported a relationship between serum natriuretic peptides and CP as well as a linear relationship between CP and BNP in HF. In the study of Hammadah et al., there was a weak but positive relationship between HF and serum CP levels (30). In addition, NT-proBNP may be correlated with serum CP levels in acute decompensated HF (36).The existence of a positive relationship between serum CP levels and the functional class of HF has been observed also (29).

CP is high in both compensated and decompensated HF. In a different study, we found an increased serum CP value both in compensated and decompensated HF compared to control patients (37). Interestingly, in that previous study, there were higher CP levels in compensated HF than there were in decompensated patients (37).

III b. Coronary Artery Disease

In coronary artery disease (CAD), CP is a serum protein that has been the subject of numerous studies. In an isolated heart model, CP was reported to be protective of ischemia/reperfusion injury due to its anti-oxidant activity (38,39). However, it is also able to act to as an oxidant under certain circumstances. Studies have shown that there is an association between protein nitration and CAD (40–42). Impaired ferroxidase I activity and/or nitrated CP may reflect global OS. In vitro, CP may show nitric oxide (NO) oxidase activity via the catalytic consumption of NO (43). There is diminished plasma NO oxidase activity in humans with congenital aceruloplasminemia (43). Because CP lacks NO oxidase activity, its elevation may diminish the NO bioavailability; as a result, endovascular dysfunction may occur, and OS is increased. In many studies, a close relationship between the presence of CAD and an increased OS has been demonstrated (44–46).

Several studies have connected CP levels with increased cardiovascular risk in both the normal population and also in patients with acute coronary syndromes (24,47–50). In addition, two case-controlled studies have identified serum CP as a risk factor for CAD (9). A prospective cohort study showed a relationship between serum CP levels and subsequent myocardial infarction (MI) (51). In

4177 stable cardiac patients who underwent a three-year follow-up, Tang et al. reported an increased incidence of major cardiovascular events (death, MI, stroke) in participants with higher CP levels (25). Grammer et al. showed that increased CP levels were independently associated with increased risk of cardiovascular and all causes mortality in CAD represented by angiography results (51). In stable cardiac patients, a three-year follow-up cohort study showed that high serum CP levels were associated with increased risk for cardiovascular events (52). In a different study conducted in patients with chronic renal failure, increased CP has been associated with CAD-related cardiac events, including nonfatal MI, nonfatal stroke, or death (53).

Both acute and chronic CAD are associated with increased serum levels of CP. Singh showed that CP levels increase transiently as an acute-phase response following MI (52). Changes in some acute phase parameters, including CP, were found when predicting the development of complications and the likelihood that the disease would have a fatal outcome (54). Another study also showed a high-level of CP in patients with acute and chronic CAD compared with the control participants (55).

III c. Cardiac Arrhythmia

In clinical studies, elevated CP may cause cardiac arrhythmias. CP was analyzed in patients with atrial fibrillation, the most frequent cardiac arrhythmia, and was shown to be important in the pathophysiology of the condition (56). In another study, elevated CP levels were associated with an increased risk of hospitalization from AF (57). Although not reported in clinical studies, in a rat heart with induced ischemia, CP treatment decreased both reversible and irreversible ventricular fibrillation but had no effect on ventricular tachycardia (58).

III d. Rheumatic and Valvular Heart Disease

There are few studies on CP in induced rheumatic and valvular heart disease. A study conducted in children with acute rheumatic fever revealed high CP levels at the time of diagnosis (59). Another study carried out in dogs with degenerative mitral valve disease showed that CP levels were no different in significant valvular disease than they were in patients with nonsignificant diseases (60).

CP levels were also statistically significantly higher in patients with acquired valvular heart disease than in controls (61).

III e. Lipids

CP has been known to play a role in the oxidative modification of low-density lipoprotein (LDL). CP has also been shown to have pro-oxidant activity and to contribute to the oxidative modification of LDL under some conditions. Atorvastatin use may also increase CP levels; a previous study demonstrated increased anti-oxidant capacity and decreased OS with statin use (62).

III f. Hypertension

Few studies on CP have been conducted amongst hypertensive patients. Vasconcelos et al. indicated that the hypertensive group had increased serum CP levels compared with the controls (63). Another study reported that the presence of hypertension and elevated blood pressure readings were associated with increased serum CP levels (32).

IV. **As a Result**

CP is a serum protein that has been investigated in a number of studies on heart disease. In heart diseases, CP may be etiologic agent, diagnostic or prognostic marker. It is not known how it varies in many forms of heart disease, and its contribution to the etiology or prognosis is also not clear. Outside of studies on HF and CAD, CP awaits the attention of researchers in many areas.

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