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# Alterations in Trace Elements and Oxidative Stress in Uremic Patients with Dementia

**Chih-Hung Guo · Wang-Sheng Ko · Pei-Chung Chen · Guoo-Shyng W. Hsu · Chia-Yeh Lin · Chia-Liang Wang**

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**Abstract** The present study was conducted to compare the trace elements and oxidative status between uremic patients with and without dementia. Chronic hemodialysis patients with dementia ($n$=20) and without dementia ($n$=25), and age-matched healthy volunteers ($n$=20) were enrolled. The nutritional status, blood levels of trace elements aluminum (Al), zinc (Zn), copper (Cu), magnesium (Mg) and iron (Fe), malondialdehyde (MDA), and protein carbonyl production, antioxidant enzymes glutathione peroxidase (GPx), and glutathione reductase (GR) activities were measured. No significant difference in nutritional status or clinical characteristics was observed between nondementia and dementia patients. However, uremic patients with dementia have significantly higher Al, Cu, and Mg and lower Zn concentrations, as well as increased Cu/Zn ratio in comparison to nondementia patients. There were statistically significant increased MDA and carbonyl production and decreased GPx and GR activities in dementia patients. Furthermore, the significant associations of Al, Mg, and Cu/Zn ratio with oxidative status in patients with dementia were noted. The dementia may initially worsen with abnormal metabolism of trace elements and oxidative stress occurrence. Our results suggest that abnormalities in trace element levels are associated with oxidative stress and may be a major risk factor in the dementia development of uremic patients.

**Keywords** Trace elements · Oxidative stress · Uremic patients · Dementia · Magnesium · Copper and zinc · Aluminum

C.-H. Guo (✉) · W.-S. Ko · P.-C. Chen
Institute of Biomedical Nutrition, Hung Kuang University, Taichung 433 Taiwan, Republic of China
e-mail: eillyguo@sunrise.hk.edu.tw

W.-S. Ko
Department of Internal medicine, Kuang Tien General Hospital, Taichung 433 Taiwan, Republic of China

G.-S. W. Hsu · C.-Y. Lin
Department of Nutritional Science, Fu Jen University, Taipei 242 Taiwan, Republic of China

C.-L. Wang (✉)
Department of Nephrology, Kuang Tien General Hospital, Taichung 433 Taiwan, Republic of China
e-mail: hollyspirit31@yahoo.com.tw

## Introduction

A number of studies have reported a high prevalence of cognitive dysfunction and dementia in chronic dialysis patients. The clinical duration until death of dementia was less than 3 years; this had suggested that dementia is an independent mortality predictor in dialysis patients [1, 2]. Dementia may occur in the course of dialysis [1]; however, the risk factors for dementia of uremic patients remain unclear.

Recent evidence has shown that oxidative damage plays a deleterious role in progressive or degenerative brain disorders [3, 4]. Oxidative stress, defined as a rupture between prooxidant and antioxidant system that further leads to oxidative damage, has been observed in hemodialysis [5], peritoneal dialysis [6], as well as predialysis patients with chronic renal failure [7]. Additional literatures indicated that plasma antioxidant enzymes glutathione peroxidase (GPx), glutathione reductase (GR), and catalase activities decreased dramatically in patients undergoing hemodialysis [8, 9]. It is therefore possible that oxidative stress is associated with increased risk for dementia of uremic patients.

The levels of essential elements that mediate oxidative stress in neurodegenerative disorders have already been described. Copper (Cu) was involved in free radical production that resulted in neuronal injury [10]. The interactions of zinc (Zn) and Cu with beta-amyloid deposition, a factor that purportedly facilitated disease processes, have been discussed [11]. Iron (Fe) is a transition metal capable of generating hydroxyl radicals, the most potent reactive oxygen species. The imbalance of brain Fe metabolism was the initial cause for neuronal death [12]. Magnesium (Mg) deprivation decreased release of neuronal glutathione (GSH) and caused oxidative death [13]. On the other hand, nonessential element aluminum (Al), a known neurotoxin, can alter the neuronal homeostasis of some essential elements in Alzheimer's disease [14] and cause extensive damage to the nervous system [15]. Among dialysis patients, insufficient dose of dialysis, Al exposure, and malnutrition have also been implicated as risk factors for dementia [16, 17]; yet, these findings have not been confirmed.

The present study aimed to determine the difference in the nutritional status, the contents of plasma elements (Al, Zn, Cu, Fe, Mg), and malondialdehyde (MDA) levels as an indicator of lipid peroxidation, protein carbonyl contents as a marker of oxidative protein damage, as well as antioxidant enzyme (GPx, GR) activities in hemodialysis patients with or without dementia.

## Materials and Methods

### Patients

The present study received ethics approval from the Kuang Tien General Hospital (Sha-Lu, Taichung County, Taiwan) Ethics in Human Research Committee, and all subjects, subject's guardian, or family member signed an informed consent statement prior to inclusion in the study.

From September of 2004 to February of 2005, the patients receiving hemodialysis were enrolled. Forty-five hemodialysis patients from dialysis unit were divided into two groups: nondementia and dementia groups. There were 12 men and 13 women aged 52–84 years (mean 64±2 years) included in the nondementia patients. In addition, the 20 dialysis patients with dementia (nine men) aged 56 to 81 years (mean 65±3 years) were based on review of the medical record. Each dialysis patient received a minimum of 12 h/week hemodialysis treatment (three sessions of 4 h each). In addition, control group consisted of

20 healthy volunteers (ten men), aged 61±3 years old with no history of dyslipidemia, renal failure, or other organ diseases.

In clinical characteristics of patients, the age, sex, body mass index (BMI), dialysis duration, diabetes mellitus, hypertension, ischemic heart disease, dyslipidemia, and some drug use were recorded. Diabetes mellitus was defined as present if patients were using insulin or oral hypoglycemic agents. The dyslipidemia was designated as fasting triglycerides of 200 mg/dl or greater or patients who were receiving medical treatment of hyperlipidemia. Ischemic heart disease was diagnosed based on the following criteria: angina pectoris, history of myocardial infarction, coronary artery bypass surgery, or percutaneous coronary intervention.

### Dementia Diagnosis

Dementia diagnosis was assessed by consensus at a conference of physicians and neuropsychologists based on medical history, neurologic examination, and neuropsychological tests. Psychiatric diagnosis is categorized by the criteria of the Diagnostic and Statistical Manual of Mental Disorders in its fourth edition [18].

The Clinical Dementia Rating scale is a numeric scale used to quantify the severity of symptoms of dementia, and all dementia patients in the present study scored at least 1 on the composite rating. In addition, the dementia severity was defined for these subjects as Chinese version of Mini-Mental Status Examination (MMSE). The MMSE cutoff scores were according to three educational levels, i.e., <17 for illiterate subjects, <21 for grade-school literate subjects, and <25 for literate subjects with an education status of junior high school and higher [19]. Literacy-dependent items of the MMSE were modified or substituted by equivalent items that were not literacy-dependent. For example, in the writing test, the respondent was asked to "say a sentence" to guard against failure on this item because of an inability to write as a result of lack of education, and the item "close your eyes" was presented orally to illiterate subjects.

### Anthropometric Observation

All anthropometric measurements were performed after the last dialysis session in a week. BMI was calculated from weight in kilograms divided by height in meters squared. Triceps skinfold thickness (TSF) was measured on opposite arm from arteriovenous fistula at the midpoint of acromion and olecranon process using skinford caliper (FAT-O-METER, USA). TSF was measured to the nearest 0.1 cm, and an average of the three measurements is used. Corrected upper arm muscle area (AMA) was also calculated from the mid-arm circumference and TSF [20].

### Laboratory Measurement

Fasting morning blood samples were obtained from the arterial site of arteriovenous fistula before the start and after the dialysis session. Plasma urea nitrogen, creatinine, albumin, and glucose levels were measured with a Hitachi 7050 automatic analyzer, using routine laboratory techniques. The total cholesterol and triglycerides levels were also determined by enzymatic methods (Merck Diagnostica, Darmstadt, Germany). The residual plasma was transferred into plastic tubes and stored at −80°C until assayed.

The plasma contents of Zn, Cu, Fe, and Mg were measured by flame atomic absorption spectrophotometer (932 plus, GBC, Australia) using an air-acetylene flame without

background correction at 213.9, 324.71, 278.8, and 285.2 nm, respectively [21]. Al level was also determined using an atomic absorption spectrophotometer (932AA, GBC, Australia) with graphite furnace as described previously [22]. Samples were digested in a $H_2O_2/HNO_3$ (1/5) mixture in a start D microwave-assisted digestion system (Milestone Microwave Labstation ETHOSD) and subsequently brought up to 5 mL with deionized water. Accuracy of the method was confirmed by comparing to serum (level 2, NO0371) reference materials (Seronorm, Nycomed, Oslo, Norway).

The plasma samples were also mixed with 3% sodium dodecyl sulfate, 0.1 N HCl, 10% phosphtungstic acid, and 0.7% thiobarbituric acid and then incubated at 95°C for 60 min. The *n*-butanol was added, and the mixture was shaken vigorously. After centrifugation at 12,000×*g* for 15 min, the thiobarbituric acid-reactive substances in the *n*-butanol layer were taken for measurement by Wallac Victor 3 1420 multilabel counter (Perkin Elmer, Turku, Finland) using 530 nm with 485 nm excitation. The MDA levels were calculated using the 1,1,3,3-tetraethoxypropane as standards [23].

The protein carbonyl was also determined by the method of Reznick and Packer [24]. Protein carbonyls reacted with 2,4-dinitrophenylhydrazine (DNPH) forming a Schiff base to produce the corresponding hydrazone, which was analyzed at 370 nm. Briefly, plasma samples were reacted with 10 mM DNPH dissolved in HCl, accompanied by blanks in HCl alone. Proteins were precipitated with an equal volume of 20% trichloroacetic acid and further centrifuged at 10,000×*g* for 10 min at 4°C. The supernatant was discarded and the pellets resuspended in the ethanol/ethyl acetate mixture. After the centrifugation, the precipitates were then redissolved in 6 M guanidine–HCI solution. The results were calculated using the extinction coefficient of 0.022 $\mu M^{-1}$ $cm^{-1}$ and given as nanomoles per milliliter.

The GPx enzyme activity was measured according to Paglia and Valentine [25]. GPx catalyzed the oxidation of GSH by cumene hydroperoxide. In the presence of GR and NADPH, the oxidized glutathione was immediately converted to the reduced form. One hundred microliters of assay buffer (50 mM Tris–HCl, pH 7.6, containing 5 mM EDTA), 50 μL of co-substrate mixture (a lyophilized powder consisting of NADPH, GSH, and GR), and 20 μL of sample plasma were pipetted. The reactions were initiated by adding cumene hydroperoxide and the mixture incubated for 10 s. The decrease in absorbance at 340 nm was recorded at 1-min intervals for 6 min. The rate of decrease in the absorbance was directly proportional to the GPx activity in the sample.

GR activity was also assessed by monitoring the oxidation of NADPH to $NADP^+$ via addition of oxidized GSH. One hundred microliters of assay buffer (50 mM potassium phosphate, pH 7.5, containing 1 mM EDTA), 20 μL of oxidized GSH, and 20 μL of plasma samples were mixed thoroughly. The reaction was then initiated by the addition of 50 μL NADPH. The absorbance was read once every minute at 340 nm with a Multiskan Ascent microplate spectrophotometer (Thermo Labsystems) at least five time points. One GR activity unit was defined as the amount of enzyme catalyzing the reduction of 1 mmoL of oxidized GSH.

## Statistical Analysis

Each value was expressed as the mean ± standard error (SE). A $p$ value less than 0.05 was considered statistically significant. The Kolmogorov–Smirnov normality test was applied to evaluate the distribution of each data set. The difference between two groups was analyzed by Mann–Whitney $U$ test. Categorical variables were compared using $\chi^2$ analysis. In addition, Pearson's correlations and linear regression analysis were performed to explore relationships among blood variables.

## Results

### Clinical Data

As shown in Table 1, no significant difference in the duration of dialysis was found between the two patient groups ($p>0.05$). Thirteen patients (52% of the participates) in nondementia group were treated with aluminum hydroxide ($Al(OH)_3$) for controlling phosphate levels. Eleven subjects (55% of the participates) had also received $Al(OH)_3$ in dementia patients. The mean dose used of $Al(OH)_3$ (Ulcerin-P® 375 mg) was one tablet per day. There was no statistically significant difference in oral dose of Al $(OH)_3$ between the two patient groups. In addition, the percentages of patients with diabetes, hypertension, dyslipidemia, administered medications, current smoking and alcohol consumption status, and ischemic heart disease were similar between the two groups of patients. There was also no significant difference in blood total cholesterol, triglyceride, and glucose concentrations.

### Nutritional Status

The nutritional status data of all subjects were given in Table 2. No significant difference was observed in dry weight, BMI, TSF, AMA measurements, and predialysis albumin levels between nondementia and dementia patients. The data also show no significant difference in the blood urea nitrogen and creatinine levels in both patient groups.

**Table 1** The Clinical Characteristics of the Patients and Control Subjects

| | Nondementia ($n$=25) | Dementia ($n$=20) | Control ($n$=20) |
|---|---|---|---|
| Dialysis duration (year) | 6.9±0.7 | 6.8±0.8 | |
| $Al(OH)_3$ treatment (%) | 52 | 55 | |
| Mean time (month) | 3.3±0.8 | 4.1±1.1 | |
| Diabetes mellitus (%) | 20 | 25 | |
| Hypertension (%) | 5 | 5 | |
| Dyslipidemia (%) | 20 | 15 | |
| Ischemic heart disease (%) | 50 | 45 | |
| Other drugs use | | | |
| Insulin (%) | 8 | 10 | |
| Sulfonylurea (%) | 16 | 20 | |
| Statin (%) | 0 | 0 | |
| $Ca^{+2}$ channel antagonists (%) | 15 | 15 | |
| ACE inhibitors (%) | 0 | 0 | |
| β-blocker (%) | 20 | 15 | |
| Angiotensin receptor blocker (%) | 0 | 0 | |
| Current smoking (%) | 8 | 5 | 0 |
| Current alcohol consumption (%) | 0 | 0 | 0 |
| Total cholesterol (mg/dL) | 163.42±6.21 | 173.21±5.03 | 162.64±3.78 |
| Triglyceride (mg/dL) | 148.07±7.42 | 151.39±8.39 | 129.63±11.45 |
| Fasting glucose (mg/dL) | 112.36±4.02 | 122.83±9.48 | 117.84±7.35 |

Values are mean ± SE. There were nonsignificant differences between the two patient groups, $p>0.05$

**Table 2** The Nutritional Status of the Dialysis Patients

| | Nondementia ($n$=25) | Dementia ($n$=20) |
|---|---|---|
| Dry weight (kg) | 57.20±2.24 | 54.33±2.01 |
| Body mass index, BMI (kg/m$^2$) | 23.07±0.74 | 22.62±0.81 |
| TSF (mm) | 19.20±2.24 | 19.11±2.53 |
| AMA (cm$^2$) | 36.73±2.43 | 42.30±4.21 |
| Predialysis albumin (g/dL) | 3.57±0.05 | 3.44 ± 0.07 |
| Predialysis creatinine (mg/dL) | 11.87±0.63 | 10.66±0.60 |
| Predialysis BUN (mg/dL) | 78.39±4.96 | 82.94±6.25 |
| Postdialysis BUN (mg/dL) | 18.69±1.68 | 23.39±1.79 |

Values are mean ± SE. There were nonsignificant differences between two groups, $p>0.05$

*TSF* triceps skinfold thickness, *AMA* arm muscle area

## Biochemical Data

The levels of plasma oxidative productions in both hemodialysis groups were significantly increased as compared to normal control values in healthy subjects (Fig. 1, $p<0.05$). The increased MDA production and protein carbonyl levels in dementia group than that in nondementia group were also observed, respectively. The antioxidant enzymes GPx and GR activities markedly decreased in the dementia patients compared to nondementia patients. The patients had lower levels of Zn and higher Mg than those values of control

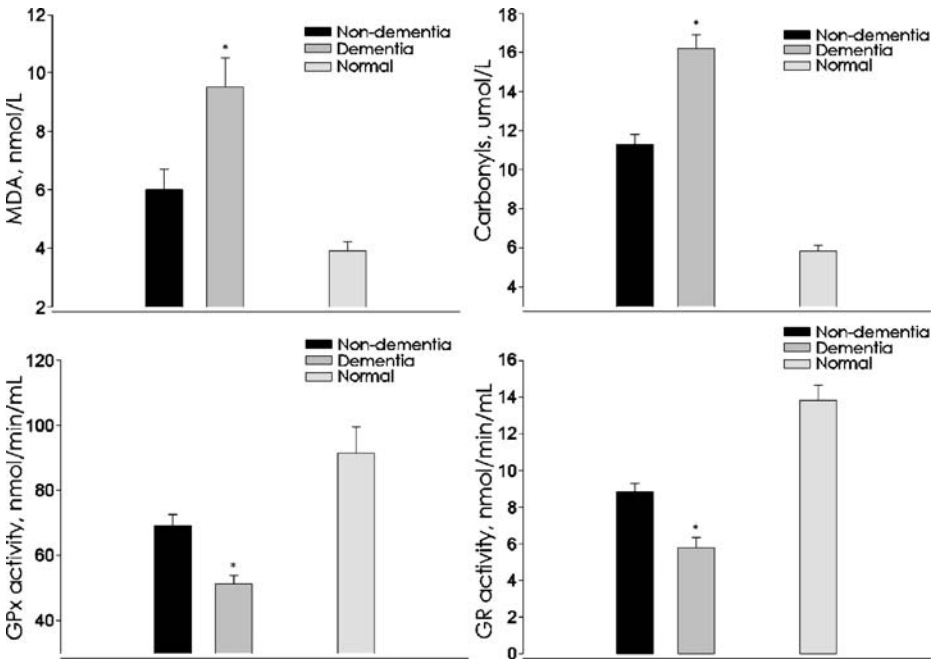


**Fig. 1** The comparison of oxidative status MDA (**a**), carbonyls (**b**), and antioxidant enzymes GPx (**c**), GR (**d**) activity. *$p<0.001$ vs nondementia

**Table 3** Blood Analysis for Trace Metals Levels in Two Patient Groups

| | Nondementia ($n$=25) | Dementia ($n$=20) | $p$ value | Control ($n$=20) |
|---|---|---|---|---|
| Zn (mg/L) | 0.70±0.05 | 0.44±0.02[a] | <0.001 | 0.89±0.03 |
| Mg (mg/dL) | 2.54±0.57 | 3.07±0.71[a] | <0.001 | 1.72±0.53 |
| Cu (mg/L) | 0.72±0.04 | 1.01±0.04[a] | <0.001 | 0.85±0.03 |
| Fe (mg/L) | 0.76±0.07 | 0.81±0.06 | <0.001 | 1.33±0.09 |
| Al (μg/dL) | 7.79±0.37 | 11.74±0.48[a] | <0.001 | 3.17±0.62 |
| Cu/Zn ratio | 1.21±0.23 | v2.49±0.21[a] | <0.001 | 0.98±0.05 |

Values are mean ± SE. Compared with nondementia

[a] Compared with nondementia

group (Table 3). Moreover, the dementia patients had significantly lower plasma Zn and higher Cu and Mg concentrations compared to the nondementia patients. In addition, plasma Al level was significantly higher in dementia patients than nondementia subjects. The lower levels of plasma Fe in both patient groups were observed. There was slight increase of blood Fe levels in dementia groups, but there was no marked difference between two groups of uremia patients. The ratio of Cu to Zn (Cu/Zn) was also significantly higher in dementia group than that in nondementia group or healthy volunteers.

### Relationships Among Metals and Oxidative Stress

There was a significantly positive correlation between blood Cu/Zn ratio and MDA ($r$= 0.7109, $p$<0.05) and between Cu/Zn ratio and protein carbonyl production ($r$=0.6223, $p$< 0.05) in dementia patients (Fig. 2). Additionally, positive correlations between blood MDA and Al, Mg levels ($r$=0.6500 and 0.6108, $p$<0.05, respectively) were obtained (Fig. 3).

## Discussion

The cognitive dysfunction and dementia may exist in up to 60% of dialysis patients, which is a major predictor of mortality in dialysis patients [2]. However, the risk factors and their prognostic significance for dementia in patients undergoing long-term dialysis have not been clearly defined.

Nutritional status significantly affected the morbidity and mortality of dialysis patients [26]. It is also related to cognitive and neuropsychiatric deficits in some neurodegenerative disorders [27]. Lower levels of serum albumin, pre-albumin, and creatinine were well established as being associated with increased mortality in dialysis patients [28]. However, the present investigation showed no significant difference at albumin, dry weight, BMI, TSF, AMA values, and creatinine levels between nondementia and dementia patients. An inflammatory–malnutrition process was associated with poor prognosis for dementia in the elderly and reduced survival rate in peritoneal dialysis patients [29]. It is therefore suggested that nutrition status alone may not be the contributory factor to dementia in dialysis patients.

The inflammatory reaction and oxidative stress were strongly associated to acceleration of neurodegeneration and dementia in older adults [30]. Recent studies have also suggested linkages between oxidative stress and inflammation in the uremic population. The patients

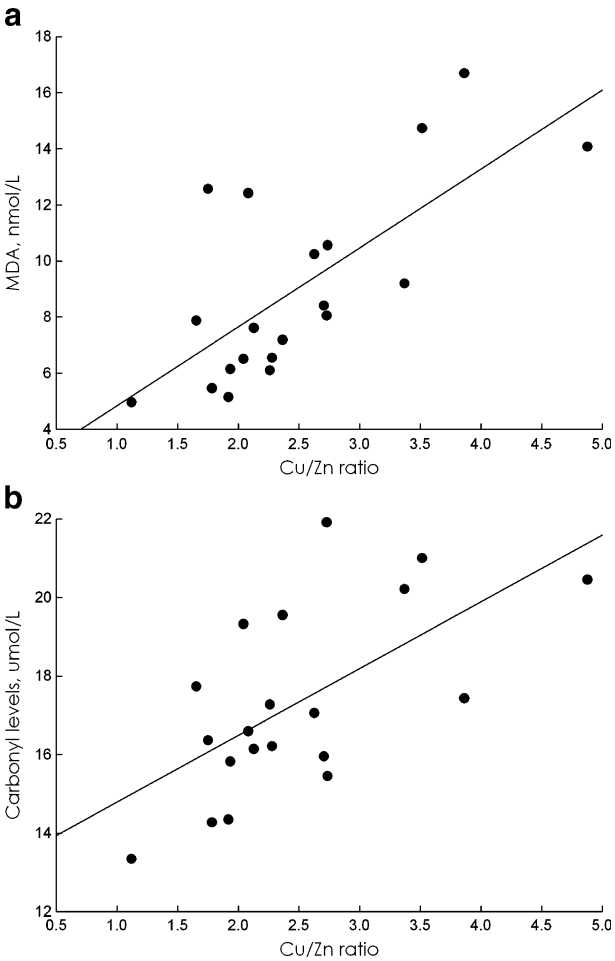


**Fig. 2** Correlations between copper to zinc ratio and MDA (**a**), protein carbonyl production (**b**) in uremic patients with dementia

with end-stage renal disease are subject to increased oxidative stress, which is closely associated with inflammation [29, 31]. Chronic inflammation induced an increased production of free radicals which cannot be counterbalanced due to defective antioxidant capability; altered redox state was responsible for the accelerated dialysis syndromes. The increasing oxidative stress is therefore among the major determinants of the dialysis syndromes [31]. The present investigation showed increased MDA and protein carbonyl production and higher Cu/Zn ratio and lower activity of antioxidant enzymes GPx and GR in dementia patients compared with the nondementia patients. Although the present data did not determine the levels of pro-inflammatory cytokines in all groups, the Cu/Zn ratio was used as a sensitive marker of in vivo inflammation and oxidative stress [32]. Therefore, oxidative stress still has a significant impact on the development of dementia in uremic patients.

Essential trace elements (Zn, Cu, Fe, and Mg) are involved in many metabolic pathways, such as enzymatic functions, oxidative damage and anti-oxidant defense, and immunological competence. These trace elements can act either as activators or inhibitors in the

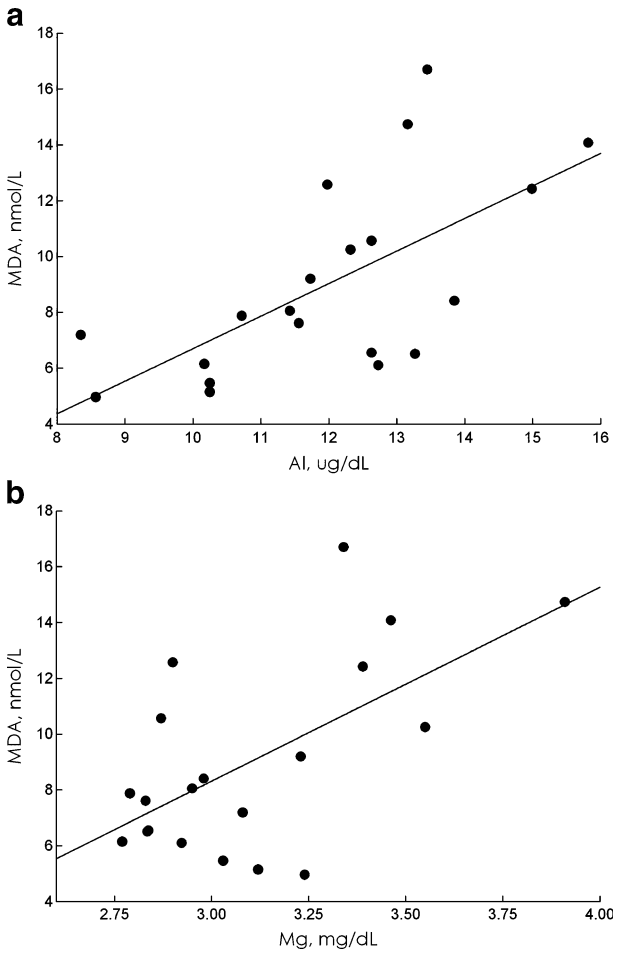


**Fig. 3** Relationships among Al (**a**), Mg (**b**), and MDA production in uremic patients with dementia

antioxidative defense systems depending on their levels in disease states. Increased oxidative stress in patients may result from changes in the levels of trace elements. Our findings further show an association between MDA and elevated Mg or Cu/Zn ratio in dementia patients. Patients with long-term dialysis were at the risks of developing trace element imbalance [33]. These trace element disturbances caused by medication, the uremic state, the dialysis process, and quality of the water used for dialysis may contribute to clinical abnormalities in dialysis patients [34]. In addition, an abnormal urinary excretion may be another important factor to affect the distribution of trace elements [35, 36]. Elements such as Zn which are extensively protein bound would be also lost in those patients. However, our study did not demonstrate a direct association between plasma levels and urinary excretion.

Zn and Cu ions are known to be sequestered in synaptic terminal vesicles and released during neuronal activity. Zn deficiency or Cu overloads elicited oxidative stress that could lead to the death of nerve cells [37, 38]. Conflicting results have been reported with respect to serum levels of Cu in hemodialysis patients. In the present study, dementia group had

comparable Cu value with that reported by Squitti et al. [39]. Serum Cu level of 1.02 mg/L was the cutoff value for the risk of getting Alzheimer's disease and poor neuropsychological performance. A significant increase was noted in plasma Cu of the patients with dementia, which may be due to hemoconcentration and liberation in the hemodialysis or impairing the hepatic metabolism of Cu [40]. However, we do not have an exact explanation for the present results. In addition, higher serum Mg concentration, resulting from increased protein catabolic rate, was observed among uremic patients [41]. Mg status imbalance may affect the *N*-methyl-D-aspartate receptor response to excitatory amino acids and ameliorated dopaminergic neurons in the substantia nigra [42, 43].

In the present results, the dialysis patients with dementia also showed a significant increase in plasma Al levels compared with the nondementia patients. Dementia was associated with elevated blood Al level that was identified in the 1980s. Such Al intoxication can now be avoided using modern techniques of water treatment. In contrast to earlier studies, a significant increase in plasma Al concentrations after a single hemodialysis was observed [44]. Serum Al was significantly higher in hemodialyzed patients than in normal subjects [45]. The continuous oral Al intake from Al-based phosphate binders and from dietary source is responsible for Al overload in dialysis patients [46]. However, the major source of high serum levels of Al still remains to be elucidated.

Al and Cu initiated the inflammatory response, which may aggravate the events associated with the Alzheimer's disease process [38]. Cu-induced reactive oxygen species production was also greatly enhanced in the presence of Al [47]. Some studies have reported interactions between Al and essential minerals, such as Zn, Cu, and Fe [22, 48]. A distinct decrease in plasma Zn concentrations among patients with raised Al levels was noted in patients with chronic renal insufficiency [49]. The neurotoxic effect of Al has also been related to the morphological and biochemical characteristics of beta-amyloid and neurofibrillary tangles and has often been related to oxidative stress [50]. The evidence in mouse neuroblastoma cells indicated that Al enhance Fe uptake and the expression of neurofibrillary tangle protein [51]. Apparently, this evidence supported that Al may still be a toxicant playing a pivotal role in the causation of uremic patients with dementia.

On the basis of the present findings, we conclude that chronic hemodialysis may lead to significant changes in the serum trace element (Zn, Cu, Mg, and Al) status that increase uremia patient susceptibility to oxidative stress and inflammation with increasing development of dementia. Although the pathophysiology of dementia in uremic patients is multi-factorial, the imbalanced trace elements status related to oxidative stress is still probably a major contributor. It is necessary to conduct a large-scale comparative investigation to explore the potential association of trace elements status to the dementia of uremic patients. Additionally, further studies are required to determine whether the simultaneous monitoring of those trace elements and antioxidant supplementation are beneficial to prevent the dementia in uremic patients.

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## References

1. Chui HC, Damasio AR (1980) Progressive dialysis encephalopathy. J Neurol 222: 145–157
2. Rakowski DA, Caillard S, Agodoa LY, Abbott KC (2006) Dementia as a predictor of mortality in dialysis patients. Clin J Am Soc Nephrol 1: 1000–1005

3. Dubinina EE, Kovrugina SV, Konovalov PV (2007) The factors of oxidative stress in neurodegenerative diseases (vascular dementia, Alzheimer disease). Adv Gerontol 20: 109–113
4. Ringman JM, Younkin SG, Pratico D et al (2008) Biochemical markers in persons with preclinical familial Alzheimer disease. Neurology 71: 85–92
5. Himmelfarb J (2008) Oxidative stress in hemodialysis. Contrib Nephrol 161: 132–137
6. Bibi G, Green Y, Nagler RM (2008) Compositional and oxidative analysis in the saliva and serum of predialysis chronic kidney disease patients and end-stage renal failure patients on peritoneal dialysis. Ther Apher Dial 12: 164–170
7. Karamouzis I, Sarafidis PA, Karamouzis M et al (2008) Increase in oxidative stress but not in antioxidant capacity with advancing stages of chronic kidney disease. Am J Nephrol 28: 397–404
8. Olszewska M (2004) The effect of hemodialysis on some parameters of the antioxidant system in the blood of patients with chronic renal failure. Ann Acad Med Stetin 50: 41–52.
9. Zachara BA, Włodarczyk Z, Masztalerz M et al (2004) Selenium concentrations and glutathione peroxidase activities in blood of patients before and after allogenic kidney transplantation. Biol Trace Elem Res 97: 1–13
10. Desai V, Kaler SG (2008) Role of copper in human neurological disorders. Am J Clin Nutr 88: 855S–858S
11. Strausak D, Mercer JF, Dieter HH et al (2001) Copper in disorders with neurological symptoms: Alzheimer's, Menkes, and Wilson diseases. Brain Res Bull 55: 175–185.
12. Ke Y, Qian ZM (2007) Brain iron metabolism: neurobiology and neurochemistry. Prog Neurobiol 83: 149–173
13. Regan RF, Guo Y (2001) Magnesium deprivation decreases cellular reduced glutathione and causes oxidative neuronal death in murine cortical cultures. Brain Res 890: 177–183
14. Kawahara M (2005) Effects of aluminum on the nervous system and its possible link with neurodegenerative diseases. J Alzheimers Dis 8: 171–182
15. Niu Q, Yang Y, Zhang Q, Niu P, He S, Di Gioacchino M, Conti P, Boscolo P (2007) The relationship between Bcl-gene expression and learning and memory impairment in chronic aluminum-exposed rats. Neurotox Res 12: 163–169
16. Kurella M, Mapes DL, Port FK, Chertow GM (2006) Correlates and outcomes of dementia among dialysis patients: the dialysis outcomes and practice patterns study. Nephrol Dial Transplant 21: 2543–2548
17. Huang YC, Kuo YW, Lee TH et al (2008) Hypoalbuminemia and not hyperhomocysteinemia as a risk factor for dementia in hemodialysis patients. J Ren Nutr 18: 347–354
18. American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. Washington, DC, American Psychiatric Press.
19. Katzman R, Zhang MY, Ouang YQ et al (1988) A Chinese version of the Mini-Mental State Examination: Impact of illiteracy in a Shanghai dementia survey. J Clin Epidemiol 41: 971–978
20. Kloppenburg WD, Stegeman CA, de Jong PE, Huisman RM (1999) Relating protein intake to nutritional status in haemodialysis patients: how to normalize the protein equivalent of total nitrogen appearance (PNA)? Nephrol Dial Transplant 14: 2165–2172.
21. Ko WS, Guo CH, Hsu GSW et al (2005) The effect of zinc supplementation on the treatment of chronic hepatitis C patients with interferon and ribavirin. Clin Biochem 38: 614–620
22. Guo CH, Huang CJ, Chiou YL, Hsu GSW (2002) Alteration of trace element distribution and testis ACE activity in mice with high peritoneal aluminum. Biol Trace Elem Res 86: 145–157
23. Guo CH, Hsu GSW, Chuang CJ, Chen PC (2009) Aluminum accumulation induced testicular oxidative stress and altered selenium metabolism in mice. Environ Toxicol Pharmacol 27:176–181
24. Reznick AZ, Packer L (1994) Oxidative damage to proteins: spectrophoto- metric method for carbonyl assay. Methods Enzymol 233: 357–363
25. Paglia D, Valentine WN (1967) Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase. J Lab Clin Med 70: 158–169
26. Avram MM, Goldwasser P, Erroa M, Fein PA (1994) Predictors of survival in continuous ambulatory peritoneal dialysis patients: the importance of prealbumin and other nutritional and metabolic markers. Am J Kidney Dis 23: 91–98
27. Ousset PJ, Nourhashemi F, Reynish E, Vellas B (2008) Nutritional status is associated with disease progression in very mild Alzheimer disease. Alzheimer Dis Assoc Disord 22: 66–71
28. Fein PA, Mittman N, Gadh R et al (2003) Malnutrition and inflammation in peritoneal dialysis patients. Kidney Int Suppl 87: S87-S91
29. Himmelfarb J (2005) Relevance of oxidative pathways in the pathophysiology of chronic kidney disease. Cardiol Clin 23: 319–330
30. Peila R, Launer LJ (2006) Inflammation and dementia: epidemiologic evidence. Acta Neurol Scand 114 Suppl 185: 102–106.

31. Rambod M, Kovesdy CP, Kalantar-Zadeh K (2008) Malnutrition-Inflammation Score for risk stratification of patients with CKD: is it the promised gold standard? Nat Clin Pract Nephrol 4: 354–355
32. Mezzetti A, Pierdomenico SD, Costantini F et al (1998) Copper/zinc ratio and systemic oxidant load: effect of aging and aging-related degenerative diseases. Free Radic Biol Med 25: 676–681
33. Krachler M, Wirnsberger G, Irgolic KJ (1997) Trace element status of hemo-dialyzed patients. Biol Trace Elem Res 58: 209–221
34. Muirhead N, Mitton R (1992) Use of bone char as an adsorbent in preparation of water for dialysis. ASAIO J 38: 334–337
35. Mahajan SK, Bowersox EM, Rye DL, Abu-Hamdan DK, Prasad AS, McDonald FD, Biersack KL (1989) Factors underlying abnormal zinc metabolism in uremia. Kidney Int Suppl 27: S269–73
36. Batista MN, Cuppari L, de Fátima Campos Pedrosa L, Almeida MG, de Almeida JB, de Medeiros AC, Canziani ME (2006) Effect of end-stage renal disease and diabetes on zinc and copper status. Biol Trace Elem Res 112: 1–12
37. Hao Q, Maret W (2005) Imbalance between pro-oxidant and pro-antioxidant functions of zinc in disease. J Alzheimers Dis 8: 161–170
38. Campbell A (2006) The role of aluminum and copper on neuroinflammation and Alzheimer's disease. J Alzheimers Dis 10: 165–172
39. Squitti R, Lupoi D, Pasqualetti P et al (2002) Elevation of serum copper levels in Alzheimer's disease. Neurology 59: 1153–1161
40. Sondheimer JH, Mahajan SK, Rye DL, Abu-Hamdan DK, Migdal SD, Prasad AS, McDonald FD (1988) Elevated plasma copper in chronic renal failure. Am J Clin Nutr 47: 896–899
41. Baradaran A, Nasri H (2006) Correlation of serum magnesium with serum parathormone levels in patients on regular hemodialysis. Saudi J Kidney Dis Transpl 17: 344–350
42. Cilliler AE, Ozturk S, Ozbakir S (2007) Serum magnesium level and clinical deterioration in Alzheimer's disease. Gerontology 53: 419–422
43. Hashimoto T, Nishi K, Nagasao J, Tsuji S, Oyanagi K (2008) Magnesium exerts both preventive and ameliorating effects in an in vitro rat Parkinson disease model involving 1-methyl-4-phenylpyridinium (MPP+) toxicity in dopaminergic neurons. Brain Res 1197: 143–151
44. Lin TH, Chen JG, Liaw JM, Juang JG (1996) Trace elements and lipid peroxidation in uremic patients on hemodialysis. Biol Trace Elem Res 51: 277–283
45. Neiva TJ, Benedetti AL, Tanaka SM, Santos JI, D'Amico EA (2002) Determination of serum aluminum, platelet aggregation and lipid peroxidation in hemo-dialyzed patients. Braz J Med Biol Res 35: 345–350
46. Arenas MD, Malek T, Gil MT, Moledous A, Núñez C, Alvarez-Ude F (2008) Use of the aluminum phosphate-binders in hemodialysis in the ultrapure water era. Nefrologia 28: 168–173
47. Becaria A, Bondy SC, Campbell A (2003) Aluminum and copper interact in the promotion of oxidative but not inflammatory events: implications for Alzheimer's disease. J Alzheimers Dis 5: 31–38
48. Guo CH, Hsu WGS, Lin LY, Wang YH, Lin CY, Yeh MS (2004) Distribution patterns of trace elements and of lipid peroxidation in plasma and erythrocytes of rat exposed to aluminum. Biol Trace Elem Res 101: 61–71
49. Zumkley H, Bertram HP, Lison A, Knoll O, Losse H (1979) Aluminum, zinc and copper concentrations in plasma in chronic renal insufficiency. Clin Nephrol 12: 18–21
50. Sharma P, Ahmad Shah Z, Kumar A, Islam F, Mishra KP (2007) Role of combined administration of Tiron and glutathione against aluminum-induced oxidative stress in rat brain. J Trace Elem Med Biol 21: 63–70
51. Abreo K, Abreo F, Sella M, Jain S (1999) Aluminum enhances iron uptake and expression of neurofibrillary tangle protein in neuroblastoma cells. J Neurochem 72: 2059–2064