


# Molecular Functions of Ceruloplasmin in Metabolic Disease Pathology

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**Abstract:** Ceruloplasmin (CP) is a multicopper oxidase and antioxidant that is mainly produced in the liver. CP not only plays a crucial role in the metabolic balance of copper and iron through its oxidase function but also exhibits antioxidant activity. In addition, CP is an acute-phase protein. In addition to being associated with aceruloplasminemia and neurodegenerative diseases such as Wilson's disease, Alzheimer's disease, and Parkinson's disease, CP also plays an important role in metabolic diseases, which are caused by metabolic disorders and vigorous metabolism, mainly including diabetes, obesity, hyperlipidemia, etc. Based on the physiological functions of CP, we provide an overview of the association of type 2 diabetes, obesity, hyperlipidemia, coronary heart disease, CP oxidative stress, inflammation, and metabolism of copper and iron. Studies have shown that metabolic diseases are closely related to systemic inflammation, oxidative stress, and disorders of copper and iron metabolism. Therefore, we conclude that CP, which can reduce the formation of free radicals in tissues, can be induced during inflammation and infection, and can correct the metabolic disorder of copper and iron, has protective and diagnostic effects on metabolic diseases.

**Keywords:** ceruloplasmin, physiological function, iron, oxidative stress, inflammatory state, metabolic disease

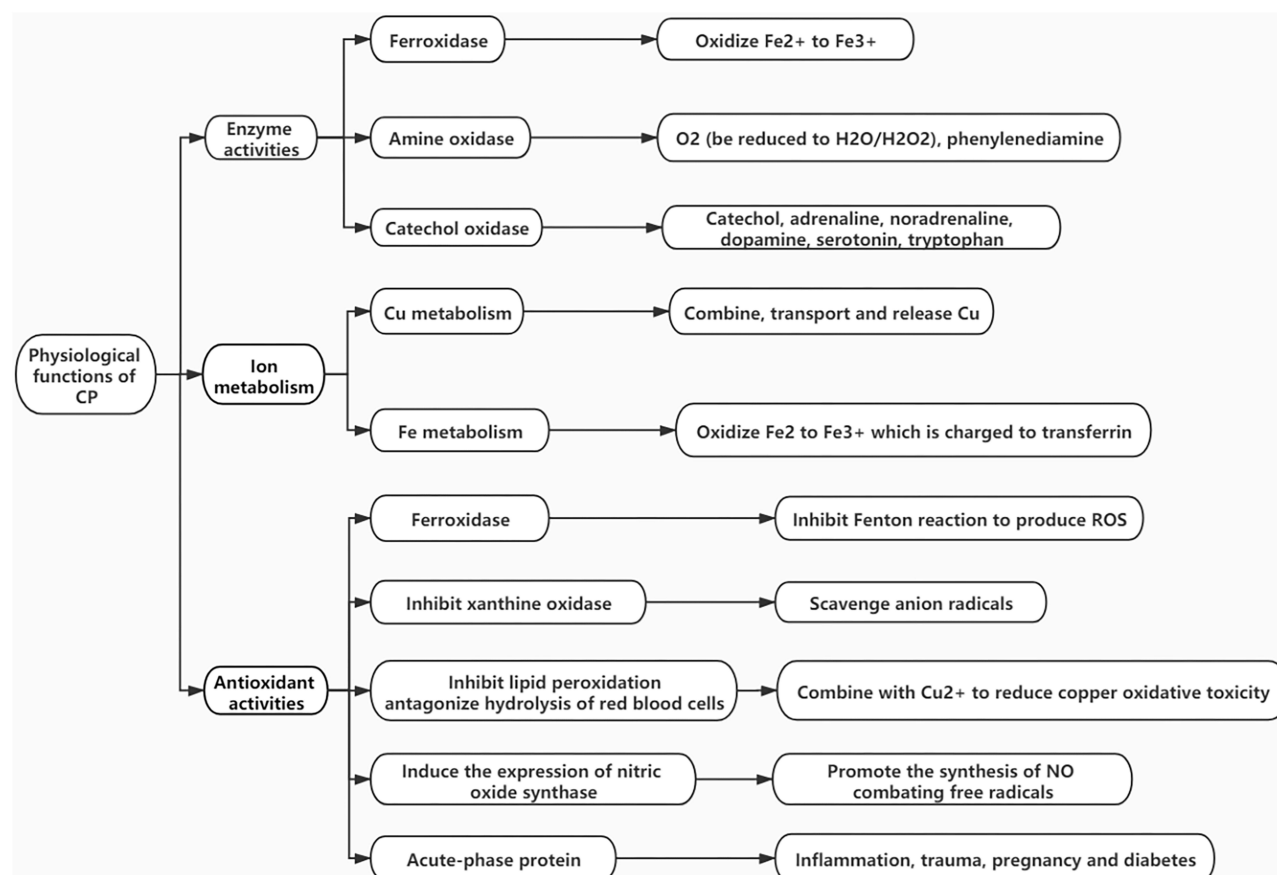
## Introduction

Ceruloplasmin (CP), also known as copper oxidase, is a blue-looking copper (Cu) glycoprotein that was first purified from human serum  $\alpha_2$ -globulin in 1948 by Holmberg and Laurell. CP exists in two molecular isoforms: secreted CP (sCP) and a membrane glycosylphosphatidylinositol (GPI)-anchored form of CP (GPI-CP); sCP is mainly produced by the liver,<sup>1,2</sup> while GPI-CP has been found in glial and sustentacular cells.<sup>3</sup> CP has multiple physiological functions (Figure 1). It carries 40–70% of Cu in plasma and plays important roles in Cu transport, iron (Fe) regulation, free radical scavenging, and antioxidant processes. It also catalyzes the oxidation of a variety of substrates, such as Cu, Fe, and other organic substrates. It is closely related to Wilson's disease, aceruloplasminemia neurodegenerative disorders and other diseases.<sup>4–6</sup>

Growing evidence shows that the abnormal metabolism of Cu and Fe, as well as the abnormal expression of CP, has been observed in metabolic diseases such as diabetes and obesity,<sup>7,8</sup> indicating that CP may have diagnostic and therapeutic potential in metabolic diseases. Herein, we summarize the latest studies on CP and discuss its role in metabolic diseases.

## CP Structure and Distribution

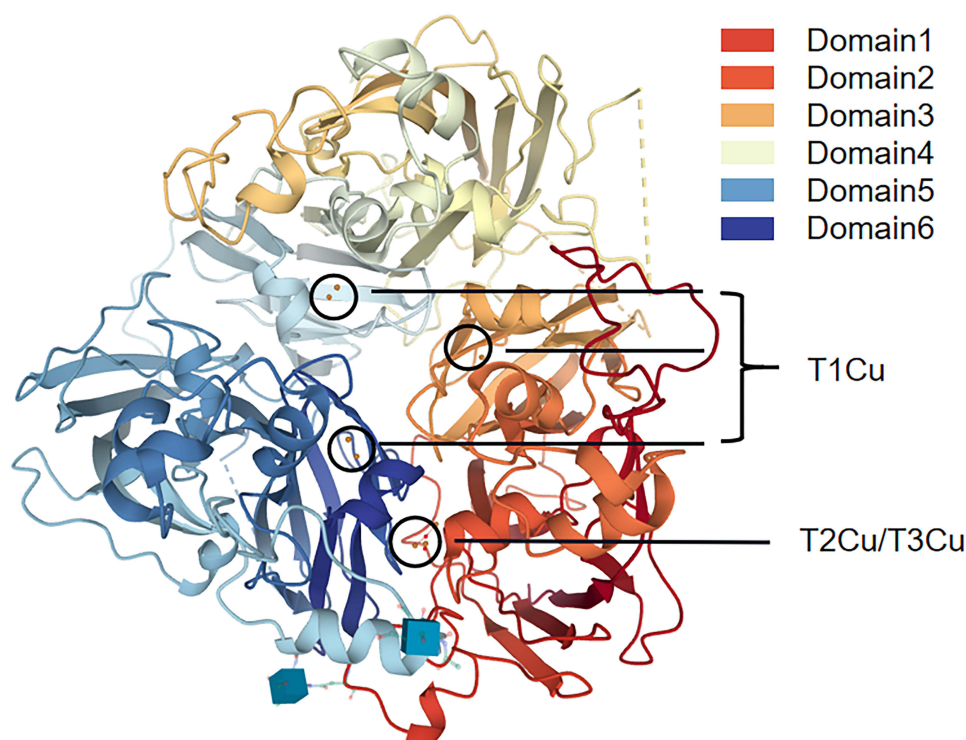
The human CP gene, located on chromosome 8, is 65 kb in length and contains 20 exons.<sup>9</sup> Human CP protein is a single polypeptide chain composed of 1046 amino acids and 4 glucosamine oligosaccharides, with a relative molecular weight of approximately 132 kDa.<sup>10</sup> The beta strand and beta turn account for approximately 50% of the CP peptide chain with almost no  $\alpha$ -helix structure. A single polypeptide chain can be hydrolyzed by protease into 3 groups of isomorphic units. The relative molecular weights are 67 kDa (480 amino acid residues), 50 kDa (405 amino acid residues), and 19 kDa (159 amino acid residues). In the complete polypeptide chain, the three units are connected by single amino acid residues, arginine R and lysine K.<sup>11</sup>



**Figure 1** CP physiological functions and mechanisms.

The 3D structure of CP is shown in [Figure 2](#). CP has six compact domains that can bind to six Cu atoms, and three of those six Cu atoms exist in the second, fourth, and sixth domains as mononuclear forms, which are three “type I Cu (T1Cu)”. The other three Cu atoms also form a trinuclear Cu cluster at the interface of the first and sixth structural domains, which are one “type II Cu (T2Cu)” and two “type III Cu (T3Cu)”. Trinuclear Cu clusters not only play an important role in the catalytic activity of CP but also contribute to the stability of the CP structure.<sup>12–14</sup> The CP that is combined with six Cu is very unstable and loses at least one T1Cu in less than a day at 37 °C, while the trinuclear Cu cluster remains intact. In addition to Cu binding sites, CP also has metal ion binding sites such as sodium, Fe, calcium, and so on.

CP in vertebrates is mainly synthesized by the liver; fat, brain, placenta, yolk sac, breast, kidney, and Sertoli cells can also synthesize CP independently.<sup>8,10</sup> First, pro-CP is synthesized in the endoplasmic reticulum (ER) of hepatocytes and then combines with Cu in the Golgi apparatus to form total CP. CP is transported from the liver through general circulation and ingested by other tissues and organs, or excreted directly through the bile into the stools.<sup>15–17</sup> CP is also produced in the process of macrophage and monocyte inflammation in the blood.<sup>18,19</sup> Arner et al<sup>20</sup> found that cultured adipose tissue could secrete CP and that the level of CP was higher in the adipose tissue of obese individuals. It has been suggested that CP could be used as a new adipose factor. The normal circulating level of plasma CP in adults is approximately 300 mg/L, and apo-CP accounts for approximately 10% of the total; apo-CP is unstable and has no enzyme catalytic activity, and it is decomposed and metabolized rapidly after half-life.<sup>4</sup> CP in plasma is mainly secreted and synthesized by the liver and cannot pass through the blood–brain barrier. CP synthesized in the brain is mainly in the form of glycosylphosphatidylinositols and bound to the membrane of astrocytes.<sup>21,22</sup> A study found that CP in the brain is associated with neurodegeneration, such as Parkinson’s disease and Alzheimer’s disease.<sup>23,24</sup> In the serum of AD patients, although the concentration of CP was not different from healthy control, the structure of CP was fragmented, resulting in altered activity of CP. Lower CP activity was similarly found in the CSF of AD patients.<sup>25</sup> This alteration may be caused by oxidative damage from incorrect or overloaded Cu into the



**Figure 2** CP three-dimensional structure. T1Cu: type I Cu, T2Cu: type II Cu, T3Cu: type III Cu.

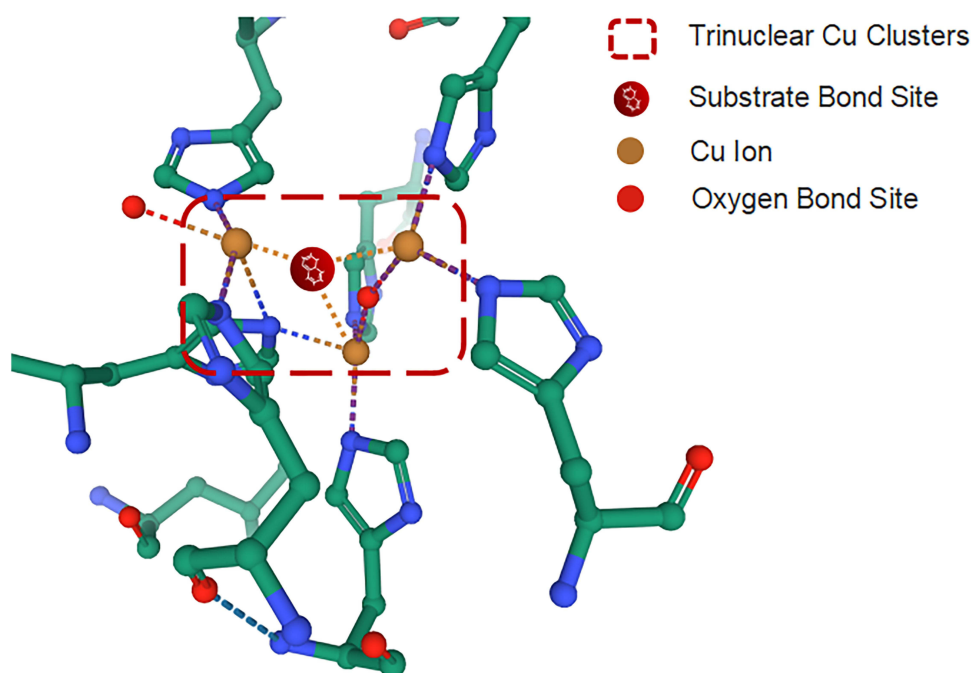
protein, or by up-regulation of oxidoreductase enzymes leading to increased oxidative stress, or downregulation of enzymes that regulate oxidative stress.<sup>26–28</sup> GPI-CP is expressed not only in the brain but also in the spleen, kidney, heart, liver, and testes in relatively small amounts.<sup>29</sup>

The activity and levels of CP depend on several major factors, including Cu deficiency, inflammatory cytokines, and estrogen or progesterone. Although studies on radioactive Cu have shown that Cu does not affect the rate of synthesis or secretion rate of CP, CP is highly sensitive to Cu deficiency. Under normal physiological conditions, the increase in Cu reserves in the liver can cause a persistent increase in CP concentration, and the decrease in CP concentration will be significant when Cu reserves are deficient.<sup>30,31</sup> In the acute phase, as an inflammatory factor, the levels of CP increase due to the response to infection and inflammation.<sup>32</sup> The role of CP in body immunity may be related to the elimination of free radicals, the oxidation and apoptosis of neutrophil granulocytes, and the inflammatory process.<sup>2,33,34</sup> Studies have found that estrogen can increase the synthesis of CP; with elevated estrogen levels during pregnancy, the concentration of CP can increase 3- to 4-fold.<sup>35</sup> On the other hand, Guller et al suggested that the high expression of CP in preeclampsia is related to its role in alleviating reperfusion injury, with Fe oxidase activity.<sup>36</sup> Dey et al<sup>37</sup> found that CP may predict the development of preeclampsia. Although much research is still needed to explore the exact role of CP in pregnancy, it may provide a new research direction for the diagnosis and treatment of gynecological diseases.

## Physiological Function of CP

### Enzyme Activity

CP is a member of the multi-Cu oxidase family and one of the few important enzymes in this family that can bind to molecular oxygen and reduce it to water. Substrate electrons may be received at its single Cu ion center and transferred to the multi-Cu ion center for molecular oxygen binding and reduction to water.<sup>38</sup> In this process, the Cu atoms of CP undergo the linear arrangement of a functional unit of redox centers, and the T2/3 site in the functional unit can take up a single electron from the substrate, transport it to the tricyclic group, and use the obtained electron to reduce the molecular oxygen into water<sup>39</sup> as shown in Figure 3. During the transformation from the T2/3 site to the oxygen bond site, the electrons in CP can consume and oxidize various substrates



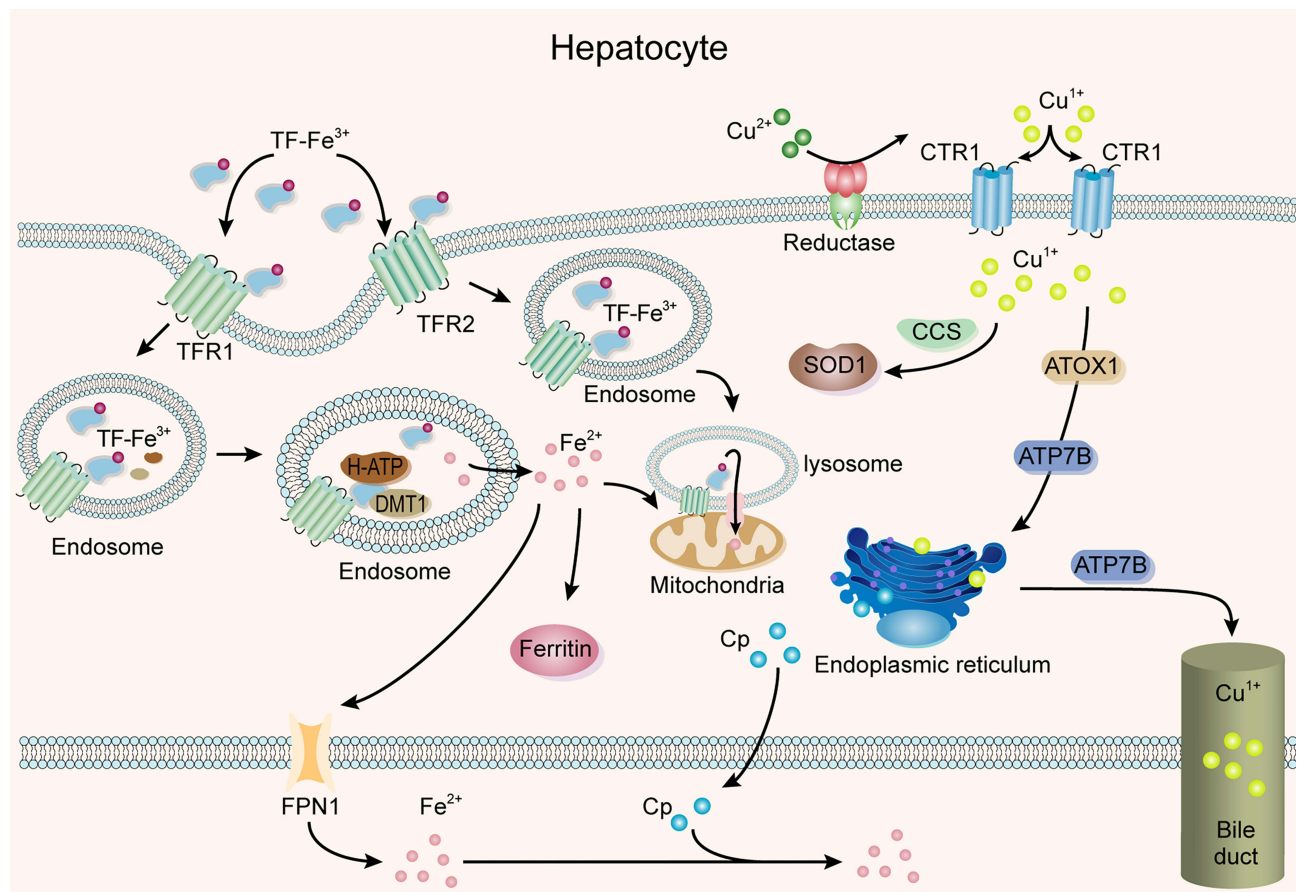
**Figure 3** The Cu atom site of CP in the functional unit can take up a single electron from the substrate, transport it to the tricyclic group, and use the obtained electron to reduce the molecule.

without releasing reactive oxygen species (ROS). Metal ions, such as Cu and Fe, can be used as substrates. CP can oxidize  $\text{Fe}^{2+}$  and  $\text{Cu}^{1+}$  to  $\text{Fe}^{3+}$  and  $\text{Cu}^{2+}$ , respectively,<sup>40</sup> so they can be transported and metabolized in the body. In addition, CP has the effect of amine oxidase on other organic substrates, such as phenylenediamine.<sup>41</sup> The amine oxidase action of CP can oxidize molecular oxygen to water or hydrogen peroxide. When the pH value of the reaction system is 5.2, its activity is the best, and the normal physiological concentration of chloride ions plays a strong role in promoting amine oxidase.<sup>42</sup> CP has the effect of oxidase in catechol and its analogs, such as dopamine, epinephrine, norepinephrine, 5-hydroxytryptamine, and tryptophan.<sup>40,43</sup>

### Cu and Fe Stability

Cu and Fe are essential metals that exist in an oxidized state and have high redox activity as enzyme auxiliary factors; further, Cu and Fe interact with each other in metabolism.<sup>44,45</sup> The deficiency or excess of both elements can lead to the impairment of cell function, which will eventually lead to cell death.<sup>46,47</sup> CP is involved in the process of Cu and Fe transport, and it is capable of oxidizing  $\text{Fe}^{2+}$  to  $\text{Fe}^{3+}$ , facilitating the incorporation of the latter into transferrin (TF), as shown in Figure 4.

CP plays an important role in Cu metabolism. Cu in the diet is mainly absorbed into the blood through ATP7A (a P-type ATP enzyme) in the small intestine, binds to albumin or  $\alpha$ -2 macroglobulin, and is delivered to hepatocytes by Cu transporter 1 (CTR1).<sup>48–50</sup> After entering hepatocytes, CTR1 donates Cu to Copper chaperone for superoxide dismutase; COX17 transfers Cu to mitochondria to synthesize cytochrome oxidase; antioxidant protein 1 (Atox1), as a Cu molecular chaperone, directs Cu to ATP7B (Wilson's disease protein) in the trans-Golgi network (TGN) and then incorporates Cu into CP.<sup>51,52</sup> In addition, ATP7B conveys excessive Cu tubule membranes and mediates the excretion of Cu into bile.<sup>53,54</sup> CP binding with Cu is the main carrier of Cu in serum. When CP reaches the surface of target cells, it interacts with corresponding receptors to release Cu, which is absorbed and utilized by target cells. Through the binding and release of Cu by CP, the distribution of Cu in the body is realized.<sup>44</sup> CP without Cu binding is an allosteric protein, which leads to changes in the sedimentation rate and electrophoresis mobility when it binds to Cu, but the secondary structure remains unchanged. This



**Figure 4** CP participates in the transport of Cu and Fe in the liver.

allosteric activity not only releases it from the ER of hepatocytes but also protects it from the acidic environment caused by bile. In the subsequent process, the structure can still be combined with Cu, indicating that the structure of Cu-free CP will also affect the metabolism of Cu.<sup>55</sup>

Cu non-bound to ceruloplasmin (nCu-Cu), also known as “free” Cu, can bind to albumin (or human serum albumin), alpha-2-macroglobulin (also reported as transcopperin), and squamous cell carcinoma. These bindings form a Cu exchangeable pool. Cu homeostasis is well regulated in the body, and the increase in exchangeable nCu-Cu is a symptom of this homeostatic disruption, and if not structurally bound to the enzyme or coordinated by proteins, Cu generates free radicals through the Harper–Weiss or Fenton reactions. Abnormal nCu-Cu levels have been recently reported in Parkinson’s disease and diabetes, as well as in abnormalities in the acute inflammatory response and stroke injury.<sup>56</sup>

Fe is very important to a variety of functions in the body, including DNA synthesis, gene expression, and the synthesis of hemoglobin and various enzymes. An increasing number of studies have found that Fe metabolism disorder leads to insulin resistance and obesity.<sup>57,58</sup> The Fe in the diet is dominated by  $\text{Fe}^{3+}$ , which is reduced to  $\text{Fe}^{2+}$  by duodenal cytochrome B (DcytB) on the top membrane of intestinal epithelial cells and then transported by divalent metal transporter-1 (DMT1) through intestinal epithelial cells and by TF to the liver through portal vein circulation.<sup>59,60</sup> After entering the liver, Fe is used to synthesize Fe-containing proteins, and the remainder is oxidized.<sup>61</sup> As ferrous oxidase, CP plays an important role in the regulation of Fe balance in vivo. The transmembrane transport of Fe in vivo requires a specific protein carrier, ferroportin (Fpn). The CP-ferroportin system is the main output pathway of intracellular Fe.<sup>62</sup> Although many proteins are involved in the absorption of Fe, the only confirmed output system of Fe in the cell is the CP-Fpn system.<sup>63</sup> CP in plasma oxidizes  $\text{Fe}^{2+}$  to  $\text{Fe}^{3+}$ , which could bind to Fpn and then transport it to target cells. After endocytosis, Fe is metabolized or



stored.<sup>62</sup> The liver is the first organ to receive Fe from the intestine, and it is also an important target organ for Fe toxicity. Fe staining in patients with liver cancer shows that excessive Fe is deposited in nontumor tissues,<sup>64</sup> and the expression of CP in nontumor tissues is significantly higher than that in tumor tissues. Fe deposition occurs in 60–95% of epithelial parenchyma cells of the liver. Histology shows that Fe deposition decreases from the portal vein to the lobular center, and the expression of CP also decreases gradually. This indicates that the high expression of CP in Fe deposition is related to the involvement of CP in iron oxidation.<sup>64</sup> In addition, Cu levels in individuals with CP-deficient genes and aceruloplasminemia are normal or decreased, but Fe metabolism is seriously dysfunctional, and the use of Fe-chelating agents could play a therapeutic role.<sup>65</sup> These results show the indispensable role of CP in the process of Fe transport.

### Antioxidant Activities

The antioxidant mechanism of plasma CP is the activity of ferrous oxidase, cuprous oxidase, and glutathione peroxidase and its ability to scavenge ROS. CP is an important antioxidant that can convert divalent Fe into less toxic trivalent Fe without releasing ROS. At the same time, CP can further utilize the antioxidant effect, reduce metal toxicity *in vivo*, and avoid tissue damage and dysfunction of the body.<sup>66,67</sup> As early as 1982, Goldstein et al<sup>68</sup> found that normal concentrations of CP in serum can inhibit the reduction of n-ferritin C regulated by xanthine oxidase, which is similar to the scavenging effect of superoxide dismutase (SOD) on  $O_2^{\cdot-}$ . In general, the Fenton reaction can occur with  $Fe^{2+}$  in  $H_2O_2$  ( $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH^{\cdot}$ ), but when CP exists,  $Fe^{2+}$  can be oxidized to  $Fe^{3+}$  through its Fe oxidase activity, so the Fenton reaction can be eliminated and the antioxidant effect can be realized.<sup>69</sup> Compared with the scavenging effect of SOD on free radicals, the effect of CP is weak, but it is relatively constant; even in the case of denaturation of the protein, it still maintains the effect of scavenging free radicals. This phenomenon may be the result of a direct chemical reaction between CP and  $O_2^{\cdot-}$ . Both active CP and denatured CP can bind to  $Cu^{2+}$  in blood and tissue fluid, significantly inhibit lipid peroxide, and effectively antagonize erythrocyte hydrolysis induced by  $Cu^{2+}$ .<sup>70</sup> In addition, CP can promote the formation of s-nitrosoglutathione (s-GSNO). When added to cultured monocytes, CP can promote the expression of inducible nitric oxide (NO) synthase. Physiologically, NO can react with hydroxyl radicals ( $\cdot OH$ ) to form nitrous acid (HONO) and reduce the damage of hydroxyl radicals to the tissue.<sup>71</sup> Paradis et al<sup>72</sup> believed that this indirect effect may provide cellular protection by protecting mercaptan from irreversible oxidation.

### CP Gene Variants

CP gene variants were found and discussed in several recent studies. Gene mutations in CP may disrupt the expression of CP. This protein generated by mutant gene expression may degrade immediately after release from the ER, and also may remain within the ER with abnormal structure, but lacks normal physiological functions, such as inability to bind copper atoms, lack of oxidase, etc.<sup>73–75</sup> To date, 172 cases of CP gene variants have been reported worldwide, and 56 were considered pathogenic; most of the cases occurred in Japan, without typical clinical symptoms such as neurological involvement and hepatic iron load.<sup>76</sup> At the same time, heterozygous patients with the same mutation may or may not be symptomatic, indicating incomplete penetrance of CP gene, and that environmental and other genetic factors may affect CP functions. Corradini et al<sup>77</sup> found that CP gene variants may be the cause of methemoglobinemia and iron overload in patients with non-alcoholic fatty liver disease, but Pelucchi et al<sup>78</sup> found that variants may have different effects under other clinical conditions.

### CP in Metabolic Disease

#### Relationship with Type 2 Diabetes

Diabetes is a common metabolic disease characterized by elevated blood glucose levels. Patients often have carbohydrate, fat, and protein metabolic disorders due to insulin deficiency or (and) insulin resistance.<sup>79</sup> Diabetes is also a global pandemic. According to the 2017 Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes, the prevalence of diabetes in China soared from 0.67 in 1980 to 10.4 in 2013.<sup>80</sup> Aberrant alterations in CP are seen in patients with type 2 diabetes mellitus (T2DM), and the results are inconsistent. Chacko et al<sup>81</sup> found that serum CP levels are elevated in patients with T2DM, and the CP levels in patients with complications

are higher than those in patients without complications. At the same time, in a similar population, Sarkar et al<sup>82</sup> showed that plasma CP and protein thiols are significantly reduced, but the level of  $\text{Cu}^{2+}$  is abnormally elevated. Those studies all show a link between CP and diabetes.<sup>83,84</sup> Diabetes is associated with abnormalities in inflammation, oxidation, and trace elements, and CP is involved in these abnormalities.

As early as the end of the 20th century, Pickup and Crook proposed that, although the innate immune system recovers quickly after the acute stimulus, activation of the innate immune system, stimulated by the living environment of long-term hyperglycemia, promotes insulin resistance, obesity, diabetes, and its complications instead.<sup>85</sup> Since then, many clinical studies have shown that diabetes is often accompanied by elevated concentrations of a variety of inflammatory factors. A large number of clinical epidemiological investigations further confirmed that a variety of inflammatory factors can predict the occurrence of diabetes. Inflammation mainly acts on the structure and function of endothelial cells and islet B cells and signal transduction of insulin receptors, which affect glucose metabolism and ultimately lead to diabetes.<sup>86–88</sup> Anti-inflammatory therapy has been shown to inhibit the development of diabetes.<sup>89–91</sup> CP is an acute-phase reactive protein; its concentration in plasma increases two- to three-fold during infection or injury. CP plays a decisive role in the regulation of innate and specific immune responses, which are the main components of the active immune system and reflect the immune-inflammatory state of the human body. It is believed that CP is an anti-inflammatory factor that inhibits the production of harmful substances during inflammation.<sup>92</sup> Therefore, as an inflammatory factor, CP may provide new diagnostic and therapeutic effects for diabetes, but more research is needed.

Oxidative stress is an important factor in the occurrence and development of T2DM.<sup>93</sup> In a physiological state, the human body has antioxidant defense systems that can clear oxidation production, such as ROS and reactive nitrogen species (RNS). With these systems, oxidation production will balance production and clearance. Oxidative stress refers to a disruption in that balance that damages tissue and biological macromolecules such as proteins and nucleic acids.<sup>94</sup> Oxidative stress can lead to damage of islet B cell function and peripheral insulin resistance, induce diabetes, and even lead to severe complications such as diabetic neuropathy,<sup>95</sup> diabetic retinopathy,<sup>96</sup> and diabetic cardiovascular disease.<sup>97</sup> Experiments in vitro showed that the nonenzymatic glycation reaction in hyperglycemia fragments and deactivates CP, and the release of  $\text{Cu}^{2+}$  participates in the Fenton reaction to produce ROS. At the same time, ROS can deactivate CP again to form a vicious cycle.<sup>98</sup> Shukla et al<sup>99</sup> suggested that unbound Cu induces excessive ROS production through the Haber–Weiss reaction and Fenton reaction in the aortic tissues of diabetic rabbit models; this phenomenon was not found in nondiabetic rabbit models. Sarkar et al<sup>82</sup> and Jeppu et al<sup>100</sup> found that the level of serum CP is inversely proportional to fasting blood glucose in patients with T2DM. This may indicate that, in the case of hyperglycemia, increased oxidative stress leads to an increased availability of transition metals such as Cu released from storage sites, which are more likely to participate in the Fenton and Haber–Weiss reactions to generate ROS.<sup>82,100,101</sup>

In recent years, it has been found that trace elements (Cr, Zn, Fe, Se, Mg, Cu) are related to glucose metabolism. Trace elements play an important role in the synthesis, excretion, storage, activity of insulin, and energy metabolism.<sup>102</sup> CP is mainly involved in the metabolism of Cu and Fe. Many studies suggest that people with T2DM have elevated levels of Cu and Fe.<sup>82,101,103</sup> The redox effect of Cu and Fe is involved in the production of ROS, which is one of the causes of diabetes.<sup>93</sup> In addition to the redox effect, Cu can also affect the action of zinc (Zn). Because Zn and Cu are a pair of antagonistic trace elements, they compete for the same carrier protein, metallothionein, during intestinal absorption. When the level of Cu increases, it will affect the absorption of Zn, which will lead to a large loss of Zn in the body; the reduction of Zn will promote the occurrence of diabetes.<sup>46,104</sup> Moreover, Cu and some Cu enzymes are involved in the synthesis of a specific protein on the surface of pancreatic islet B cells, GIUT2, which promotes insulin production. When the body is seriously short of Cu, the synthesis of GIUT2 protein is insufficient, affecting the production of insulin. The secretion of insulin is also regulated by the central nervous system. Cu plays an important role in maintaining the functional stability of the central system, and its deficiency can affect nerve transmission and reduce insulin secretion, thus causing or aggravating diabetes.<sup>102</sup> Lee et al and other studies also found that when  $\text{Cu}^{2+}$  combines with human amylin (HA), this combination can

stabilize the nontoxic conformation of HA and block the polymerization and apoptosis of cells, suggesting that the complex of  $\text{Cu}^{2+}$  and HA may protect islet cells.<sup>105</sup>

An increasing number of studies have shown that Fe overload can increase the risk of diabetes. Fe deposition in the liver leads to oxidative stress disorder, increases apoptosis, decreases the expression of IRS2 and GIUT2 in the liver, causes insulin resistance, and eventually leads to abnormal glucose metabolism.<sup>106</sup> Moreover, Fe is involved in the synthesis of hemoglobin *in vivo*, and Fe deficiency can induce anoxia of pancreatic tissue, which can affect the synthesis and release of insulin.<sup>107</sup> There are many proteins involved in Fe transport, not only CP. When CP is dysfunctional, the body has a strong compensation effect on Fe metabolism, but CP is involved in the main process of Fe excretion.<sup>63,108</sup> When CP is dysfunctional, it will cause Fe accumulation in tissue and lead to diabetes mellitus. To study the effect of tea polyphenols on glucose metabolism in CP gene knockout mice, it was found that CP gene knockout mice suffer from insulin resistance and abnormal glucose metabolism more easily due to Fe overload.<sup>106</sup>

CP also plays an important role in diabetic complications. It has been found that serum CP can be used as an independent predictor of type 2 diabetic nephropathy.<sup>109</sup> This may be because the increase in oxidative stress and the oxidative modification of low-density lipoprotein are related to the progression of diabetes,<sup>110</sup> and CP can reflect the degree of oxidation.<sup>98</sup> It has also been found that the selective  $\text{Cu}^{2+}$ -chelating agent trientine can significantly increase ventricular ejection fraction and decrease left ventricular mass index in patients with T2DM complicated by left ventricular hypertrophy. This shows that CP can also improve T2DM with left ventricular hypertrophy, but clinical research is still needed to verify this hypothesis.<sup>111</sup> To summarize the articles on diabetic retinopathy, we found that CP, as a biological enzyme, plays a key role in the pathogenesis of diabetic retinopathy.<sup>112</sup>

In summary, CP has a close relation with the generation and development of diabetes and may play a protective role in abnormal glucose metabolism, providing a new research direction for the diagnosis and treatment of diabetes.

### Relationship with Hyperlipidemia

Hyperlipidemia is a pathological state of lipid metabolism disorder. The clinical manifestations are elevated levels of serum total cholesterol (TC), triglyceride (TG), and low-density lipoprotein (LDL) and decreased levels of serum high-density lipoprotein (HDL). According to a study, the total prevalence of hyperlipidemia in patients over 18 years old in China is 40.40%; the prevalence of LDL-C was the highest (33.9%), followed by high TG (13.1%).<sup>113</sup> Studies indicate that between 2010 and 2030 the number of patients with cardiovascular diseases (CVDs) in China will increase by 9.2 million.<sup>114</sup> Hyperlipidemia is divided into primary and secondary categories. Primary hyperlipidemia has a familial tendency.<sup>115</sup> Secondary hyperlipidemia is dyslipidemia caused by other diseases, such as diabetes and hypertension. In addition, age, weight, and lifestyle factors, such as diet, exercise, and mental stress, can also affect blood lipid levels. It is now believed that the pathological mechanism of hyperlipidemia is related to endoplasmic reticulum (ER) stress, gene polymorphism, inflammatory state, oxidative stress, intestinal flora, and trace elements.<sup>116</sup> Studies have shown that CP is related to dyslipidemia and can participate in multiple stages of hyperlipidemia.

ER stress plays an important role in lipid metabolism and protein synthesis.<sup>117</sup> Various physiological and pathological disturbances can affect the folding process of primary synthetic proteins in the ER cavity, causing the increase and accumulation of unfolded and misfolded proteins, which is ER stress.<sup>118</sup> SR-BI is a major receptor for HDL, and ER stress induces downregulation of SR-BI gene expression, leading to lipid metabolism disorders.<sup>119,120</sup> GRP78 is a molecular marker of ER stress. Zhou et al<sup>121</sup> found that the mRNA and protein expression of GRP78 in hyperlipidemic rats was significantly decreased, and, after treatment, serum TC, TG, and LDL-C were significantly decreased, and GRP78 gene expression and protein content were significantly increased. All these studies indicated that ER stress plays an important role in the pathogenesis of hyperlipidemia.<sup>121</sup> Studies on Cu-loaded hepatocytes cultured *in vitro* showed significant ER stress in hepatocytes, so the damage to Cu-loaded hepatocytes is closely related to excessive ER stress.<sup>122</sup> Moreover, Kono et al<sup>123</sup> observed that individuals with aceruloplasminemia have ER stress leading to cell death. Therefore, we speculated that CP could avoid ER stress caused by increased Cu levels by regulating Cu metabolism, thus reducing the occurrence of hyperlipidemia. However, the preventive effect of CP on hyperlipidemia still needs to be confirmed by relevant studies.



It is now believed that the inflammatory response is accompanied by the occurrence and development of hyperlipidemia, which can accelerate the accumulation of fat in liver cells. The accumulation of fat continues to aggravate the inflammatory response in a vicious cycle, resulting in lipid disorders. Studies have shown that the level of related inflammatory factors such as C-reactive protein in patients with hyperlipidemia is significantly increased and is positively correlated with TC, TG, and LDL-C.<sup>124</sup> CP, as an acute reactive protein, may play a certain role in predicting the occurrence and prognosis of hyperlipidemia. The exact role of CP in inflammation needs further study.

In patients with hyperlipidemia, the level of oxidative stress *in vivo* increases, while the overall antioxidant capacity decreases. Therefore, it is likely that the mechanism of oxidative stress is involved in the occurrence of abnormal lipid metabolism. Hydroxyl radicals, oxidative products, can react directly with lipids, inducing lipid peroxidation and cause structural and functional damage to various biomolecular membranes,<sup>125,126</sup> ultimately accelerating the process of atherosclerosis and increasing the risk of coronary heart disease.<sup>127</sup> As an important antioxidant, CP has a therapeutic effect on oxidative stress in the body. Studies have found that CP can significantly eliminate hydroxyl radicals and improve the lipid peroxidation state.<sup>128</sup> However, studies still show that oxidative stress may change CP from a protective factor to a vascular pathological factor.<sup>129</sup> These data showed that CP, based on its structure and integrity in combination with Cu, could play an effective oxidant role in LDL rather than having an antioxidant effect. This also proves that the destruction of this combination may change the antioxidant function of CP.<sup>130</sup> Therefore, CP may have preventive and predictive effects on hyperlipidemia, but the corresponding pathophysiological mechanism has not been studied.

### Relationship with Obesity

Obesity is a chronic metabolic disease that is usually caused by the interaction of heredity, environment, and other factors, such as weight gain caused by abnormal fat distribution or excessive fat accumulation in the body. Obesity can cause a variety of complications and is closely related to the incidence of various acute and chronic diseases and symptoms, such as dyslipidemia, metabolic syndrome, T2DM, atherosclerosis, and CVD. According to a 2015 survey, obesity and overweight rates among children aged 6 to 17 in China reached 6.4% and 9.6%, respectively, which were 5.1 and 4.3 percentage points higher than percentages in 2002.<sup>131,132</sup> The study found that CP is associated with obesity, and Tajik et al observed a decrease in plasma CP levels in obese women after losing weight through diet.<sup>133</sup> CP can participate in the inflammatory response and oxidative stress in the occurrence and development of obesity, and it can also affect obesity by regulating intestinal flora and complications.

Current research suggests that obesity is a chronic low-grade systemic inflammation that results from the interaction between adipocytes, macrophages, and other immune cells that permeate and dilate adipose tissue. The inflammatory development of obesity leads to adipocyte hypertrophy, which is the most representative feature of adipose tissue dysfunction, and this feature increases the production of proinflammatory cytokines.<sup>134</sup> CP, as an inflammatory factor, can be used to measure the degree of inflammation and distinguish inflammatory diseases. Kim et al,<sup>8</sup> using the protein differential display technique, found that an increase in CP is significantly associated with obesity, indicating that CP may be used as a biomarker of obesity. Moreover, compared with fibrinogen, C-reactive protein (CRP), and IL-6, CP is a better predictor of long-term prognosis for obesity inflammation.<sup>135</sup> However, whether CP plays an important mediating or inducing role in obesity inflammation, whether its increase can affect the status of obesity inflammation, or whether it is only a simple marker still needs research.

Many studies have shown that the level of oxidative stress in patients with obesity is increased for many reasons, in which mitochondrial function changes play a decisive role. Mitochondrial dysfunction of adipose tissue in patients with obesity is characterized by decreased mitochondrial biosynthesis and activity, excessive production of ROS, and increased autophagy.<sup>136–138</sup> All these factors can adversely affect adipose tissue function. CP can promote metabolism by regulating the metabolism of Cu and Fe, promoting mitochondrial biosynthesis and activity, improving oxidative stress in adipose tissue, and inhibiting autophagy.<sup>139</sup> Studies have found that intestinal flora is involved in the metabolic process of human nutrition and energy. Intestinal flora can mediate the occurrence and development of obesity not only by affecting the absorption of energy metabolism and intestinal wall permeability but also by participating in the metabolic process of the body and interacting with human tissues and organs.<sup>140</sup> The disorder of trace elements such as Cu and Fe can also affect the

composition and function of intestinal flora, including the function of lipid metabolism.<sup>141,142</sup> However, the role of CP in intestinal flora is still incompletely understood.

The World Cancer Research Fund concluded in 2007 that obesity is associated with an increased risk of pancreatic (postmenopausal) breast, endometrial, and renal cancer.<sup>143</sup> A study found that CP is a novel adipokine with increased expression in the adipose tissue of obese subjects and cells of obesity-related cancers.<sup>144</sup> Whether there is a causal relationship between overexpression of CP and cancer development in patients with obesity still needs further study. When Safavi et al<sup>145</sup> observed the relationship between serum CP level and obesity, they found that there was no correlation, but the serum CP level was positively correlated with serum triglyceride level. The relationship between CP and obesity still needs much research.

### Relationship with Other Metabolic Diseases

In addition to diabetes and obesity, CP is also associated with other metabolic diseases, such as coronary heart disease (CHD). Göçmen et al<sup>146</sup> found that CP levels increase in patients with CHD. In their study, they found that CP level is an independent risk factor for CVD.<sup>146</sup> Mori et al<sup>147</sup> separated the risk contributed by CP from that of inflammation ( $\alpha$ 1-antitrypsin,  $\alpha$ 1-acid glycoprotein,  $\alpha$ 2-macroglobulin, haptoglobin, fibrinogen, C4b binding protein, lipoprotein, and CRP) and suggested that CP could serve as an independent risk factor for coronary atherosclerosis and as a marker for the severity of disease.<sup>147</sup> Many studies have found an association between CP and CHD, but have not reached a unified conclusion about the mechanisms for the role of CP in CHD. Some studies have suggested that the oxidation of LDL leads to the initiation or acceleration of the process of atherosclerosis, and CP is an effective catalyst for the oxidation of LDL. CP, by influencing NO levels, can reduce the bioavailability of NO in plasma, inhibiting its protective effect on cardiac ischemia and failure. However, there are also studies suggesting that CP is an antioxidant that plays a protective role in the development of CHD. For a better observation on achievements about the role of CP in CVD gathered from clinical studies, we report in brief the main points of relevant researches in recent years, as shown in Table 1. To explore the latest research trends, Web of Science was used to retrieve CP studies published from 2016 to 2020. The search yielded 2098 original studies and reviews, which were exported to CiteSpace for burst analysis, as shown in Figure 5.

As shown, studies on CP in the past five years have focused on in vitro experiments, antioxidation, immune response, and metabolic diseases. Moreover, since 2018, research on immunity and diabetes has become a hot topic and trend for CP. At present, an association between CP and metabolic diseases such as diabetes has been found, and it is believed that CP mainly plays a role in diseases by regulating copper and iron metabolism, oxidative stress, and inflammation. Although the mechanism of CP in the metabolism of copper and iron has been thoroughly studied, questions remain. Does CP mainly work as an antioxidant or oxidant in oxidative stress? Does it play an anti-inflammatory role in the inflammatory response? Why do studies of CP, using different research methods on similar populations, find different or even opposite research results? Furthermore, the stability of CP's physiological functions has not been determined. Therefore, future research might study the mechanism of CP in metabolic diseases, especially its involvement in oxidative stress and the immune response to uncover the specific link between CP and metabolic disease and find the precise target for its function.

## Conclusion

An increasing number of studies have found correlations between CP and metabolic diseases such as diabetes and hyperlipidemia and have observed that CP can be involved in the physiological and pathological processes of these diseases. A large number of studies have shown that CP plays an important role in the balance of Cu and Fe through its oxidase activity. CP exhibits antioxidant activity and can protect tissue from oxidative damage. The study found that the level of CP increased in the inflammatory state, and attenuated the activation of neutrophils, indicating that CP can be used as a predictor and antagonist of inflammation.<sup>66</sup> At present, it is believed that CP plays a protective role in metabolic diseases, mainly by participating in oxidative stress and the metabolism of Cu and Fe and acts as an inflammatory factor to predict those diseases. However, some studies have also found that CP plays the role of antioxidant. The causal relationship between CP and metabolic diseases in the human body is not clear. While a large number of studies have

**Table I** Summary of Achievements About the Role of CP in CVD Gathered from Clinical Studies

Author and Year of Publication	Study Type	Sample Size (Case/Control)	Assessment Results	Conclusions Related to CP	Association Between CP Levels and Risk of CHD
Reunanen et al <sup>148</sup> 1992	Nested case control study	104/104	Incidence of myocardial infarction and stroke	Higher serum CP level is a risk factor for myocardial infarction	✓
M. Manttari et al <sup>149</sup> 1994	Nested case control study	136/136	Nonfatal myocardial infarction or cardiac death	Patients with elevated CP had an increased coronary risk	✓
Mori et al <sup>147</sup> 1995	Cohort study	225	Severity of coronary atherosclerosis	CP may be an independent risk factor for coronary atherosclerosis and determine the severity of the disease	✓
Enbergs et al <sup>150</sup> 1998	Cohort study	275	Severity of CHD	Serum CP levels have not been identified as a risk factor in the CHD range	×
Klipstein-Grobusch et al <sup>151</sup> 1999	Nested case control study	83/127	Incidence of myocardial infarction	The association between serum CP and CHD may be attributed to inflammatory processes	✓
Engström et al <sup>152</sup> 2003	Cohort study	6075	Incidence of myocardial infarction	CP levels increased the incidence of myocardial infarction	✓
Engström et al <sup>153</sup> 2004	Cohort study	6075	Nonfatal myocardial infarction or cardiac death	CHD deaths were higher in men who had low-grade inflammation years earlier	✓
Verma et al <sup>154</sup> 2005	Cohort study	250	Severity of CHD	There was an inverse relationship between CP and coronary risk factors	×
Brunetti et al <sup>155</sup> 2008	Cohort study	123	Acute myocardial infarction. Early left ventricular systolic function	CP was the most important marker of acute heart failure	✓
Göçmen et al <sup>146</sup> 2008	Case control study	26/26	Risk of CVD	High CP levels were found to be an independent risk factor for CVD	✓
Deepa et al <sup>156</sup> 2009	Case control study	100/50	Acute myocardial infarction with and without diabetes	CP may serve as an indicator of oxidative stress	✓
Kumar et al <sup>157</sup> 2009	Case control study	165/165	Myocardial infarction	CP levels in patients with myocardial infarction were higher than those in the control group	✓
Tang et al <sup>158</sup> 2010	Cohort study	3828	Subclinical myocardial infarction	The presence of subclinical myocardial infarction was associated with increased CP levels	✓
Tang et al <sup>159</sup> 2012	Cohort study	4177	Major adverse cardiovascular events (death, myocardial infarction, stroke) occur in patients with stable heart disease	Serum CP levels were associated with a higher risk of myocardial infarction	✓
Xu et al <sup>160</sup> 2013	Case control study	78/124	Degree of heart failure	CP levels were significantly higher in both ischemic and non-ischemic cardiomyopathy	✓
Grammer et al <sup>161</sup> 2014	Cohort study	3253	All-cause mortality and cardiovascular mortality	CP concentration was independently associated with an increased risk of all-cause and cardiovascular death	✓
Daybanyrova et al <sup>162</sup> 2015	Cohort study	117	Mortality in patients with ischemic heart disease	CP could be used to predict the occurrence of acute coronary events	✓
Bao et al <sup>163</sup> 2018	Cohort study	4658	Risk of CVD	CP levels could predict the risk of CVD	✓

**Notes:** ✓, Yes; ×, No.

**Abbreviations:** CP, ceruloplasmin; CVD, cerebrovascular disease; CHD, coronary heart disease.

Keywords	Year	Strength	Begin	End	2016 - 2020
in vitro	2016	2.71	<b>2016</b>	2017	
glutathione	2016	2.56	<b>2016</b>	2017	
metabolic syndrome	2016	2.24	<b>2016</b>	2017	
exposure	2016	1.92	<b>2016</b>	2017	
cow	2016	1.92	<b>2016</b>	2017	
disorder	2016	2.59	<b>2017</b>	2018	
lactoferrin	2016	2.59	<b>2017</b>	2018	
myeloperoxidase	2016	1.93	<b>2017</b>	2018	
immunity	2016	1.94	<b>2018</b>	2020	
diabetes mellitus	2016	1.94	<b>2018</b>	2020	

**Figure 5** Top 10 important CP keywords with high burst values. Bold text indicates the year of the keyword appearance, blue indicates the timeline, and red indicates the time occupied by the keyword.

found a correlation between CP and metabolic diseases, future research should focus on solving the molecular mechanism of CP in metabolic diseases and studying its other roles.

## Statement of Ethics

This article does not contain any studies with human or animals performed by any of the authors.

## Acknowledgments

We would like to thank the researchers for their contributions. This paper was supported by the Clinical Research Plan of SHDC (No. SHDC2020CR3028A and No. SHDC12019X16).

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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