# A Possible Deleterious Effect of Increased Serum Copper on Myocardial Function in Patients with Dilated Cardiomyopathy Awaiting Transplantation

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## ABSTRACT

• ***Objective:*** *We aimed to evaluate the possible contribution of alterations in serum copper and zinc levels to cardiac dysfunction in patients with dilated cardiomyopathy.*

• ***Material and Method:*** *We determined blood copper and zinc levels in 16 patients with dilated cardiomyopathy awaiting heart transplantation and 16 control patients. Clinical severity of heart failure was assessed by New York Heart Associaton criteria and left ventricular ejection fraction by echocardiography.*

• ***Results:*** *The mean serum copper level was significantly higher in the patient group than in control group (1.28±0.5 ppm and 0.81±0.21 ppm, respectively; p=0.01). Correlations between copper and heart failure severity and ejection fractions were not significant (r=0.303, p=0.30 and r=-0.33, p=0.21, respectively). There was no difference in zinc level between the patient and control group (0.85±0.82 ppm and 0.87±0.5 ppm, respectively; p=0.336). The correlation between zinc and heart failure severity was not significant (r=-0.23, p=0.4). A negative correlation was found between zinc and ejection fraction (r=-0.55, p=0.03).*

• ***Conclusion:*** *The significantly increased copper level, the positive correlation between copper and the severity of heart failure and the negative correlation between ejection fraction (although without reaching statistical significance) suggest that it may have a role in cardiac dysfunction. The insignificant alteration of the zinc level compared to the controls may be reflecting the small size of the patient population. We suggest that further studies on larger patient populations are needed to define the role of these trace elements in the pathogenesis of dilated cardiomyopathy.*

• ***Key Words:*** *Copper, zinc, dilated cardiomyopathy, heart transplantation* ***Nobel Med 2010; 6(2): 32-36***

## ÖZET

### TRANSPLANTASYON BEKLEYEN DİLATE KARDİYOMİYOPATİLİ HASTALARDA YÜKSEK SERUM BAKIR DÜZEYİNİN MİYOKARD İŞLEVİ ÜZERİNDEKİ MUHTEMEL KÖTÜ ETKİSİ

• **Amaç:** Serum bakır ve çinko düzeylerindeki değişikliklerin dilate kardiyomiyopatideki kardiyak işlev bozukluğuna muhtemel katkısını değerlendirmek.

• **Materyal ve Metod:** Kalp transplantasyonu bekleyen dilate kardiyomiyopatili 16 hasta ve 16 kontrolde kan bakır ve çinko düzeyleri ölçüldü. Kalp yetersizliğinin klinik düzeyi New York Heart Association kriterlerine göre ve ejeksiyon fraksiyonu da ekokardiyografik olarak değerlendirildi.

• **Bulgular:** Ortalama serum bakır düzeyi hasta grubunda kontrol grubundan anlamlı olarak daha yüksekti (sırasıyla 1,28±0,5 ppm ve 0,81±0,21 ppm, p=0,01). Bakır düzeyi ile kalp yetersizliğinin derecesi ve ejeksiyon fraksiyonu arasında anlamlı bir korelasyon yoktu (sırasıyla r=0,303, p=0,30 ve r=-0,33, p=0,21). Hasta ve komtrol grubunda çinko düzeyleri arasında istatistiksel farklılık yoktu (sırasıyla 0,85±0,82 ppm ve 0,87±0,5 ppm, p=0,336). Çinko ve kalp yetersizliğinin derecesi arasında anlamlı bir korelasyon yoktu (r=-023, p=0,4). Çinko ve ejeksiyon fraksiyonu arasında anlamlı bir negatif korelasyon bulundu (r=-0,55, p=0,03).

• **Sonuç:** Hasta grubunda bakır düzeyinin anlamlı olarak yüksek bulunması ve istatistiksel anlamlılığa ulaşmamakla birlikte kalp yetersizliğinin derecesi ile pozitif, ejeksiyon fraksiyonu ile de negatif korelasyon göstermesi dilate kardiyomiyopatideki kardiyak işlev bozukluğunda rol oynayabileceğini düşündürmektedir. Çinko düzeylerinde anlamlı bir fark saptanmamasının ise hasta sayısının yetersizliği ile ilişkili olabileceğini düşünüyoruz.

Bu eser elementlerin dilate kardiyomiyopatideki rollerinin tanımlanması için daha büyük hasta popülasyonlarında çalışmalar yapılması gerektiği inancındayız.



• **Anahtar Kelimeler:** Çinko, bakır, dilate kardiyomiyopati, kalp transplantasyonu **Nobel Med 2010; 6(2): 32-36**


## INTRODUCTION

Dilated cardiomyopathies are a group of cardiac disorders characterized with myocardial involvement, which, may be primary or secondary to the effects of systemic hypertension, congenital or acquired abnormalities of the valves, arteries or the pericardium and coronary ischemia.[1] A panethnic disease affecting mainly middle aged men, dilated cardiomyopathy can also be associated with various infectious, toxic/metabolic, infiltrative and neuromuscular disorders. Nutritional factors have also been implicated in the development of dilated cardiomyopathy; among them, reduced thiamine intake, alcohol abuse and deficiencies of various trace elements are worth to mention.[2] The role of selenium deficiency in the genesis of cardiac failure has drawn much attention.[3]

However, the effect of other trace elements on myocardial degeneration is less extensively studied. In the present study we aimed to analyze serum zinc and copper levels in a population of patients with dilated cardiomyopathy awaiting cardiac transplantation and their relation to clinical heart failure severity assessed by New York Heart Association (NYHA) criteria and ejection fraction.

## MATERIAL and METHOD

The patient group consisted of 16 individuals (female/male: 2/14; mean age 34±11) with dilated cardiomyopathy awaiting cardiac transplantation. In 7 of the patients, the etiology was ischemic heart disease and other patients had been diagnosed with idiopathic dilated cardiomyopathy. The degree of the severity of the heart failure was classified between I-IV according to NYHA criteria; ejection fraction was calculated by echocardiography. The control group involved 16 healthy individuals (female/male: 4/12; mean age: 29±4).

Serum zinc and copper levels were determined as previously described.[4] Blood taken in sterile silicon tubes was centrifuged at 2500 rpm for 20 minutes and then the serum was taken into a sterile tube and was kept at -20 C. Before serum zinc and copper measurement, the samples kept at -20 C were taken into room temperature and then were diluted with trichloroacetic acid (TCA) (1:4). In order to precipitate; TCA was added and then centrifugated at 3000 rpm for 5 minutes and clear supernatant was analyzed by means of flame atomic absorption spectrometry (Varian spectra AA 220/FS). Informed consent was obtained from all the patients. The study was approved by the local ethics committee.

Statistical analyses were performed with the Mann-Whitney U test and by calculating the Spearman and Pearson correlation coefficients. →

**Table:** Correlations between various parameters.

| Parameters | | r | p |
|---|---|---|---|
| Cu and HF severity | | 0.303 | 0.30 |
| Cu and EF | | -0.33 | 0.21 |
| Zn and HF severity | | -0.23 | 0.4 |
| Zn and EF | | -0.55 | 0.03 |
| Cu and Zn | Patients | 0.182 | 0.5 |
| | Controls | 0.144 | 0.59 |

Cu: Copper; Zn: Zinc; HF: heart failure; EF: ejection fraction. HF severity was assessed by the New York Heart Association criteria

## RESULTS

In the patient group, the median heart failure severity assessed by the New York Heart Association criteria was III, while the mean ejection fraction was 26±6%. The mean serum copper level was significantly higher in the patient group compared to the controls (1.28±0.5 ppm and 0.81±0.21 ppm, respectively; p=0.01). Correlations between copper and heart failure severity and ejection fractions were not significant (r=0.303, p=0.30 and r=-0.33, p=0.21, respectively). The mean serum zinc level was not different between the patient and control group (0.85±0.82 ppm and 0.87±0.5 ppm, respectively; p=0.336). There was a statistically insignificant and negative correlation between zinc level and heart failure severity (r=-0.23, p=0.4). On the other hand, a moderately negative correlation was found between zinc and ejection fraction which was statistically significant (r=-0.55, p=0.03). There was a weak and insignificant correlation between copper and zinc levels in the patient (r=0.182 and p=0.5) and control (r=0.144 and p=0.59) groups (Table).

## DISCUSSION

In the present study, we found that serum copper level is significantly higher in patients with dilated cardiomyopathy compared to controls (1.28±0.5 ppm and 0.81±0.21 ppm, respectively; p=0.01). However, copper level did not correlate with heart failure severity and ejection fraction (r=0.303, p=0.30 and r=-0.33, p=0.21, respectively).

Of various trace elements, selenium is the most widely recognized micronutrient deficiency of which has been shown to be associated with dilated cardiomyopathy. It was suggested that selenium deficiency does not cause cardiomyopathy directly but rather causes a change in the genome of myocarditis-causing coxsackie virus which makes it more virulent.[5,6]

Of the other trace elements, copper and zinc have also been linked to cardiomyopathies. In one of the earliest studies, serum zinc was found to be decreased while copper was increased in children with congestive heart failure. Interestingly, after digoxin therapy, copper and zinc levels changed towards normal.[7] In another study, similar changes (decrease in zinc and increase in copper) were found in patients with dilated cardiomyopathy.[8]

Most recently, Topuzoglu et al found higher copper and lower zinc levels in patients with idiopathic dilated cardiomyopathy compared to healthy controls.[9] In agreement with the aforementioned studies, we found significantly increased copper levels compared to controls. The zinc level was not different between the two groups, although there was a negative correlation between zinc and ejection fraction. All these findings raise the question whether copper and zinc abnormalities participate in the pathogenesis of dilated cardiomyopathy.

Although the clinical spectrum associated with zinc deficiency is well defined, little is known about its consequences on cardiac function. Since the classical report by Prasad describing that zinc deficiency is associated with iron deficiency anemia, hypogonadism and dwarfism, it has been known that zinc is necessary for general health status.[10] However, the mode of action of zinc in regulating physiological body functions remains largely unknown. It has been observed that zinc deficiency has an adverse effect on the immune system.[11] Zinc is also necessary for the maintenance of epithelial and tissue integrity and is an antioxidant agent which protects cells against free radicals produced during inflammatory reactions.[12] It has been reported that zinc deficiency induces programmed cell death in many cell types including hepatocytes, kidney cells and fibroblasts.[13] However, overt heart failure has not been reported and precise evaluation of myocardial function (by echocardiography, hemodynamic studies, etc.) has not documented in states of chronic zinc depletion. In the present study, the mean zinc level was not different between the patient and control group.

Currently available data concerning the role of copper in heart failure is conflicting. There are a few animal studies to address this question: electrocardiographic changes and alterations of mitochondrial structure were observed in the myocardium of rats fed on a copper deficient diet.[14] In mice, copper restriction results in reduced expression of genes involved in contractility, calcium recycling, fibrosis and inflammation, which returned to control levels after copper repletion.[15] Also, dietary copper restriction has been shown to cause cardiac pathology including increased diastolic measures of ventricular wall and a significantly greater heart weight:body weight ratio in pigs.[16] Interestingly, it has been reported that submaximal aerobic exercise training→

and increased dietary fat intake worsens the cardiomyopathy associated with copper deficiency.[17,18] Conversely, copper chelation by trianterine in streptozotocine-induced diabetic rats significantly alleviated heart failure without lowering blood glucose.[19] In clinical trials, it has been reported that supplements containing copper improves ventricular function and the quality of life in elderly patients with chronic heart failure.[20] Not in agreement with this finding, another study found that baseline copper levels are increased in patients with chronic heart failure which correlated with one-year mortality and morbidity.[21] It has also been reported that serum copper levels predict short term outcome (re-admission to the hospital or death within 12 months) in high risk patients with chronic heart failure.[22] However, they found no correlation between serum copper level and ejection fraction, a finding which is in agreement with our findings in the present study.

The mechanism by which copper participates in the pathogenesis of cardiomyopathy is not clear; its deficiency has been proposed to be associated with impaired oxidative defense and contribute to myocardial damage.[23] It has been suggested that alterations of activities of various cuproenzymes (enzymes containing copper in their structure such as lysyl oxidase, cytochrome-c oxidase, and superoxide dismutase) may be involved.[24] High levels of copper also seem to be deleterious as a consequence of its redox activity such as free copper may catalyze the reaction between superoxide anion and $H_2O_2$ producing the hydroxyl radical.[23]

It is difficult to infer results from these experimental studies with respect to heart failure in general and dilated cardiomyopathy in particular. It appears that there is a delicate equilibrium in copper homeostasis so that both extremes (low and high levels) are harmful.

Although the copper level was significantly high in our patient group, there was no statistically significant correlation between heart failure severity or ejection fraction. However, it should be noted that the direction of the correlation were consistent with a possible deleterious effect of copper on myocardial function: a positive one (r=0.303) between copper and heart failure severity and a negative one (r=-0.33) between copper and ejection fraction.

In the present study, the negative correlation between ejection fraction and zinc also deserves attention. Recently, in an animal study, it has been described that, aldosteron/salt treatment leads to hypozincemia in rats; however, this is associated with increased tissue zinc which was accompanied by microscopic scars and perivascular fibrosis of intramural coronary arteries in both ventricles.[25] It should be noted that this finding is not in agreement with the negative correlation between zinc level and ejection fraction observed in the present study. Also, although statistically insignificant, the positive correlation between zinc and heart failure severity is not consistent with this finding. Therefore, it needs to be determined whether hypozincemia and increased tissue zinc have a direct effect on the myocardium or they are just adverse events that accompany heart failure.

## CONCLUSION

To conclude, increased levels of copper seem to be related with impaired cardiac function in dilated cardiomyopathy. Although the zinc level was not different between the patient and control groups, this may be reflecting the small size of patient population. We suggest that further studies with larger number of patients are needed to define clearly the role of these trace elements in the pathogenesis of dilated cardiomyopathy.

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