Original Article

Status of Some Trace Elementsin Idiopathic and Ischemic Cardiomyopathy and Coronary Artery Disease: Echocardiographic Correlation

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Fac Med Baghdad
2010; Vol. 52, No. 3
Received Mar, 2010
Accepted May. 2010

Summary:

Background: The most principal mechanisms of cardiomyopathies are;high preload and afterload and low myocardial contractility, imbalance of trace elements may cause myocardial metabolic dysfunction and may have a role in aetiology of cardiomyopathy, particulary in IDC. Trace elements are being increasingly recognized as essential mediators of the development and progression of heart diseases.

Methods: Study design Multi case-control study and single center estimation of trace elements concentrations in a number of volunteer **settings** this study was conducted in the Department of Cardiology, Ibn Albitar Hospital, and in the Physiological Chemistry Department of the College of Medicine, Baghdad University, from June 2005 to July 2006. **Subjects** Twenty-five patients with IDC, 15 patients with ICM, 16 patients with coronary artery disease(CAD) who have normal LV function, and seventeen healthy individuals as controls were included in this study. Investigations included serum estimation of zinc (Zn), copper (Cu), and magnesium (Mg) concentrations in these groups of patients and controls.

Results: The mean (±SD) value of serum zinc was significantly decreased in CAD patients compared with controls (P< 0.003). Serum Cu values (mean±SD) were significantly higher in IDC, ICM and CAD groups than in controls (P< 0.0001, P< 0.002, and P< 0.007, respectively). Serum Mg (mean±SD) value was significantly decreased in ICM patients compared to controls (P<0.007). Furthermore, there was a significant positive correlation between serum Mg levels and the values of LVEF % in IDC patients (r=0.522, P< 0.007).

Conclusion: This study confirmed that heart failure (IDC and ICM) and CAD are associated with serum trace elements (Zn, C u, and Mg) abnormalities.

Key Words: Trace elements, Cardiomyopathy, Coronary Artery Disease.

Introduction:

Cardiomyopathy is a group of diseases affecting heart muscle. 1 They were defined as primary myocardial disorders of unknown cause; heart muscle disorders of known aetiology and associated with systemic disorders were classified as secondary. 2 Recently(2008), an expert committee of the American Heart Association(AHA) proposed a new definition in which the primary is used to describe diseases in which the heart is the sole or predominantly involved organ and secondary to describe disease in which myocardial dysfunction is part of a systemic disorders. 3 Dilated cardiomyopathy (DCM) is defined by the presence of left ventricular (LV) dilatation and LV systolic dysfunction in absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease (CAD) sufficient to cause global systolic Impairment. Right ventricular dilatation and dysfunction may present but are not necessary for the diagnosis. Non- familial cardiomyopathies are subdivided into idiopathies (no identifiable cause) and acquired cardiomyopathies in which ventricular dysfunction is a complication of the disorder rather than an intrinsic feature of the disease. 2Ischemic cardiomyopathy (ICM) results when the arteries that bring blood and oxygen to the heart muscle are blocked. These may be a build up of cholesterol and other substances (plaques in the arteries that bring blood to the heart muscle tissue). The heart ability to pump blood is decreased when the LV is enlarged, dilated due to ischemic heart failure. 1, 4, 5. The most principal mechanisms of cardiomyopathies are high preload and afterload and low myocardial contractility, imbalance of trace elements may cause myocardial metabolic dysfunction and may have a role in aetiology of cardiomyopathy, particulary in IDC. 6 Trace elements are being increasingly recognized as essential mediators of the development and

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progression of heart diseases; Keshan disease, heart failure, cardiomyopathy and CAD. 7On theoretical grounds, trace elements may be protective against oxygen free radicals in the development of cardiovascular diseases. 8,9Enzymes such as superoxide dismutase(SOD) and glutathione peroxidase(GPX) contain trace elements like selenium, copper and zinc. Therefore, these trace elements have an antioxidant role in many essential enzyme systems. 10 In the lack of SOD enzyme, superoxide free radical react with H2O2 to form hydroxide radical (OH·) and cause lipid membrane peroxidation and destruction of the cell membranes. 7 Magnesium (Mg) is a cofactor for more than 300 enzymes in the human body. It is required for enzyme substrate formation (e.g. MgATP). Mg is important in oxidative phosphorylation, glycolysis, cell replication, nucleotide metabolism and protein biosynthesis. 10

Subjects and Methods:

This multicase controlled study was carried out in Ibn Albitar Hospital, Baghdad and in the Physiological Chemistry Department, College of Medicine, Baghdad University, Iraq, from June 2005 to July 2006. Fifty-six patients with heart disease and 17 healthy control subjects were included in this study. The patients are classified according to their type of cardiac disease into following groupes:

Group I (IDC): It comprised 25 patients aged 19 - 69 years (8 females and 17 males), mean(±SD) age 47.80±14.88 years with idiopathic dilated cardiomyopathy(IDC).

Group II (ICM) : It consisted of 15 patients aged 45 - 70 years (6 females and 9males), mean age 56.07±7.23 years with ischemic cardiomyopathy(ICM).

Group III (CAD without HF): It consisted of 16 patients aged 42 -70 years (4females and 12 males), mean age 53.50±9.04 years with CAD who have normal LV function.

Seventeen healthy volunteers (6 females and 11 males), mean age 40.00± 10.68years were included as control group. The diagnosis criteria of IDC were based on the WHO/ISFC criteria. 2 It was made when the echocardiogram showed a LV ejection fraction (LVEF) of less than 50 % in the absence of angiographic coronary artery disease. Patients were excluded from the study if they had a history of primary valvular disease, severe hypertension, heavy alcohol abuse or other known causes of DCM. Diagnosis criteria of CAD and ICM depended on the basis of cardiac catheterization and left ventriculopathy. Patients with proved CAD angiographically and who have had preserved LV function (LVEF more than 50 %) were included in group III, while those with ICM who had CAD angiographically in the presence of LVEF of less than 50 % were involved in group II. In each patient of these groups detailed history and physical examination were performed. ECG was reviewed by a senior cardiologist for changes suggesting recent or old myocardial infarction and for changes suggestive of ischemia. There was no clinical history suggestive of cancer, underlying infection and inflammatory disease. Five milliliters of an overnight fasting (10 - 12 hours) blood sample was aspirated from peripheral vein of each patient and control subjects. The aspirated blood transferred into plain test tube, left to clot and then centrifuged for 10 minutes at 3000 r.p.m. The clear separated serum was stored at -20 ° C until used for measurements of the concentrations of zinc, copper and magnesium.

Serum Zn, Cu and Mg were determined using flame atomic absorption spectrophotomer(AA– 646 Shimazdzu, Japan). Samples were diluted 1:10 with n-butanol solution as diluents. This method achieved 30 % increase in sensitivity compared to the use of deionized water only. [11]This effect is due to decrease in viscosity and difference in droplet formation and this technique is widely used. [12] Levels of Zn, Cu and Mg were calculated after application of absorbancies on suitable calibration curve for each element made from standard solutions.

Echocardiographic parameters including left ventricular end-diastolic diameter(LVEDD), LV end-systolic diameter(LVESD) and LV ejection fraction(LVEF %) were measured in all patient groups(IDC, ICM, and CAD) by consultant cardiologist at echocardiographic unit by M-mode echocardiography in Ibn-Albitar Hospital-Baghdad.

SPSS version 6 for window was used for all statistical analysis. Statistical significance was assessed by ANOVA, and student t-test. The linear regression test was applied for the correlation between different parameters and the significance of the r-values were checked using t-test. P –value of less than (0.05) were considered significant. Formal consent was taken from each patient, after full explanation regarding: nature of disease, course, prognosis and its complication. The ethical approval was made by the Scientific Committee of the Department of Physiological Chemistry, College of Medicine, University of Baghdad, Iraq.

Results:

Table (1) showed the clinical and biochemical data for healthy controls patients and with IDC, ICM, and CAD.The mean (±SD) value of serum Zn concentrations of patients with IDC and ICM(0.85±0.20 mg/l, 0.85±0.22 mg/l, respectively) did not differ significantly from that of controls(0.96±0.22mg/l).Value of CAD patients(0.74±0.18 mg/l) was significantly lower than that of controls(P< 0.003). There was no significant differences in serum Zn concentrations among the three groups of patients. The results of the present study also revealed that the mean (±SD) values of serum Cu concentrations of patients with IDC(1.99±0.51 mg/l), ICM(1.75±0.35 mg/l), and CAD(1.68±0.34 mg/l) were significantly higher than that of healthy controls(1.30±0.26mg/l, P<0.0001, P<0.002, P<0.007; respectively). Moreover, the mean (±SD) value of serum Cu levels was significantly increased in IDC patients compared to that of CAD (P<0.018). Table 1 also showed that serum concentrations of Mg (mean±SD) of IDC patients (2.45±0.26 mg/dl) and CAD patients (2.27±0.19 mg/dl) were comparable to that of controls (2.40±0.28 mg/dl). However, ICM patients had significantly lower serum Mg levels (2.17±0.14 mg/dl) than controls (P<0.007). In addition, IDC patients have had significantly higher serum Mg concentrations compared with those of ICM (P<0.0001) and CAD patients (P<0.018). With regard to gender, serum Zn, Cu, and Mg concentrations did not differ significantly between males and females of patient groups (IDC,ICM and CAD) and controls(data are not represented in table(1)).

Table 2revealed the values of the measured echocardiographic parameters including; LVEF %, LVEDD, and LVESD in IDC, ICM and CAD patient groups. The lower value of the measured LVEF % parameter was observed in patients with IDC (33.08±9.40, as mean+SD).

Table 1 : Clinical and Biochemical Data of Patients with Idiopathic Dilated Cardiomyopathy(IDC), Ischemic Cardiomyopathy(ICM), Coronary Artery Disease(CAD) with normal LV Function and Control Group

Parameter	**IDC**	**ICM**	**CAD with normal LV function**	**Control**
Number	25	15	16	17
Females(males)	8(17)	6(9)	4(12)	6(11)
Age(year) (range)	47.80±14.88 (19-69)	56.07±7.23 (45-70)	53.50±9.04 (42-70)	40.0±10.68 (21-60)
Weight(Kg)	79.48±11.03 NS	76.40±3.18 NS	77.50±6.83 NS	74.59±5.72
Zinc(mg/l)	0.85±0.20 NS	0.85±0.22 NS	0.74±0.18 •	0.96±0.22
Copper(mg/l)	1.99±0.51••	1.75±0.35••	1.68±0.34 ••	1.30±0.26
Magnesium (mg/dl)	2.45±0.26 NS	2.17±0.14 •••	2.27±0.19 NS	2.40±0.28

Results expressed as mean (±SD)
NS: No significant differences between patient groups(IDC , ICM) and controls.
•Significant difference between CAD group and controls: P<0.003.
••Significant differences between each of IDC,ICM,CAD patient groups and controls; P<0.0001, P<0.002,and p<0.007, respectively..
••• Significant difference between ICM patient group and controls; P<0.007.

Table2:Echocardiographic Parameters(as; mean±SD) Values in Patients with IDC, ICM, and CAD with Normal LV Function

Parameter	**IDC(n=25)**	**ICM(n=15)**	**CAD with normal LV function(n=16)**
LVEF %	33.08±9.40 •,••	38.67±5.26 •	64.25±5.47
LVEDD(mm)	67.08±9.62 •	61.86±6.16 •	50.27±7.37
LVESD(mm)	55.56±10.37•,••	48.71±7.08 •	33.07±5.73

LVEF %: Left ventricular ejection fraction, LVESD: Left ventricular end systolic diameter, LVEDD:Left ventricular end diastolic diameter

•Significant differences between each of IDC and ICM patient groups with CAD group patient; P<0.0001, P<0.0001, respectively.
••Significant difference between IDC and ICM groups; P<0.02.

In IDC group, a significant positive correlation was observed between serum Zn concentrations and serum Cu levels(r=0.4; P<0.047) as well as between serum Mg concentrations and the values of LVEF% (r=0.522; P<0.007). In female IDC patients, serum Cu levels was significantly negatively correlated with LVEF % values(r=-0.799; P<0.017) on one hand and significantly positively correlated with LVEDD values(r=0.778;P <0.023) on the other hand. In patients with ICM, an important negative correlation was observed between serum Cu concentrations and LVEF % values, but on borderline level(r=-0.513; P<0.051). Female CAD patients revealed a significant positive correlation between serum Zn levels and the values of LVEF %(r=0.927; P<0.008) as well as borderline negative correlation between serum Cu levels and LVEF % readings(r=-0.806; P<0.053).

Discussion:

In the present study serum zinc, copper, and magnesium concentrations were measured in 25 patients with IDC, 15 patients with ICM, 16 patients with CAD, and 17 healthy controls. Serum Zn levels was significantly lower in CAD patients who have normal LV function than controls (P<0.003). In both IDC and ICM patients, serum Zn was lower than controls, but not reach significant level (Table 1). In agreement with our results, Kosar et al.2007 13 observed significant decrease in serum Zn in their CAD patients compared to controls(0.001), and concluded that this element may play an important role in pathogenesis of CAD. Moreover, Nouraei et al.2007 14 , Salehifar et al.2008, 15 and Shokrzadeh et al.2009 16 have observed lower serum Zn concentrations in their patients with both IDC and ICM when compared to healthy controls, but without significant value. In contrast, Kosar et al.2006 7 and Topuzoglu et al.2003 6 observed that patients with heart failure (HF), irrespective of their aetiology had significant lower serum Zn levels in comparison to controls. However, the IDC patients did not differ significantly from ICM with regard to serum Zn levels. 7 This latter finding is similar to our observations in that serum Zn concentrations were the same in both IDC and ICM patient groups, no significant difference.

The results of the present study also showed that serum Cu concentrations was significantly higher in patients with IDC, ICM, and CAD than controls (Table 1). Kosar et al.2007 13 reported that serum Cu levels did not differ significantly between CAD patients and controls. However, several reports 6,7,16 documented significant increased of serum Cu concentrations in patients with HF, both IDC and ICM, than in controls. These authors suggested that high serum Cu concentrations could related to chronic infections or inflammation. Shokrzadeh et al.2009 16 proposed that a raised serum Cu may have a role in the development of heart failure and interventions such as administrations of Cu chelators to relieve the symptoms or to decrease the progression of heart failure is needed to be examined. Trace elements such as Zn and Cu are known to have a key role in myocardial metabolism. Enzymes such as superoxide dismutase and glutathione peroxidase which contain trace elements like selenium, zinc, and copper are important factors that influence antioxidant status. Then that an important biological function of trace elements is as antioxidant. The deficiency of trace elements has been known to result in extensive oxidative damage in many tissues, including the myocardium, and may also lead to the damage of vascular structure and be one of the underlying causes of CAD and heart failure. Hypothetically, these antioxidant enzymes may reduce myocardial damage by inhibiting the reactive and injurious free radicals and reactive oxygen species, e.g; hydrogen peroxide and superoxide anion. 7,13

The results of the present study also revealed that serum magnesium (Mg) concentrations was significantly decreased in ICM patients than controls (P<0.007). The study also showed that the aetiology of heart disease play a role in changes of serum Mg concentrations, as ICM and CAD patients have had significantly lower serum Mg levels than IDC patients. Topuzoglu et al.2003 **6** reported insignificant changes of serum Mg levels between patients with IDC and controls. Cohen et al.2003 17 concluded from their study that hypomagnesaemia have a direct underlying cause of the increased mortality in patients with congestive heart failure(CHF), mainly but not entirely by compromising cardiac performance. The authers suggested that these patients with CHF who are at risk of hypomagnesaemia require frequent serum Mg determinations and the provision of Mg supplementation once hypomagnesaemia is detected. Ohtsuka and Yamaguch, 2005 18 suggested that hypomagnesaemia and depletion of intracellular Mg stores have been held responsible for a variety of cardiovascular and other functional abnormalities, including various arrhythmias, impairment of cardiac contractility, and vasoconstriction. Overstimulation of rennin-angiotensin-aldosterone system, long –term administration of diuretics, digoxin, poor oral intake and impaired intestinal absorption and renal reabsorption contribute to Mg element abnormalities**.** 18

The significant positive correlation that observed in our study between serum Mg and the values of LVEF % in IDC patients as well as the borderline negative correlation between serum Cu and LVEF % values in ICM patients suggest that serum concentrations of these trace elements are related to the severity of heart failure.

To our knowledge, study of the status of these serum trace elements (Zn, Cu, and Mg) in ischemic (ICM) and idiopathic (IDC) heart failure patients as well as in CAD patients who have normal LV function has not been evaluated before. In our study, there were some limitations in intracellular determination of studied elemens.

Conclusion:

This study confirmed that ischemic and nonischemic heart failure (ICM and IDC) and CAD are associated with serum trace elements (Zn, C u, and Mg) abnormalities. These trace elements changes may play (even partially) an important role in the pathogenesis and progression of heart failure and CAD. The findings of the important significant correlations between serum levels of trace elements and echocardiographic parameter values in IDC and ICM female patients may need further investigations to elucidate the mechanism and difference from that of male patients. Moreover, an appropriate dose of Mg supplementation and copper binder substance may need to be involved in further studies.

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