How to Change Ceruloplasmin Levels in Heart Disease?

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ABSTRACT

Ceruloplasmin (CP) is a blue serum protein found in human serum; it 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 causes underlying atherosclerotic heart disease. Several studies have indicated a close association between high serum CP and several types of heart disease. However, the CP levels are still unknown in many heart diseases. To gather the studies of CP in heart disease and to prepare the ground for new studies for researchers, we designed this review.

Key Words: Ceruloplasmin; oxidative stress; heart disease

Kalp Hastalıklarında Seruloplazmin Değerleri Nasıl Değişir?

ÖZET

Kanda yaygın olarak bulunan ve mavi protein olarak adlandırılan seruloplazmin (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 etyolojisinde 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

INTRODUCTION

Ceruloplasmin (CP) is a blue serum protein found in humans; it 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 mainly synthesized in the hepatocyte (95%) but is also produced by other cell types, such as monocytes, astrocytes, and Sertoli cells[5]. Currently, heart disease is the leading cause of death in the world[6]. Oxidative stress (OS), inflammation, and DNA damage are the main causes underlying atherosclerotic heart disease (AHD)[7-9]. The relationship of CP with OS, inflammation, and DNA damage has been demonstrated in previous studies[10-12]. Several 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. This review aims to gather studies regarding CP in heart disease and also to prepare the ground for new studies for researchers.

Structure and Functions of Human Ceruloplasmin

CP contains seven Cu atoms per molecule, and its average concentration is approximately 300 μg/ml in plasma[1,2]. Its best-known function is Cu transport. 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 family that includes fibrinogen, haptoglobin, αl-antitrypsin, and

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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]. Hence, 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 anti-oxidant[27]. CP helps control membrane lipid peroxidation by providing the oxidation of the cation; it takes place in the structure of high-density lipoproteins (HDL) and also blocks the function of 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]. Its 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, after which Cu is 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].

Heart Failure

There have been numerous studies regarding CP in heart failure (HF). The main anti-oxidant 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 anti-oxidant 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 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 CP measurement may help 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 up 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 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 EF[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 by 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 also been observed[29].

CP is high in both compensated and decompensated HF. In another study, we found an increased serum CP value both in compensated and decompensated HF compared with control patients[37]. Interestingly, in that previous study, there were higher CP levels in compensated HF than there were in decompensated patients[37].

Coronary Artery Disease

CP is a serum protein that has been the subject of numerous studies concerning coronary artery disease (CAD). In an isolated heart model, CP was reported to be protective of ischemia/reperfusion injury because of its anti-oxidant activity[38,39]. However, it is also able to act to as an oxidant under certain circumstances. Studies have shown that protein nitration is associated with 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; hence, endovascular dysfunction may occur, leading to increased OS. A close relationship between the presence of CAD and increased OS has been demonstrated in several studies[44-46].

Several studies have connected CP levels with increased cardiovascular risks in 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, and 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-cause 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 another 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 transiently increase 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 high-levels of CP in patients with acute and chronic CAD compared with that in the control participants[55].

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].

Rheumatic and Valvular Heart Disease

There are few studies concerning 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 significantly higher in patients with acquired valvular heart disease than in controls[61].

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].

Hypertension

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

CONCLUSION

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

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