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TRANSPLANTOLOGY

Disturbances of trace element metabolism in ESRD patients receiving hemodialysis and hemodiafiltration

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Introduction. Accumulation of trace elements occurs in conditions of decreased kidney function. In some conditions, increased trace elements can have toxic features. On the other hand, studies are showing that concentration of some trace elements could be decreased in ERSD patients as well. The most important factor affecting trace element concentration in ERSD patients is the degree of renal failure and the usage of replacement therapy.

Materials and methods. We analyzed the trace elements' (boron, aluminum, vanadium, chromium, manganese, cobalt, nickel, copper, zinc, arsenic, selenium, rubidium, strontium, cadmium, cesium, barium and lead) concentration in the whole blood of 41 ESRD patients who were treated with hemodialysis and hemodiafiltration and also of 61 healthy blood donors. In addition, comparison of trace element blood levels of patients receiving hemodialysis and hemofiltration was carried out. Whole blood trace element concentration was determined using inductive coupled plasma mass-spectrometry (ICPMS).

Results. Levels of boron, aluminum, vanadium, chromium, manganese, zinc, strontium, cadmium, barium and lead were significantly increased in ESRD patients. Significantly decreased levels were observed for nickel, arsenic, selenium and rubidium. Blood levels of cobalt, copper, cadmium and lead in hemodialysis patients were significantly higher compared to patients receiving hemodiafiltration.

Conclusions. ESRD is accompanied with serious and multidirectional changes of trace element blood levels. The highest degree of blood level increases were observed for nonessential and toxic trace elements. Disorders of essential trace elements were manifested in a minor degree. Besides this, there were observed differences of trace element concentrations between ESRD patients receiving hemodialysis and hemo-diafiltration.

Key Words: trace elements ‹› end stage renal disease ‹› hemodyalisis ‹› hemodiafiltration

INTRODUCTION

Uremia is characterized by functional and biochemical disturbances that are primarily a result of diminished kidney capacity to remove organic solutes from the body. Most researches on uremic toxicity have focused on retention and removal of these organic compounds. However, subtle changes in the concentrations of inorganic compounds, including trace elements, may also cause functional or biochemical disturbances [1].

In ESRD (end-stage renal disease) patients, different factors affect whole blood and serum concentrations of trace elements, such as increased oral intake, failure of renal excretion, degree of renal failure and metabolic alterations associated with renal failure [2].

Decreased concentration is mainly related to nutritional intake, intestinal uptake and altered distribution. In addition, protein-bound trace elements may be lost more readily in the presence of proteinuria. Increased trace element concentrations can be a result of decreased elimination, excessive homeopathic intake, industrial or environmental exposures, inhalation of cigarette smoke, administration of paren-

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teral fluids or blood contact with contaminated dialysate.

Hemodialysis is the most common modality of renal replacement therapy which saves more than one million lives in the world. Unfortunately, dialysis is associated with considerable morbidity and mortality due to accelerated cardiovascular disease and infection. Hemodialysis patient blood is in contact with very high volumes (>300 liters/week) of dialysate. Therefore, even minute levels of toxic substances in source water could lead to tiny concentration gradients between blood and dialysate, which can lead to clinically relevant toxicity. Substances present in dialysate, but not in blood will tend to accumulate in the patient. From the other hand, the lack of renal clearance in hemodialysis patients might theoretically lead to toxicity of ingested trace elements even when they are not present in dialysate.

Hemodiafiltration is technology that combines diffusion and convection. Usage of this method involves massive ultrafiltration and replacement by sterile officinal solution. Solution that is prepared by a hemodiafiltration machine (hemodiafiltration online) can also be used during the procedure [3]. Thus, hemodialysis patients are at theoretical risk for both deficiency and accumulation of trace elements, depending on dietary intake, removal by dialysis, the composition of the source water used for hemodialysis and residual kidney function [4, 5].

Achieved information about trace element disorders in ESRD patients receiving replacement therapy could assist in the process of developing a microelement correction strategy. Thus, it would improve the nutritional status of these patient groups.

MATERIALS AND METHODS

Studies included 41 ESRD patients who received replacement therapy. Mean age of the patients was 52 ±12.6 years. There were 20 (48.8%) males and 21 (51.2%) females. 20 patients received hemodialysis and 21patients received hemodiafiltration as replacement therapy. The quantity of patients who received replacement therapy less than 3 years ago was 32%, from 3 to 6 years – 21% and more than 6 years – 47%. The control group was represented by 61 healthy blood donors.

During the study, content of 17 trace elements was analyzed (boron, aluminum, vanadium, chromium, manganese, cobalt, nickel, copper, zinc, arsenic, selenium, rubidium, strontium, cadmium, cesium, barium and lead). Determination of whole blood trace element content was conducted by inductive coupled plasma mass-spectrometry after microwave digestion of samples (Bruker MS 820, Australia).

Data was presented in form of M ±m, were "M" is mean value and "m" is standard error mean. The null hypothesis that two populations are the same was conducted by non-parametric Mann–Whitney U test.

RESULTS

Obtained results of whole blood trace element content we have ranged in 2 groups. There was the group with increased and the group with decreased levels of trace elements (p <0.05).

The first group (increased trace elements) is presented by boron, aluminum, vanadium, chromium, manganese, cobalt, zinc, copper, strontium, cadmium, barium and lead (Table 1).

Table 1. *Comparison of increased trace element blood levels in control group and ESRD patients*

Element	Trace elements concentration in controls (mg/L)	Trace elements concentration in ESRD (mg/L)	Degree of changes (times)	p-value
Boron	0.00979 ±0.0046	0.194 ±0.0083	19.8	<0.000001
Aluminum	0.027 ±0.010	0.206 ±0.0217	7.53	<0.000001
Vanadium	0.0267 ±0.0007	0.0832 ±0.0029	3.12	<0.000001
Chromium	0.0925 ±0.0077	0.242 ±0.0018	2.62	<0.000001
Manganese	0.0120 ±0.0004	0.0403 ±0.005	3.36	<0.000001
Cobalt	0.00022 ±0.00011	0.00006 ±0.00010	3.94	0.501
Zinc	4.93 ±0.07	5.81 ±0.14	1.18	<0.000001
Copper	0.669 ±0.0077	0.716 ±0.025	1.07	0.114
Strontium	0.0234 ±0.00090	0.0349 ±0.0013	1.5	<0.000001
Cadmium	0.0006 ±0.0002	0.0014 ±0.00012	2.34	<0.000001
Barium	0.0030 ±0.0006	0.0206 ±0.0052	6.92	0.000001
Lead	0.0196 ±0.0021	0.0708 ±0.0058	3.62	<0.000001

Obtained results (Table 1) shows that the fluctuation of degree of significant changes in increased trace elements is in wide ranges from 1.18 to 19.8 times. The biggest degrees (more than 5 times) of significant increased changes were observed for boron, aluminum and barium; moderate changes (1.5–5 times) were incurred by lead, manganese, chromium, cadmium, strontium. The least changes (less than 1.5 times) were observed for zinc.
Decreasing content in whole blood trace elements of patients with ESRD in comparison with controls has been observed in cases of nickel, arsenic, selenium, cesium and rubidium (Table 2).
According to our data the biggest degrees (more than 2 times) of significant decrease in trace elements was observed for nickel, arsenic and rubidium; the least changes (less than 2 times) occurred with selenium.
Trace element content with insignificant changes (p >0.05) in ESRD patients were represented by cobalt, copper and cesium.
During the study, we compared and analyzed blood trace element content in ESRD patients who have been treated with hemodialysis and hemodiafiltration (Table 3). Obtained data showed that blood concentrations of cobalt, cobalt, copper, cadmium and lead, in hemodialysis patients, is significantly higher that in hemodiafiltration patients.
Trace element content of water that was used for dialysis therapy corresponded to the Recommendations of the European Pharmacopoeia [6].

DISCUSSION

Depending on changes of metabolism direction, trace elements are divided into 3 groups: cation, anion

Table 2. *Comparison of decreased trace element blood levels in control group and ESRD patients*

Element	Trace elements concentration in controls (mg/L)	Trace elements concentration in ESRD (mg/L)	Degree of changes times	p-value
Nickel	0.0808 ±0.019	0.025 ±0.0052	3.20	0.0152
Arsenic	0.0069 ±0.0008	0.0020 ±0.00046	3.49	<0.000001
Selenium	0.139 ±0.003	0.121 ±0.0059	1.15	0.0118
Rubidium	1.94 ±0.036	0.898 ±0.022	2.16	<0.000001
Cesium	0.00188 ±0.00015	0.00152 ±0.00006	1.24	0.112

Table 3. *Blood levels of trace elements in patients receiving hemodialysis and hemodiafiltration*

Element	Trace element concentration in hemodialysed patients (mg/L)	Trace element concentration in hemofiltrated patients (mg/L)	p-value
Boron	0.2020 ±0.01	0.1860 ±0.0092	0.446
Aluminum	0.2408 ±0.041	0.1740 ±0.013	0.525
Vanadium	0.0833 ±0.003	0.0849 ±0.005	0.525
Chromium	0.248 ±0.013	0.241 ±0.010	0.852
Manganese	0.0503 ±0.008	0.0303 ±0.004	0.0994
Cobalt	0.00043 ±0.00021	0.00002 ±0.00001	0.0046
Nickel	0.0258 ±0.0064	0.0267 ±0.0081	0.832
Zinc	5.99 ±0.23	5.71 ±0.17	0.375
Copper	0.780 ±0.040	0.662 ±0.026	0.0444
Arsenic	0.0018 ±0.0008	0.0020 ±0.0005	0.225
Selenium	0.116 ±0.010	0.127 ±0.007	0.432
Rubidium	0.929 ±0.039	0.894 ±0.032	0.699
Strontium	0.0378 ±0.0018	0.0328 ±0.0016	0.0893
Cadmium	0.0017 ±0.0002	0.0011 ±0.0001	0.0020
Cesium	0.0015 ±0.0001	0.0016 ±0.0001	0.755
Barium	0.0192 ±0.0070	0.0211 ±0.0074	0.931
Lead	0.0936 ±0.0088	0.0498 ±0.0034	<0.000001

elements and elements that exist in complex with organic compounds. Cation (zinc, iron, manganese, copper) are elements with variable absorption, its homeostasis is controlled by the liver and gastrointestinal tracts. Anion elements (chromium, vanadium, cadmium, selenium, boron, strontium, rubidium and cesium) are very efficiently absorbed in the gastrointestinal tract and excreted by the kidneys. Metabolism of elements that are existing in complex with organic compounds is difficult (lead) [7].

Our data shows that the increasing amounts of the majority trace elements in blood levels (boron, aluminum, vanadium, chromium, manganese, cobalt, zinc, copper, strontium, cadmium, barium and lead) is observed for ESRD patients, in comparison with controls. Thus, the biggest increase of blood level trace elements are observed for anion unessential and toxic trace elements, which could be explained by its kidney exertion.

A systemic review and meta-analysis of 128 studies of trace elements in hemodialysis patients was completed in 2009. It has been shown that cadmium, chromium, vanadium, nickel, copper and lead probably accumulates in hemodialysis patients, which corresponds to our achieved results from our studies (except that nickel and copper were not increased in our results) [8]. Unfortunately, information about the concentration of boron and barium in ESRD patients is poor. High blood levels of aluminum have been described by others studying both: ESRD patients without dialysis and those receiving hemodialysis [9]. Several trace elements including aluminum, cadmium, iron and strontium have been implicated in renal osteodystrophy which is commonly observed in ESRD patients [1]. Contrariwise, as is well known, bones are the site of the physiological accumulation of trace elements. Thus, bone tissue demineralization could lead to the transfer of accumulated trace elements (boron, aluminum, zinc, manganese, lead, strontium and barium) to blood circulation.

Difficult to explain is the high increased blood concentration of manganese in ESRD patients (3.36 times). We have to admit that our work results, concerning the accumulation of manganese and zinc, are not corresponding to a majority of previous studies where deficiency of these microelements has been shown [8].

Decreasing selenium blood level in ESRD patients could be related to the participation of selenium in glutathione peroxidase structure, which is one of the main antioxidant enzymes. There is the possibility that selenium is mobilizing in the participation in anti-inflammatory reactions. This fact is confirmed by researchers of lipids peroxide oxidation activity in ESRD patients [10]. Decreased bloods selenium levels is a prevailing trace element disorder in ESRD patients [1, 8].

Other trace elements (arsenic, nickel and rubidium) are decreased in spite of its renal excretion. Besides these decreased trace elements, decrease in cesium and rubidium in ESRD patients have also been described in other studies [1, 11]. In our opinion, it could be explained by the usage of renal replacement therapy. Elimination activity of hemodialysis and hemodiafiltration against arsenic is described in literature [12]. We are assuming that selective elimination activity of dialysis therapy could be observed toward other trace elements as well. In support of this hypothesis, there is existing data that indicates a 25% decrease of rubidium blood content after hemodialysis administration [13]. Furthermore, hypoproteinemia that is commonly observed in ESRD patients could potentially lead to compartmentation of trace elements in tissues, resulting in decreasing blood capacity for its transport [1].

Significant increasing ($p < 0.05$) blood levels of cobalt, copper, cadmium and lead in patients receiving different extracorporeal therapy could be explained by modality features of dialysis therapy (HD and HDF). Trace element changes could be caused by direct and indirect effects of dialysis therapy. Direct effects could be related with filter features (HD and HDF), mediating appearance of indirect homeostatic functions effects.

CONCLUSIONS

ESRD is accompanied with substantial and multidirectional changes of trace element blood levels. The highest degree of blood level increases are observed for nonessential and toxic trace elements. Disorders of essential trace elements are manifested in a minor degree. Thus, microelement correction strategy has to be aimed at increasing the selenium uptake and elimination of accumulated toxic trace elements. Blood levels of cobalt, copper, cadmium and lead in hemodialysis patients are significantly higher in comparison with patients receiving hemodiafiltration. Further investigations need to be performed to determine the reasons for this difference.

References

1. Vanholder R, Cornelis R, Dhondt A, Lameire N. The role of trace elements in uraemic toxicity. Nephrol Dial Transplant. 2002; Suppl 2: 2-8.
2. Miura Y, Nakai K, Suwabe A, Sera K. Trace elements in renal disease and hemodialysis. Nuclear instruments and methods in physics research. 2002; 189: 443-449.
3. Henderson LW, Beans E. Successful production of sterile pyrogen-free electrolyte solution by ultrafiltration. Kidney Int. 1978; 14: 522-552.
4. Zima T, Tesar V, Mestek O, Nemecek K. Trace elements in end-stage renal disease. Clinical implication of trace elements. Blood Purif. 17; 1999: 187-198.
5. D'Haese PC, De Broe ME. Adequacy of dialysis: trace elements in dialysis fluids. Nephrol Dial Transplant. 1996; 11 Suppl 2: 92-97.
6. Mactier R, Hoenich N, Breem C. Renal Association Clinical Practice Guideline on haemodialysis. Nephron Clin Pract. 2011; 118 Suppl 1: c241-286.
7. Obierlic D, Charland B, Skalnyi A. Biologic role of macro- and microelements in humans and animals. Sankt-Petersburg, Nauka, 2008, p. 542 [rus.].
8. Tonelli M, Wiebe N, Hemmelgarn B, Klarenbach S, Field C, Manns B, et al. Trace elements in hemodialysis patients: a systematic review and meta-analysis. BMC Medicine. 2009; 7: 25.
9. Marumo F, Tsukfmoto Y, Iwanami S, Kishimoto T, Yamagami S. Trace elements concentrations in hair, fingernails and plasma of patients with chronic renal failure on hemodialysis and hemofiltration. Nephron. 1984; 38: 267-272.
10. Richard MJ, Arnaud J, Jurkovitz C, Hachache T, Meftahi H, Laporte F, et al. Trace elements and lipid peroxidation abnormalities in patients with chronic renal failure. Nephron. 57; 1991: 10-15.
11. Thomson N, Stevens B, Humphery T, Atkins R. Comparsion of trace elements in peritoneal dialysis, hemodialysis and uremia. Kidney Int. 1983; 23: 9-14.
12. Mathieu D, Mathieu-Nolf M, Germain-Alonso M, Neviere R, Furon D, Wattel F. Massive arsenic poisoning-effect of hemodialysis and dimercaprol on arsenic kinetics. Intensive Care Med. 1992; 18: 47-50.
13. Allain P, Mauras Y, Tafforeau C, Houssin A, Cartier F. Changes in the plasma and erythrocyte concentrations of rubidium in patients with renal failure. Presse Med. 1984; 13: 2249-2251.