Trace element status (Se, Zn, Cu) in heart failure

Kalp yetersizliğinde eser elementlerin statüsü (Se, Zn, Cu)

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ABSTRACT

Objective: It has been speculated that trace elements may play a role in the pathogenesis of heart failure. In the present study, we aimed to assess serum concentrations of selenium (Se), zinc (Zn) and copper (Cu) in patients with heart failure (HF) and to compare idiopathic dilated cardiomyopathy (IDCM) and ischemic cardiomyopathy (ICM) patients with healthy controls.

Methods: This study population included 54 HF patients (26 IDCM patients and 28 ICM patients) and 30 healthy subjects. Serum levels of selenium, zinc, and copper were assessed by atomic absorption spectrophotometry method.

Results: Serum concentrations of Se and Zn in HF patients were significantly lower than in healthy controls (p=0.000 and p<0.01, respectively). However, serum Cu concentrations in these patients were significantly higher than in controls (p=0.000). There were no significant difference in the trace elements status between IDCM and ICM patients (p>0.05 for all parameters). Relationships of the serum trace element concentrations studied with echocardiographic and hemodynamic parameters were not statistically significant.

Conclusion: Our study showed that heart failure is associated with lower Se and Zn concentrations, and higher Cu concentration, and serum Se, Zn and Cu element profiles were similar in IDCM and ICM. *(Anadolu Kardiyol Derg 2006; 6: 216-20)*

Key words: Selenium, Zinc, Copper, 'idiopathic dilated cardiomyopathy, ischemic cardiomyopathy

ÖZET

Amaç: Eser elementler kalp yetersizliğinin patogenezinde rol oynadıkları ileri sürülmektedir. Biz bu çalışmada kalp yetersizliği (KY) olan hastalarda serum selenium (Se), çinko (Zn) ve bakır (Cu) konsantrasyonlarını değerlendirmeyi ve idyopatik dilate kardiyomiyopati (İDKMP) ve iskemik kardiyomiyopati (İSKMP) hastalarında sağlıklı bireyleri karşılaştırmayı amaçladık.

Yöntemler: Bu çalışmanın popülasyonu 54 KY hastasını (26 İDKMP ve 28 İSKMP) ve 30 sağlıklı bireyi içerdi. Eser elementler (Se, Zn, Cu) atomik absorpsiyon spektrofotometri metodu ile değerlendirildi.

Bulgular: Kalp yetersizliği olan hastalarda selenyum ve çinko konsantrasyonları sağlıklı bireylerden daha düşüktü (sırasıyla, p=0.000 ve p<0.01). Fakat bu hastalarda serum bakır konsantrasyonları sağlıklı bireylerden önemli oranda yüksekti (p=0.000). Ayrıca İDKMP ve İSKMP alt grupları arasında serum Se, Zn ve Cu statüslerinin fark yok idi (tüm parametreler için p>0.05). Çalışılan serum eser element konsantrasyonları ile ekokardiyografik ve hemodinamik parametreler arasında istatistiksel açıdan anlamlı bir ilişki yoktu.

Sonuç: Bizim çalışmamız kalp yetersizliğine düşük Se ve Zn konsantrasyonları ve yüksek Cu konsantrasyonları eşlik ettiğini ve İDKMP ve İSKMP hastalarında eser element profillerinin benzer olduğunu göstermektedir. *(Anadolu Kardiyol Derg 2006; 6: 216-20)*

Anahtar kelimeler: Selenium, Çinko, Bakır, idyopatik dilate kardiyomiyopati, iskemik kardiyomiyopati

Introduction

Trace elements are being increasingly recognized as essential mediators of the development and progression of heart diseases. It is well known that Se, Zn, and Cu in serum can affect certain heart diseases such as Keshan disease, heart failure, cardiomyopathy, and atherosclerosis (1-11). Therefore, trace elements may play an important role in the etiopathogenesis of the diseases.

Selenium is a part of glutathione peroxidase in the cytosol and mitochondria, which protects biomembranes against destruction. Selenium is also a central enzyme for eliminating oxygen free radicals and peroxidase. Enzymes such as superoxide dismutase and glutathione peroxidase contain either copper and zinc or manganese. Therefore, trace elements like Se, Zn and Cu have an antioxidant role in many essential enzyme systems (12-17). In the lack of superoxide dismutase, superoxide anions react with hydrogen peroxide to form hydroxide radicals, and cause lipid peroxidase and destruction of the cell membranes. On theoretical grounds, trace elements may be protective against oxygen free radicals in the development of cardiovascular disease (18-20).

The aims of the present study was (1) to evaluate the status of selenium, zinc, and copper trace element in patients with

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chronic heart failure (2), to compare these trace element concentrations in patients with IDCM and ICM subgroups of chronic heart failure, and (3) to investigate potential relation between serum trace element concentrations and the clinical, laboratory and haemodynamic parameters in order to reproduce some findings reported in the literature and to produce new findings.

Methods

Study Design and Patients

We studied 26 patients with idiopathic dilated cardiomyopathy (IDCM) (14 males, 12 females, mean age 60±12 years) and 28 patients with ischemic cardiomyopathy (ICM) (16 males, 12 females, mean age 62±10 years) who were admitted to our hospital because of dyspnea or fatigue on modest exertion or at rest (New York Heart Association class II-IV) (30 males, 24 females, aged 32 to 72 years). The sex and age-matched control subjects in this study included 30 healthy volunteers (18 males, 12 females, mean age 56±8 years). All patients were being treated with diuretics; most were receiving an angiotensin converting enzyme inhibitor and digoxin. None were taking other group drugs and there was no clinical history suggestive of underlying infection, inflammatory disease and cancer. All patients and controls gave their consent for the study and the protocol was approved by the Ethics and Committee of our institution.

Clinical Evaluation

Heart disease was diagnosed in the patients on the basis of medical history, physical findings, electrocardiography, radiography, echocardiography, and coronary angiography. The diagnosis of IDCM was established on the basis of finding of a normal-appearing coronary angiography, the absence of valvular or pericardial heart disease by transthoracic echocardiography and the absence of a clinical history that would suggest myocarditis. The clinical diagnosis of ICM was made on the basis of a history of prior myocardial infarctions and known coronary artery disease documented by coronary angiography. Apparently normal subjects were determined by a careful review of history, by physical examination and laboratory analysis of diagnostic variables to exclude cardiac, hematological, renal, or hepatic dysfunction.

Echocardiographic and Hemodynamic Evaluation

The left ventricular ejection fraction (EF), diastolic (LVDD) and systolic diameter (LVSD) of these patients were determined by M-mode echocardiography. Also, besides transthoracic echocardiography, all patients were performed right-and left-heart catheterization, coronary angiography. All haemodynamic data were obtained from the invasive and non-invasive cardiac examination.

Collection of Blood Samples and Analysis of Serum Trace Elements

Patients with cardiac disease had blood drawn at the time of or shortly after admission to hospital. Blood from study subjects and controls was drawn in sterile syringes containing 0.1 ml of sodium citrate anticoagulant, transferred into special metal-free tubes, and centrifuged at 11.000xg or 10 minutes. During this procedure there was no loss or contamination of the investigated elements of the sample as confirmed by pre-analyzed samples. The sample was centrifuged immediately and the separated serum was stored at -80C until assay. Values from these samples were combined for the healthy reference range.

Values of trace elements such as selenium, zinc, and copper were determined in serum from patients with cardiac disease and in healthy subjects. Serum selenium, zinc, and copper concentrations were determined by using the standard atomic absorption spectrophotometry (21). The concentrations of selenium in serum were determined by using a furnace atomic absorption spectrometer with Zeeman background correction. Serum zinc and copper concentrations were measured using a flame atomic absorption spectrophotometry, Model PU 9100 X (Philips).

Statistical Analysis

All values are presented as mean ± SD. A comparison of the data was performed using Student's independent-samples T test. The differences according to the underlying heart diseases and the functional class groups were compared by Kruskal Wallis variance analysis method as appropriate. The relations between parameters in each group were evaluated by correlation analysis. A p value < 0.05 was considered statistically significant.

Results

Table 1 summarizes data on serum concentrations of selenium, zinc, and copper elements in the patients with chronic heart failure and in the controls. No age and sex related differences between heart failure and control groups were found. Patients with heart failure had lower serum selenium and zinc concentrations than the controls (p=0.000 and p<0.01, respectively). However, serum copper concentrations in heart failure patients were higher than in the control group (p=0.000). At the time of the evaluation, IDCM and ICM patients were treated with angiotensin-converting enzyme (ACE) inhibitors (73% vs. 75%, p<0.05), angiotensin II antagonists (23% vs. 25%, p>0.05), diuretics (61.5% vs. 64%, p>0.05), aldosterone antagonists (30.7 vs. 32%, p>0.05), and aspirin (80.7% vs. 82%, p>0.05)). None of them received anti-inflammatory agents and antibiotics.

Table 2 shows the mean serum concentrations of selenium, zinc, and copper in the patients with IDCM and ICM. The IDCM patients did not differ from ICM patients as regards to age and sex (60±10 years vs. 62±10 years, p>0.05, 14 males (53%) vs. 16 males (57%, p>0.05). In addition, there were no significant differences between patients with IDCM and ICM according to all trace element concentrations studied (p>0.05) (Figure 1, 2 and 3). No significant differences were found in these two subgroups with respect to echocardiographic and hemodynamic para-

Table 1. Serum trace element concentrations in patients with heart failure and in healthy controls

Parameters	Patients (n=54)	Controls (n=30)	P
Age, years	62±10	56±8	NS
Men/women, n (%)	30/24 (55)	18/12 (60)	NS
Se, µg/l	121±5	147±13	0.000
Zn, µg/l	555±104	620±130	<0.01
Cu, µg/l	880±185	644±179	0.000

Values are means ± standard deviation
Cu- copper, NS- not significant, Se- selenium, Zn- zinc

meters (p>0.05). When each group was compared with respect to all parameters, no significant difference was found among the subgroups according to the NYHA functional classification (Table 3).

Correlation analysis showed that all these trace element concentrations did not related to the clinical, echocardiographic and hemodynamic parameters (for all, p>0.05) (Table 4).

Discussion

Dietary factors such as inadequate intake of vitamins, minerals and trace elements, may contribute to the development of heart diseases. In addition, these diseases can be prevented by adding the adequate nutritive supply. The relationship between trace elements and heart disease are areas of increasing investigation. For example, a cardiomyopathy in China, the so-called Keshan disease, is due to selenium deficiency in the diet (1, 2). The Keshan disease is characterized by the presence of multifocal necrosis and fibrous replacement of the myocardial tissue. The disease manifests itself as heart failure and is clearly influenced by the dietary selenium intake. Additionally, many recent studies (1-11) suggest that there is an association between various heart diseases such as heart failure, cardiomyopathy, and atherosclerosis, and certain trace elements status (Se, Zn, and Cu). However, the etiopathogenetic role of these changes is not entirely clear up to now. In addition, the concentrations of serum trace elements have been not investigated in detailed manner previously in the heart failure subgroups.

Trace elements are known to have a key role in myocardial metabolism. Trace elements including selenium, zinc, and copper may be protective against cardiovascular disease (12-17). In contrast, the trace elements deficiency causes cardiomyopathy

Table 2. Comparison of serum trace element concentrations in heart failure according to the etiology

Parameters	IDCM group (n=26)	ICM group (n=28)	P
Se, µg/l	120±5	121±5	NS
Zn, µg/l	568±116	542±92	NS
Cu, µg/l	886±143	874±146	NS
LVDD, mm	62±10	61±12	NS
LVSD, mm	42±7	41±8	NS
EF, %	32±5	34±5	NS
PAP, mmHg	48±8	45±6	NS
ACE inhibitor, n(%)	19 (73)	21 (75)	NS
ARB, n(%)	6 (23)	7 (25)	NS
Diuretics, n(%)	16(61.5)	18 (64)	NS
AD, n(%)	8(30.7)	9(32)	NS
Aspirin, n(%)	21(80.7)	23 (82)	NS

Values are means ± standard deviation

ACE- Angiotensin-converting enzyme inhibitors, AD- Aldosterone antagonist, ARB- Angiotensin II receptor blockers, Cu- copper; EF- Ejection fraction, ICM- Ischemic cardiomyopathy, IDCM- Idiopathic dilated cardiomyopathy, LVDD- Left ventricular diastolic diameter, LVSD- Left ventricular systolic diameter, NS- not significant, PAP- Pulmonary artery pressure, Se- selenium; Zn- zinc

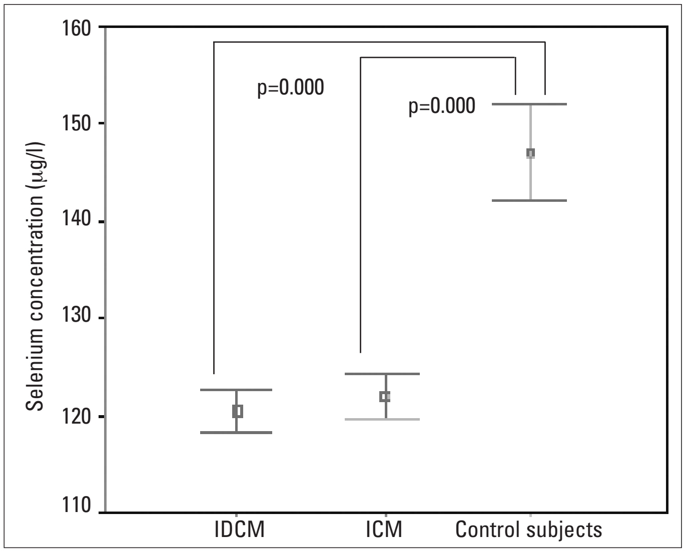

Figure 1. Serum selenium concentrations according to groups

ICM- Ischemic cardiomyopathy, IDCM- Idiopathic dilated cardiomyopathy

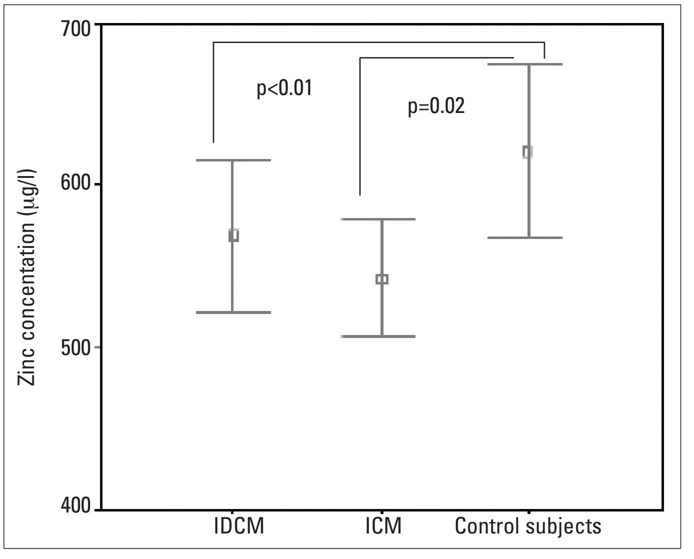

Figure 2. Serum zinc concentrations according to groups

ICM- Ischemic cardiomyopathy, IDCM- Idiopathic dilated cardiomyopathy

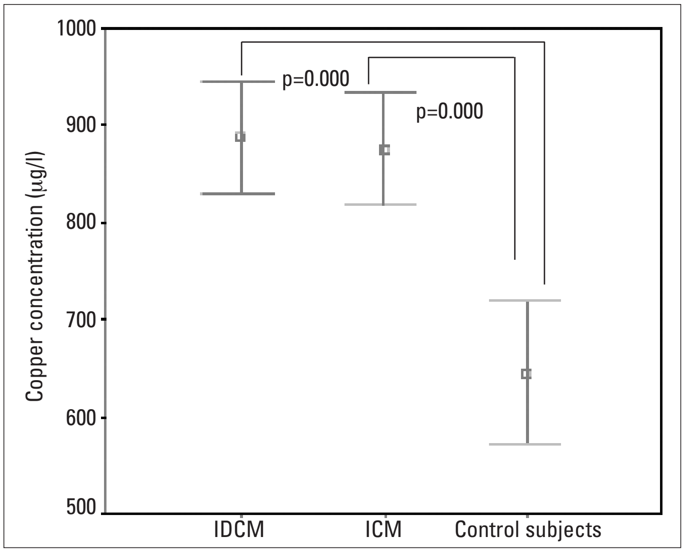

Figure 3. Serum copper concentrations according to groups

ICM- Ischemic cardiomyopathy, IDCM- Idiopathic dilated cardiomyopathy as a result of the depletion of essential enzymes, which protect cell membranes from damage by free radicals. Because the trace elements have a key role in essential enzymes such as glutathione peroxidase (GPx) and superoxide dismutase (SOD). It is therefore not surprising that one of the important biological functions of the trace elements is antioxidation. Glutathione peroxidase and SOD reduce the production of hydrogen peroxide and superoxide, therefore diminishing the propagation of free radicals and reactive oxygen species. Hypothetically, these enzymes may reduce myocardial damage by inhibiting the reactive and injurious hydrogen peroxide and superoxide anion. Oxygen-derived free radicals can either depress directly contraction or lead to apoptosis. Support for the idea that free radicals contribute to myocardial injury comes from the observation that antioxidants improve contractile function (18-20). The role of the trace elements in the synthesis of proteins and collagen and maintaining collagen integrity is well established and deficiencies of these trace elements have been shown to lead to myocardial friability and necrosis. Consequently, trace element deficiency may be responsible for cardiovascular diseases.

In the literature, there are several studies performed in patients with idiopathic dilated cardiomyopathy and healthy controls (1,6-11), and coronary artery disease and healthy controls (2-5) evaluate status of trace elements such as Se, Zn, and Cu. Few studies (9,10) have addressed the relationship between certain trace element concentrations and clinical, laboratory and hemodynamic parameters in idiopathic dilated cardiomyopathy. The previous studies (6-11) showed that patients with idiopathic dilated cardiomyopathy and coronary artery disease had a low selenium and zinc concentrations and higher copper concentrations. However, the causes and mechanisms resulting in decreased serum selenium and zinc concentrations and increased copper concentrations in dilated cardiomyopathy and coronary artery disease remain to be unexplained yet. In the present study we demonstrated that heart failure patients had lower serum selenium and zinc, and higher copper concentrations compared to healthy controls. In our study, serum trace elements status in heart failure patients was similar to that of the previous studies (6-11). In addition, our study is important since the status of these trace elements in patients with IDCM and ICM was compared. Our data revealed that all these trace concentrations of IDCM and ICM patients did not differ significantly. In other words, these findings indicate that these changes are nonspecific feature or may be independent of the type of heart disease and trace element disorders are associated with dilated cardiomyopathy and coronary artery disease. However, the precise origin of these changes in serum trace element concentrations following heart failure is not well known. Hypoxic damage of myocardial tissue may increase the activity of some endogenous mediators, which help the hepatic uptake and sequestration of circulating trace elements. On the basis of these findings, we speculate that these changes in some serum trace element concentrations may either predispose to heart failure, or permit expression of some contributory factors, leading to development of myocardial failure. As a result of, although we cannot fully explain the underlying precise mechanism for decreased serum selenium and zinc concentrations and increased copper concentrations, heart diseases associated with increased oxidative stress or inflammation may be expected to be decrease serum selenium and zinc concentrations and increase serum copper concentrations. High serum copper concentrations could depend on chronic infections or inflammation. Therefore, we excluded other clinical situations such as infections and inflammatory diseases. Also, these changes may be due to inadequate dietary intake of trace element and due to concomitant therapy agents such as diuretics or by plasma expansion due to water ingestion. In order to minimize these conditions, we included the patients on similar drug regimens.

Table 3. Comparison of laboratory, echocardiography and hemodynamic parameters in heart failure according to the NYHA classification

Parameters	NYHA Class II (n=24)	NYHA Class III (n=20)	NYHA Class IV (n=10)	P
Se, µg/l	120±6	122±5	120±6	NS
Zn, µg/l	565±107	543±106	553±66	NS
Cu, µg/l	861±156	895±133	936±97	NS
LVDD, mm	59±9	63±11	62±11	NS
LVSD, mm	38±6	41±7	44±9	NS
EF, %	36±5	35±4	30±4	NS
PAP, mmHg	43±5	47±7	51±9	NS

Values are means ± standard deviation
Cu- copper, EF- Ejection fraction, LVDD- Left ventricular diastolic diameter, LVSD- Left ventricular systolic diameter, NS- not significant; PAP- Pulmonary artery pressure; Se- selenium, Zn- zinc

Table 4. Correlation of trace element and echocardiography and hemodynamic parameters in heart failure patients

Variables	Selenium		Zinc		Copper	
	r	p	r	p	r	p
LVDD	0.11	NS	0.08	NS	0.09	NS
LVSD	0.06	NS	0.05	NS	0.07	NS
EF	0.19	NS	0.14	NS	0.15	NS
PAP	0.21	NS	0.18	NS	0.24	NS

EF- Ejection fraction, LVDD- Left ventricular diastolic diameter,
LVSD- Left ventricular systolic diameter, PAP- Pulmonary artery pressure

The early studies (9, 10) reported that serum selenium and zinc show a positive correlation with both cardiac index and ejection fraction in patients with IDCM. Also, they found an inverse correlation of serum copper concentration with these two parameters. In contrary to these previous studies, we found no correlation between trace element levels and echocardiographic parameters including LVDD, LVSD, EF, and pulmonary artery pressure. Also, no correlation was observed between their concentrations and the degrees of NYHA class. Our findings suggest that serum trace element concentrations are not related to the degrees of functional class and hemodynamic data.

In conclusion, this study confirmed that heart failure is associated with decreased serum Se and Zn element concentrations and increased serum Cu element concentrations. These changes in certain trace elements (Se, Zn, Cu) may play an important role in the pathogenesis of myocardial damage in chronic heart failure regardless of their etiologies. In this sense, these findings may be expressive in light of the etiopathogenesis and therapy of these diseases in which trace element concentrations were evaluated.

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