

# Significance of Cu/Zn-Superoxide Dismutase Levels in Hemodialysis Patients: A Mini Review

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## Abstract

Cu/Zn-superoxide dismutase (Cu/Zn-SOD) is an enzyme that is ubiquitously present in the cytoplasm and causes dismutation of superoxide radicals, therefore Cu/Zn-SOD is primarily used as an antioxidant marker. Levels of Cu/Zn-SOD are higher in the serum of hemodialysis patients than in serum of healthy volunteers. The increase of serum Cu/Zn-SOD levels is related to the decrease of kidney function with aging and arteriosclerosis in hemodialysis patients. Moreover, infection, vascular puncture, and hemostasis may be related to the increase in serum Cu/Zn-SOD levels. As it is associated with numerous factors in hemodialysis patients, Cu/Zn-SOD may serve as a complex marker for arteriosclerosis, vascular, and inflammatory conditions. It is important to investigate various agents that decrease serum Cu/Zn-SOD levels to improve the life-span of hemodialysis patients.

## Keywords

Cu/Zn-Superoxide Dismutase, Hemodialysis, Complex Marker

## 1. Introduction

Cu/Zn-superoxide dismutase (Cu/Zn-SOD) is an enzyme that is ubiquitously present in the cytoplasm and causes dismutation of superoxide radicals, which are produced by nicotinamide adenine dinucleotide phosphate oxidase and xanthine oxidase, into hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and molecular oxygen (O<sub>2</sub>). The copper and zinc ions in Cu/Zn-SOD play essential roles in enzyme activity and structure stability, respectively. Several studies have reported that levels of

Cu/Zn-SOD are high in patients on hemodialysis and this is closely related to end-stage renal failure. However, there are very few reviews that summarize the significance of Cu/Zn-SOD. In this brief review, we reconsider the significance of Cu/Zn-SOD levels in dialysis patients.

## 2. High Levels of Serum Cu/Zn-SOD in Hemodialysis Patients

Several reports have shown that levels of Cu/Zn-SOD are higher in the serum of hemodialysis patients than in serum of healthy volunteers [1]-[26]. Such high levels are related to decrease in renal excretion with low renal function [8]. Moreover, Akiyama *et al.* reported that Cu/Zn-SOD mRNA levels were also high in the white blood cells of these patients, thus leading to increased Cu/Zn-SOD production [12]. On the other hand, Futenma *et al.* examined Cu/Zn-SOD isomers using gel column chromatography and revealed that despite a decrease in tetramers or octamers of Cu/Zn-SOD, there was a marked increase in Cu/Zn-SOD levels in hemodialysis patients owing to an increase in monomers of Cu/Zn-SOD that are immunologically active but enzymatically inactive [26]. Thus, both immune status and enzymatic activities may be important for Cu/Zn-SOD measurements in hemodialysis patients.

## 3. Factors Affecting Serum Cu/Zn-SOD Levels in Hemodialysis Patients

Serum Cu/Zn-SOD levels are related to many factors [5] [6] [8] [9] [11] [13] [19] [21] [22] [27]. Pawlak *et al.* found that serum Cu/Zn-SOD levels in peritoneal dialysis and hemodialysis patients are associated with several factors, such as age, creatinine clearance, dialysis period, arteriosclerosis (medial intima complex thickening, malondialdehyde modified low-density lipoprotein), vascular injury, hemostasis, coagulation, vascular repair, angiogenesis (thrombomodulin, vascular endothelial growth factor, von Willebrand factor, urokinase-type plasminogen activator, plasmin/antiplasmin, matrix metalloproteinases, tissue inhibitors of metalloproteinases, tissue factor pathway inhibitor, tissue factor), inflammation (vascular cell adhesion molecule-1, tumor necrosis factor-alpha, macrophage inflammatory proteins, monocyte chemoattractant protein, Regulated on Activation, Normal T-cell Expressed and Secreted), hepatitis, and hepatocyte growth factor. In these reports, the increase of serum Cu/Zn-SOD levels is related to the decrease of kidney function with aging and arteriosclerosis. Moreover, infection, vascular puncture, and hemostasis may be related to the increase in serum Cu/Zn-SOD levels in peritoneal dialysis and hemodialysis patients. Cu/Zn-SOD is primarily used as an antioxidant marker. However, as it is associated with numerous factors in hemodialysis patients, it may serve as a complex marker for arteriosclerosis, vascular, and inflammatory conditions. The onset of arteriosclerotic disease and vascular infection are especially poor prognostic factors in dialysis patients and such complex marker is important, thus necessitating further study.

#### 4. Agents Reducing Serum Cu/Zn-SOD Levels in Hemodialysis Patients

Two reports have revealed the agents reducing serum Cu/Zn-SOD. Washio *et al.* reported that serum Cu/Zn-SOD and leukocyte Cu/Zn-SOD mRNA levels decreased in hemodialysis patients who were administered vitamin E or who were treated with vitamin E-coated dialyzer membranes [28]. Vitamin E, an antioxidant agent, might suppress Cu/Zn-SOD production in the blood cells. Pawlak *et al.* reported that erythropoiesis-stimulating agent (ESA) treatment caused a decrease in Cu/Zn-SOD levels in peritoneal dialysis patients with diabetes [29]. It is important to investigate such agents that decrease serum Cu/Zn-SOD levels as it is a complex marker indicating arteriosclerosis as well as vascular and inflammatory conditions.

#### 5. Conclusion

Cu/Zn-SOD is the antioxidant marker as well as a complex marker indicating arteriosclerosis, vascular, and inflammatory conditions. Thus, further studies on serum Cu/Zn-SOD levels are necessary to improve the life-span of hemodialysis patients.

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