Biol Trace Elem Res (2011) 144:351–359
DOI 10.1007/s12011-011-9103-0

The Correlation of Serum Trace Elements and Heavy Metals with Carotid Artery Atherosclerosis in Maintenance Hemodialysis Patients

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Received: 15 April 2011 / Accepted: 26 May 2011 /
Published online: 7 June 2011

Abstract Changes in essential trace elements and heavy metals may affect the atherosclerotic state of patients on maintenance hemodialysis (HD). The aim of the study was to evaluate the relation between the serum levels of some trace elements and heavy metals (iron, zinc, manganese, copper, magnesium, cobalt, cadmium, lead, and copper/zinc ratio) and carotid artery intima–media thickness (CIMT) in HD patients. Fifty chronic HD patients without known atherosclerotic disease and 48 age- and sex-matched healthy individuals were included in the study. The serum levels of trace elements (iron, zinc, manganese, copper, and magnesium) and heavy metals (cobalt, cadmium, and lead) were measured by Atomic Adsorption Spectrophotometer (UNICAM-929). CIMT was assessed by carotid artery ultrasonography. The serum levels of iron, zinc, and manganese were lower; levels of copper, magnesium, cobalt, cadmium, lead, and copper/zinc ratio were higher in HD patients compared to controls. CIMT in HD patients were higher than the control group (0.64±0.11 vs 0.42±0.05, $p<0.001$). There was a significant negative correlation between CIMT and serum levels of zinc ($r=-0.70$, $p<0.01$), iron ($r=-0.71$, $p<0.01$), and manganese ($r=-0.47$, $p<0.01$), while there was a significant positive correlation

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between CIMT and serum levels of copper (r=0.63, p<0.01), magnesium (r=0.77, p<0.01), cobalt (r=0.63, p<0.01), cadmium (r=0.48, p<0.01), lead (r=0.38, p<0.01), and copper/zinc ratio (r=0.68, p<0.01). A linear regression analysis showed that serum levels of magnesium, cadmium, lead, and copper/zinc ratio were still significantly and positively correlated with CIMT. We propose that copper/zinc ratio, magnesium and toxic metals cadmium and lead are independent determinants of CIMT in maintenance HD patients without known atherosclerotic disease.

Keywords Atherosclerosis · Carotid artery · Cu/Zn ratio · Hemodialysis · Trace elements

Introduction

Accelerated atherosclerosis and increased cardiovascular events have been extensively documented in patients with end stage renal disease (ESRD) [1, 2]. Classical cardiovascular risk factors such as age, male gender, smoking, hypertension, dyslipidemia, and diabetes exist in the general population and in patients undergoing hemodialysis (HD) [3]. Classical cardiovascular risk factors alone have been reported to be inadequate predictors of atherosclerosis in these patients [4]. Additional non-classical risk factors such as oxidative stress, dysparathyroidism, hyperhomocysteinemia, dialytic inadequacy, malnutrition, and disruption of calcium–phosphate homeostasis play more important roles in cardiovascular disease in HD patients [3, 4].

Patients undergoing HD are potentially at risk of both deficiency and excess of trace elements [5]. HD exposes patients to large volumes of water (>120 L/week) in the form of dialysate. Essential trace elements play key roles in multiple biological systems; it has been hypothesized that the increased morbidity and mortality seen in HD patients may in part be due to the imbalance of trace elements [5, 6]. It is not yet known if changes in serum levels of trace elements and heavy metals may affect the accelerated atherosclerosis in HD patients.

It is postulated that the atherosclerotic changes in the carotid artery predicate pathologic events of generalized atherosclerosis. Ultrasound measurements of carotid artery intima–media thickness (CIMT) and plaque occurence in the carotid arteries are used as indicators of coronary atherosclerosis in the general population as well as in studies involving patients with ESRD [7, 8]. The assessment of CIMT using high-resolution B-mode ultrasonography is a reliable, reproducible, and non-invasive method for detecting and monitoring the progression of atherosclerosis [8]. We established the present study to investigate the relation of CIMT with serum levels of trace elements (iron, zinc, manganese, copper, magnesium, and copper/zinc ratio) and heavy metals (cobalt, cadmium, and lead) in HD patients.

Subjects and Methods

Subjects

Fifty non-diabetic HD patients without evidence of atherosclerotic disease and 48 age- and sex-matched healthy controls were included in the study. Atherosclerotic disease was excluded by patient history, physical, electrocardiographic, and echocardiographic examination. The study was approved by the local ethics committee and all participants gave written informed consent. Patients in the HD group all had creatinine clearance less than 10 ml/min/1.73 m^2 and had been on chronic HD treatment for at least 1 year. They were dialyzed three times a week with synthetic membrane, each session lasting 4 h with bicarbonate dialysate. The calcium concentration of the dialysate was 1.5 mmol/L and the magnesium concentration of the dialysate was 0.5 mmol/L in all patients for the last 6 months. None of the patients had received magnesium-containing medications for at least 6 months prior to the beginning of the study. Healthy individuals without any of chronic disease were included as the control group. All study subjects were non-smokers and did not consume alcohol. None of the subjects received antibiotics, corticosteroids, anti-inflammatory drugs, cytotoxic drugs, vitamins, or magnesium-containing medications during the study period.

Measurement of Blood Pressure

All study subjects were monitored with Spacelab1 90207 ambulatory blood pressure monitor (Spacelabs Medical, Redmond, WA, USA) for 24 h, every 20 min from 0700 to 2300 hours and every 30 min from 2300 to 0700 hours. Ambulatory blood pressure monitoring data included 24-h systolic blood pressure (SBP), 24-h diastolic blood pressure (DBP), 24-h mean arterial blood pressure (MAP), daytime SBP, daytime DBP, and daytime MAP measurements. Hypertension was defined according to JNC-7 criteria [9].

Sample Collection and Analysis

Trace elements were measured prior to the midweek hemodialysis session. Samples of the blood were collected into tubes without coagulant. Serum was obtained by centrifugation at 2,500 rpm for 15 min, processed immediately, placed in deionised polyethylene tubes, and stored at −80°C until assayed. Serum concentrations of iron (Fe), zinc (Zn), manganese (Mn), copper (Cu), magnesium (Mg), cobalt (Co), cadmium (Cd), and lead (Pb) were determined by Atomic Adsorption Spectrophotometer by UNICAM-929 (Unicam Ltd, Cambridge, UK). Wavelengths of each element were measured (Fe, 248.3; Zn, 213.9; Mn, 279.5; Cu, 324.8; Mg, 285.2; Co, 530.0; Cd, 228.8; Pb, 283.3) and the results were calculated as micrograms per deciliter. To improve the sensitivity of flame atomic adsorption spectrometry, a slotted tube atom trapcom was used for measured variables. The standard addition method was used to remove possible interferences caused by the matrix. The slopes of the calibration curves for all studied elements were compared with those obtained by the standard addition method to avoid chemical interference.

Determination of CIMT

Carotid artery ultrasound scanning was performed using a high-resolution ultrasonography device (Toshiba Corevision high-resolution B-mode ultrasonography) provided with a 7.5-MHz linear transducer. The power output, focus, depth of measurement, and gain were standardized by employing the preset program incorporated within the software package of the ultrasound equipment. All measurements were done blindly by the same operator.

Patients were examined in a supine position with the neck extended and the probe in the anterolateral position. All measurements of CIMT were made in the longitudinal plane at the point of maximum thickness on the far wall of the common carotid artery along a 1-cm section of the artery proximal to the carotid bulb at the diastolic phase. CIMT was defined as the distance between the inner echogenic line representing the intima–blood interface and the outer echogenic line representing the adventitia–media junction. Measurements were repeated three times and CIMT was expressed as the mean of six measurements (three on each side) [10]. No measurement was made on the sites where a plaque existed.

Statistical Analysis

Descriptive statistics for continuous variables were expressed as mean±SD. Student's *t* test was used to compare means of control and patient groups for trace elements and CIMT variables. Pearson's correlation test was performed to explore the linear relationships between CIMT and trace elements. A multiple linear regression analysis was used to determine the independent predictor of CIMT. A p value <0.05 was interpreted as statistically significant. All statistical analyses were performed with statistical analysis program (SPSS 13.0 for Windows).

Results

Clinical and demographic characteristics of the patient and control groups are given in Table 1. There were no significant differences in age, body mass index, gender, blood pressure parameters, glucose, calcium (Ca), mean total cholesterol, low-density lipoprotein, and high-density lipoprotein among groups. However HD patients had lower hemoglobin levels than controls. They also had higher phosphorus (P), calcium X phosphorus product (CaXP product), parathyroid hormone (PTH), serum C-reactive protein and uric acid levels than the control group (Table 1).

The mean serum levels of trace elements (Fe, Zn, Mn, Cu, Mg, and Cu/Zn ratio) and heavy metals (Co, Cd, and Pb) are shown in Table 2. The levels of Fe, Zn, and Mn were significantly lower in HD group whereas the levels of Cu, Mg, Co, Cd, Pb, and Cu/Zn ratio were significantly higher as compared to the control group ($p<0.001$). HD patients had significantly higher CIMT than healthy subjects ($p<0.001$). Correlation analysis showed that CIMT was negatively correlated with serum levels of Zn, Fe, and Mn and positively correlated with serum levels of Cu, Co, Cd, Pb, Mg, and Cu/Zn ratio (Table 3).

Multiple linear regression analysis was used to define independent determinants of CIMT in HD patients. Fe, Zn, Mn, Cu, Mg, Co, Cd, Pb levels and Cu/Zn ratio were incorporated into the model as independent variables. The R^2 of the model was 0.731 with $p<0.001$. The linear regression model revealed that levels of Mg, Cd, Pb, and Cu/Zn ratio were independent predictors of CIMT. Regression coefficients for Mg level=0.014 ($p=0.001$), Cd level=1.643 ($p=0.035$), Pb level=0.101 ($p=0.013$), and Cu/Zn ratio= 0.020 ($p<0.001$) (Table 4).

Discussion

In this study, we assessed the relationship between serum levels of trace elements, heavy metals, and the presence of early subclinical atherosclerosis in HD patients. The main finding of this study is the demonstration of a correlation between CIMT and serum trace and toxic elements as well as the independent effects of serum levels of Mg, Cd, Pb, and Cu/Zn ratio on carotid atherosclerosis in this patient population.

Table 1 Clinical and demographic characteristics of the study groups

	Hemodialysis group (*n*=50)	Control group (*n*=48)	*p* value
Age (years)	38±8	39±11	NS
Sex (male/female)	25/25	24/24	NS
BMI (kg/m2)	23.18±3.20	24.06±4.04	NS
Dialysis duration (months)	40±17		
SBP (mmHg)	119.60±18.16	116.64±16.20	NS
DBP (mmHg)	68.06±9.50	65.80±8.63	NS
MAP (mmHg)	85.24±12.30	82.74±11.15	NS
Glucose (mg/dl)	88.40±14.70	85.53±13.90	NS
Total cholesterol (mg/dl)	178.00±22.80	180.10±27.10	NS
LDL cholesterol (mg/dl)	109.55±24.30	111.40±22.08	NS
HDL cholesterol (mg/dl)	37.16±15.46	40.04±16.30	NS
Triglycerides (mg/dl)	124.50±36.54	130.58±28.48	NS
Hemoglobin (g/dL	11.65±2.25	13.25±1.98	<0.05
sCRP (mg/dL)	0.68±0.24	0.18±0.21	<0.05
Uric acid (mg/dL)	6.90±1.40	4.80±1.90	<0.05
Calcium (mg/dl)	9.44±1.88	9.26±0.90	NS
Phosphorus (mg/dl)	5.33±1.57	3.77±1.65	<0.05
CaXP product (mg^2/dl^2)	49.85±15.22	34.91±11.48	<0.05
PTH (pg/ml)	238.60±42.70	33.46±13.30	<0.01

Data is presented as mean±SD

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *sCRP* sensitive C-reactive protein, *CaXP product* calcium X phosphorus product, *PTH* parathyroid hormone

The importance of essential trace elements in health and disease is indisputable because of their essential role in specific concentration ranges and their toxic role at relatively high levels. HD patients are at risk for both a deficiency of certain essential trace elements and an excess of toxic trace elements. We hypothesized that the trace element status may influence the risk of cardiovascular morbidity in HD patients without known atherosclerotic disease.

Table 2 Levels of trace elements and heavy metals of study groups

	Hemodialysis group (*n*=50)	Control group (*n*=48)	*p* value
Zn (μg/dL)	0.53±0.30	1.47±0.32	<0.001
Fe (μg/dL)	0.51±0.32	1.23±0.24	<0.001
Mn (μg/dL)	0.02±0.01	0.19±0.16	<0.001
Cu (μg/dL)	1.54±0.34	0.72±0.23	<0.001
Mg (μg/dL)	21.27±2.42	12.62±1.38	<0.001
Co (μg/dL)	0.32±0.15	0.04±0.02	<0.001
Cd (μg/dL)	0.03±0.02	0.01±0.01	<0.001
Pb (μg/dL)	0.41±0.38	0.10±0.05	<0.001
Cu/Zn ratio	3.97±0.47	0.53±0.03	<0.001
CIMT (mm)	0.64±0.11	0.42±0.05	<0.001

Data is presented as mean±SD

Zn zinc, *Fe* iron, *Mn* manganese, *Cu* copper, *Mg* magnesium, *Co* cobalt, *Cd* cadmium, *Pb* lead, *Cu/Zn ratio* copper/zinc ratio, *CIMT* carotid artery intima–media thickness

Table 3 Pearson correlation coefficients among variables

	Zn (μg/dL)	Fe (μg/dL)	Mn (μg/dL)	Cu (μg/dL)	Co (μg/dL)	Cd (μg/dL)	Pb (μg/dL)	Mg (μg/dL)	Cu/Zn ratio	CIMT (mm)
Zn (μg/dL)	1									
Fe (μg/dL)	0.69[a]	1								
Mn (μg/dL)	0.39[a]	0.51[a]	1							
Cu (μg/dL)	−0.72[a]	−0.67[a]	−0.49[a]	1						
Co (μg/dL)	−0.71[a]	−0.71[a]	−0.46[a]	0.69[a]	1					
Cd (μg/dL)	−0.39[a]	−0.48[a]	−0.30[a]	0.58[a]	0.65[a]	1				
Pb (μg/dL)	−0.50[a]	−0.31[a]	−0.26[a]	0.53[a]	0.59[a]	0.67[a]	1			
Mg (μg/dL)	−0.80[a]	−0.76[a]	−0.52[a]	0.78[a]	0.78[a]	0.62[a]	0.59[a]	1		
Cu/Zn ratio	−0.65[a]	−0.53[a]	−0.33[a]	0.67[a]	0.65[a]	0.37[a]	0.50[a]	0.59[a]	1	
CIMT (mm)	−0.70[a]	−0.71[a]	−0.47[a]	0.67[a]	0.63[a]	0.48[a]	0.38[a]	0.77[a]	0.68[a]	1

[a] Correlation is significant at the 0.01 level (two-tailed)

Zn zinc, *Fe* iron, *Mn* manganese, *Cu* copper, *Co* cobalt, *Cd* cadmium, *Pb* lead, *Mg* magnesium, *Cu/Zn ratio* copper/zinc ratio, *CIMT* carotid artery intima–media thickness

According to our results, HD patients have lower serum levels of Zn, Fe, and Mn and higher serum levels of Cu, Mg, Pb, Cd, Co, and Cu/Zn ratio as compared to healthy controls. Our findings are consistent with current literature [5, 6, 11, 12]. Our results also demonstrated that CIMT as a determinant of subclinical atherosclerosis is negatively correlated with serum levels of Zn, Fe, and Mn and positively correlated with serum levels of Cu, Mg, Pb, Cd, Co, and Cu/Zn ratio. Even though mineral substance and toxic trace element status have been studied many times in HD patients, to the best of our knowledge, no study examined the relationship between trace and toxic element status and CIMT among HD patients. Moreover, linear regression analysis validated the independent effects of serum levels of Mg, Cd, Pb, and Cu/Zn ratio on CIMT in these patients (Table 4).

Zn has antioxidant and anti-inflammatory properties and oral Zn supplementation can reduce inflammation in HD patients [13]. Cu has a role in hemoglobin synthesis and immune function and is a cofactor for Cu/Zn-superoxide dismutase and ceruloplasmin [14]. High blood copper concentration is thought to be an independent risk factor for cardiovascular disease [15]. Chronic inflammation, as indicated by increased levels of

Table 4 Regression analysis for defining the independent determinants of CIMT

Independent variables	β (coefficient)	Standart error	p value*
Cd (μg/dL)	1.643	0.766	0.035
Pb (μg/dL)	0.101	0.040	0.013
Mg (μg/dL)	0.014	0.004	0.001
Cu/Zn ratio	0.020	0.004	<0.001

R^2 =73.1%

Zn zinc, *Fe* iron, *Mn* manganese, *Cu* copper, *Co* cobalt, *Cd* cadmium, *Pb* lead, *Mg* magnesium, *Cu/Zn ratio* copper/zinc ratio

*p<0.001

serum C-reactive protein, is associated with elevated levels of Cu and ceruloplasmin [16]. It has been shown that Cu/Zn ratio is a better indicator of infection, vascular complications, and prognosis than Zn or Cu status alone [17, 18]. According to our results, HD patients have higher Cu/Zn ratio than controls. Recently, Guo et al. reported the relation between Cu/Zn ratio and oxidative stress, inflammation, and immune abnormalities in peritoneal dialysis patients [19]. Although the mechanism remained doubtful, increased oxidative stress, decreased antioxidant capacity, and/or inflammation may cause higher Cu/Zn ratios in our study population. We also demonstrated that Cu/Zn ratio is positively associated with carotid atherosclerosis. Possible mechanisms for this association may be oxidative stress and/or inflammation. Further studies are needed to shed more light on the pathophysiological mechanisms of this association.

The biological significance of either accumulation or depletion of serum trace elements and heavy metals is largely unknown. Several studies link increased and decreased levels of various trace elements with cardiovascular disease in subjects without renal disease. It is reported that minor elevations in blood lead levels are associated with hypertension, cardiovascular morbidity, and electrocardiographic changes in healthy people [20–22]. Cadmium is reported to be an independent risk factor for early atherosclerotic vessel wall thickening in healthy subjects [23]. So far, there are not any data concerning the cardiovascular effects of these trace elements among HD patients. In our study, we found independent effects of Cd and Pb as well as Mg and Cu/Zn ratio on carotid atherosclerosis. The precise mechanisms by which these substances are increased in the serums of HD patients should be further investigated in order to prevent the acceleration of cardiovascular disease in this population. Excess dietary intake, inadequate removal by dialysis, and the composition of the source water used for HD may be potential mechanisms for accumulation.

Our results are particularly different from the findings of Tzanakis et al. who reported that intra- and extracellular magnesium levels may play an important protective role in the development and/or acceleration of arterial atherosclerosis in patients with chronic renal failure [24]. The difference between our study and that of Tzanakis et al. may have resulted from difference(s) between demographic characters and laboratory discrepancy of the study groups. Our study population was homogeneous for the confounders of classical cardiovascular risk factors, such as diabetes, hypertension, hyperlipidemia and smoking status, and non-classical cardiovascular risk factors such as serum levels of Ca, P, CaXP product, and PTH. We showed that serum Mg levels were positively correlated with carotid artery atherosclerosis in normocalcemic, normophosphatemic patients. Although an absolute or a relative Mg depletion may be a non-traditional cardiovascular risk factor in HD patients [24], according to our results, hypermagnesemia (serum Mg level$>$1.5 mEq/L) may also be another non-traditional cardiovascular risk factor in these patients. Chronic kidney disease and particularly ESRD is the only clinical condition where sustained hypermagnesemia may occur and net Mg balance may be positive. Further studies are needed to assess the role of Mg on accelerated atherosclerosis in ESRD patients.

In conclusion, present data show that serum levels of Mg, Cd, Pb, and Cu/Zn ratio are independently associated with carotid atherosclerosis in maintenance HD patients. The trace and toxic mineral status seems to play a role in the pathophysiology of accelerated atherosclerosis in HD patients. Further prospective, randomized, controlled studies are needed to determine the possible beneficial effects of supplementation or suspension of these elements on carotid artery atherosclerosis in these patients.

Conflicts of interest None

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