European Review for Medical and Pharmacological Sciences 2014; 18: 58-65

The influence of antihypertensive drugs on mineral status in hypertensive patients

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Abstract. – OBJECTIVES: Long-term therapy of hypertension may influence mineral status in patients. However, drug–micronutrient interactions are largely unexplored in practice. This study intended to evaluate the effect of hypotensive monotherapy on iron, zinc, and copper levels, as well as on selected biochemical parameters, in newly diagnosed patients with hypertension, and to assess the influence of diet with optimal mineral levels on the mineral balance in these subjects.

PATIENTS AND METHODS: Forty-five patients, aged 18-65 years with diagnosed essential hypertension, beginning monotherapy treatment with diuretics, calcium antagonists, angiotensin-converting enzyme inhibitors, and β-blockers, were employed. Over three months, the patients underwent monotherapy (stage II). Next, patients were randomly divided into a diet group (of 27 subjects) and a control group (of 18 subjects). In this stage, which lasted one month, patients were given the same drug but also followed an optimal mineral-content diet (for the diet group), or else continued drug use without any change in diet (for control group) (stage III).

Lipids, glucose, ceruloplasmin, and ferritin-along with superoxide dismutase and catalase activities-were assayed in serum. Iron, zinc, and copper concentrations in serum, erythrocytes, and urine were determined using flame atomic absorption spectrometry. Blood pressure was measured. Diet intake was monitored at each stage.

RESULTS: It was found that the zinc level in serum significantly decreased following treatment, and that the use of the optimal-mineral diet during antihypertensive treatment markedly increased zinc serum concentration. After treatment, a significant increase in zinc excretion in the urine was observed. Glucose levels in the serum of patients in stage II were significantly higher than in the baseline. In patients in the diet group, glucose levels markedly decreased. Moreover, a negative correlation was found between serum glucose and zinc levels in patients.

CONCLUSIONS: Antihypertensive treatments should include monitoring of mineral status. It seems that the zinc balance of patients on long-term therapy with hypotensive drugs may benefit from an optimal-mineral diet.

Key Words:
Hypertension, Hypotensive drugs, Iron, zinc, Copper, Minerals, Diet, Drug-minerals interaction.

Introduction

High blood pressure is a global public health problem. Hypertension is the most important risk factor for adverse cardiovascular events, and patients diagnosed with hypertension are usually treated with hypotensive drugs that are prescribed long-term. There are six major classes of antihypertensive drugs, each with multiple members: angiotensin-converting enzyme inhibitors (ACEi), diuretics, calcium-channel blockers, beta blockers, alpha blockers, and angiotensin receptor blockers (ARB). Monotherapy is recommended as an initial approach for reducing blood pressure. In some patients, combined therapy is used from the beginning[1,2]. The long-term use of hypotensive drugs can cause side effects. Drug treatment may have a detrimental effect on nutritional status, especially by impairing the intake of food or the absorption, metabolism, or excretion of nutrients. Long-term therapy may influence carbohydrate and lipid metabolism, oxidative stress, and electrolyte status[3,4].

In clinical and experimental researches, including our own, disorders in sodium, potassium, magnesium, calcium, zinc, and iron in hypertension patients were observed[5,6,7]. The clinical studies available have identified that zinc, magnesium, and potassium levels are affected by the long-term use of several commonly prescribed antihypertensive drugs[6,8,9] It has been found that treatment with angiotensin-converting enzyme

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inhibitors (ACE-I) and some diuretics can result in deficits of magnesium, potassium, and zinc[6,8,9,10]. It is known that mineral deficiencies can result in lipid, glucose, and antioxidant status disorders[11]. The findings of some investigations have also indicated that mineral supplementation introduced a long side treatment with drugs may have a positive effect on mineral status in patients[12,13,14]. Some reports have shown the impact of optimal-mineral-content diets on mineral status in hypertensive patients with monotherapy.

The aim of this work was, thus, to evaluate the effect of antihypertensive monotherapy on iron, zinc, and copper levels, as well as on biochemical parameters, in patients newly diagnosed with hypertension. Also assessed was the effect of a diet with optimal mineral contents on the mineral balance in the hypertensive patients undergoing treatment.

Patients and Methods

Participants

The protocol was approved by the Research Ethics Committee at Poznaƒ University of Medical Sciences, registered as no. 86/09. It conformed to all ethical issues included in the Helsinki Declaration.

Forty-five patients with primary hypertension were selected. The inclusion criteria were as follows: age 18-65 years, diagnosed essential hypertension, beginning monotherapy treatment with a hypotensive drug, stable body weight (less than 3 kg self-reported change during the previous 3 months), and no use of mineral supplements during the previous 3 months.

The exclusion criteria were: history of coronary artery disease, heart failure, peripheral artery disease, diabetes mellitus, abnormal renal and liver function, clinically significant inflammatory processes, alcohol abuse, thyroid disorder, and mental illness.

Study Design

The study was carried out in three stages. In the first stage, patients were diagnosed with essential hypertension and begun hypotensive therapy. Over three months, the patients underwent monotherapy: 38% of subjects received diuretics, 31% were given calcium antagonists, 18% received angiotensin-converting enzyme inhibitors, and 13% received β-blockers (second stage). In the third stage of the study, the patients were divided into two groups: a diet group (of 27 subjects) and a control group (of 18 subjects). The division of subject into the groups was randomized. In this stage, which lasted one month, patients were given the same drug, and also either followed an optimal-mineral-content diet (for diet group) or continued drug use without any change in diet (in the case of the control group). Drug administration was comparable between groups and between stages I and II. Dietary recommendations for the diet group were submitted by a dietician. During the study, patients were forbidden to use mineral supplements and to change their lifestyle. All treated subjects underwent consultation with a dietician and were instructed to maintain their diets and physical activity for the duration of the study. Three days before each laboratory test, dietary intake was determined by obtaining 24-hour dietary recall from the subjects. After each stage, blood and urine samples were taken from the subjects, and blood pressure and anthropometry parameters were measured. All patients were under medical supervision during the period of this research.

Anthropometry

Patients were measured wearing light clothing and no shoes. Weight was measured to the nearest 0.1 kg, and height to the nearest 1 cm. The body mass index (BMI) was calculated by dividing the weight (kg) by the height squared (m^2).

Blood Pressure Measurement

Blood pressure was measured according to the guidelines of the European Society of Hypertension, using a digital electronic tensiometer (model 705IT, Omron Corporation, Kyoto, Japan). Regular or large adult cuffs were used, depending on the patient's arm circumference. The measurements were taken while fasting and resting in a sitting position in the morning hours. Blood pressure was taken as the average of three measurements from the left arm.

Biochemical Assays

Blood samples were collected following an overnight fast and after 30 min in the supine position. All participants had blood taken from a forearm vein in serum-separated tubes, and in another with heparin sodium to obtain erythrocytes. The coagulated blood was left to clot at room temperature and then centrifuged. The supernatant fluid was separated. Serum samples were stored at –20 °C for analysis.

For erythrocyte separation, the total blood was centrifuged for 15 min at 2000×g at 4 °C, and the plasma was separated. Blood cells were washed three times with 5 ml of 0.9% saline solution and centrifuged at 2000×g for 10 minutes at 4 °C. Following each centrifuging, the saline solution was separated and the erythrocyte mass was placed in demineralized Eppendorf tubes and stored at -20 °C for mineral analysis.

Serum levels of lipids – including total cholesterol (TCH), high-density lipoprotein cholesterol (HDL), and triglycerides (TG) – and of glucose were assayed by routine enzymatic methods. Low-density lipoprotein cholesterol (LDL) was calculated from Friedewald's formula. The accuracy and precision of the techniques used to assay the lipids and glucose were validated. Reproducibility was checked with a human serum control (Randox). Accuracy was assessed by means of the recovery value, which ranged between 95% and 109%. The variability coefficient did not exceed 10%.

The concentration of ferritin and ceruloplasmin in the serum was determined by enzyme immunoassay (ADVIA Centaur XP analyzer, Siemens Healthcare, Bohemia, NY, USA).

Superoxide dismutase (SOD) activity was determined in the erythrocyte hemolysate using a modification of the epinephrine-adenochrome detection system. Erythrocyte catalase (CAT) was determined using a spectrophotometric method for measuring the breakdown of hydrogen peroxide by catalase. Erythrocyte enzyme activity was expressed as units per g of hemoglobin.

The hemoglobin concentration in mg per mL was determined using the cyanmethemoglobin method.

Urine was collected during the final day of each stage, with the collection performed in the morning, following an overnight fast. Urine was collected in sterilized vessels and stored at 4°C. The volume of urine was measured. A representative sample of daily urine was then taken and stored at –20°C for material analysis.

Determination of Minerals

The iron, zinc, and copper contents of serum, erythrocytes, and urine were determined following digestion in 65% (w/w) spectra pure HNO_3 (Merck) in the Microwave Digestion System (MARS 5, CEM Corp., Matthews, NC, USA). Thereafter, the concentrations of iron, zinc, and copper in the mineral solutions were measured using the flame atomic absorption spectrometry method (AAS-3, Carl Zeiss, Jena, Germany). The mineral contents of serum and tissues were determined at the following wavelengths: for iron, 248.3 nm; for zinc, 213.9 nm; for copper, 324.8 nm. The accuracy of the method was verified with certified reference materials (HUM ASY CONTROL 2 and URN ASY CONTROL 2, Randox and seronorm Trace Elements Whole Blood L-2), and was 95-98% for iron, 95-96% for zinc, and 99–103% for copper.

Statistical Analysis

Detailed statistical analysis was performed using Statistica for Windows 10.0 (StatSoft, Poland). The results were expressed as arithmetic means and standard errors. Comparisons between groups were carried out using the Mann-Whitney U-test and the Wilcoxon rank-sum test. The associations between variables were calculated as the Spearman coefficient of correlation. Significance was set at the $p < 0.05$ level.

Results

The characteristics of patients in all stages are described in Table I. There were no significant differences in gender, age, or BMI parameters at any stage. Following treatment with hypotensive monotherapy, the values of SBP and DBP were significantly lower in stage II and III, as compared with the baseline. The use of an optimal-mineral diet did not influence the SBP and DBP values in the patients.

The glucose levels in serum of patients in stage II were significantly higher than in the baseline (Table II). In patients in the diet group, glucose markedly decreased, while in the control group, the level of glucose was higher than at the beginning of the treatment. It was found that the activity of SOD and CAT tended not to significantly decrease following treatment, and in patients on the optimal-mineral diet, the activity of the enzymes slightly increased. The other parameters were comparable across all stages and also between the diet and control groups (Table II).

It was found that zinc levels in serum significantly decreased after treatment (Table III). The use of the optimal-mineral diet during antihypertensive treatment markedly increased the zinc serum concentration. Treatment with no change in diet led to a lower level of zinc than in the case of the baseline. However, a merely insignif-

Table I. Characteristic of the patients.

Parameters	Stages			
	I	II	III	
			Diet	Control
N	45	45	27	18
Gender (F/M)	26/19	26/19	16/11	10/8
Age (year)	51.3 ± 14.2	51.3 ± 14.2	51.0 ± 14.3	51.4 ± 14.1
BMI (kg/m^2)	33.4 ± 6.2	33.6 ± 5.9	32.9 ± 6.5	33.5 ± 6.1
SBP (mmHg)	165.2 ± 28.3	143.8 ± 20.3*	142.8 ± 19.5*	144.3 ± 20.5*
DBP (mmHg)	98.5 ± 14.7	85.8 ± 14.1*	83.2 ± 11.8*	85.1 ± 13.5*

F-female, M-male, N-number of subjects, SBP-systolic blood pressure, DBP-diastolic blood pressure, I-baseline, II-after 3-months treatment with hypotensive monotherapy, III-after 1 month treatment with optimal mineral diet (Diet) or without dietary recommendations (Control), *Significance differences with stage I.

icant change in the zinc level was found in erythrocytes (Table III).

After treatment, a significant increase in zinc excretion in urine was observed (Table III). Hypotensive treatment did not influence iron or copper levels in serum, erythrocytes, or urine (Table III).

The dietary intake of nutrients is shown in Table IV. It was found that the energy supply and percentage of energy from fat, protein, and carbohydrate were rather comparable in every stage of the study. By design, patients in the diet group consumed more minerals than did those in the control group and in comparison with the baseline; however, a significant difference was seen only in the case of zinc (Table IV).

A negative correlation between glucose level in serum and zinc serum concentration in patients (in all stages, I-III) was found (Figure 1).

Discussion

The influence of antihypertensive treatment on iron, zinc, and copper status in hypertensive patients with monotherapy is a new finding of this study. To the best of our knowledge, this study is furthermore the first to show a positive result on zinc homeostasis in response to the use of an optimal-mineral diet during hypotensive therapy in hypertensive newly diagnosed patients with monotherapy.

Table II. Biochemical parameters in serum of the patients.

Parameters	Stages			
	I	II	III	
	N = 45	N = 45	Diet N = 27	Control N = 18
TCH (mmol/L)	5.3 ± 1.0	5.2 ± 0.9	4.9 ± 0.8	5.1 ± 0.8
LDL (mmol/L)	3.2 ± 0.5	3.0 ± 0.4	2.8 ± 0.5	2.9 ± 0.6
HDL (mmol/L)	1.4 ± 0.3	1.3 ± 0.3	1.2 ± 0.3	1.4 ± 0.4
TG (mmol/L)	1.7 ± 0.5	2.0 ± 0.6	1.9 ± 0.4	1.9 ± 0.5
Glucose (mmol/L)	5.2 ± 0.4	5.6 ± 0.5*	5.3 ± 0.4	5.5 ± 0.5*
CRP (mg/L)	5.1 ± 2.0	4.8 ± 1.8	4.8 ± 1.9	4.9 ± 1.9
Ferritin (μg/L)	87.2 ± 31.0	88.9 ± 31.9	101.8 ± 35.2	92.8 ± 32.8
Ceruloplasmin (mg/dl)	44.0 ± 21.1	38.3 ± 23.3	41.3 ± 24.4	45.6 ± 25.5
SOD (U/g Hg)	2255.1 ± 202.4	1948.5 ± 231.4	2240.2 ± 199.8	1931.8 ± 235.7
CAT (U/g Hg)	75.3 ± 9.2	64.7 ± 5.2	68.4 ± 10.8	68.9 ± 6.2

N-number of subjects, TCHOL-total cholesterol, LDL-cholesterol LDL, HDL-cholesterol HDL, TG-triglycerides, CRP-C reactive protein, SOD-superoxide dysmutase, CAT-catalase, I-baseline, II-after 3- months treatment with hypotensive monotherapy, III-after 1 month treatment with optimal mineral diet (Diet) or without dietary recommendations (Control), *Significance differences with stage I.

Table III. Minerals concentration in serum, erythrocytes and urine of the patients.

Parameters	Stages			
	I	II	III	
	N = 45	N = 45	Diet N = 27	Control N =18
		Serum		
Fe (μmol/L)	18.1 ± 4.3	18.5 ± 4.6	17.9 ± 4.2	18.7 ± 4.7
Zn (μmol/L)	9.8 ± 1.0	8.2 ± 1.3*	10.9 ± 1.0	8.5 ± 1.1*,**
Cu (μmol/L)	15.9 ± 3.2	15.3 ± 3.4	16.1 ± 3.6	15.5 ± 3.3
		Erythrocytes		
Fe (μmol/gHb)	48.7 ± 9.0	49.2 ± 8.5	49.7 ± 8.4	49.3 ± 8.4
Zn (μmol/gHb)	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.4 ± 0.1
Cu (nmol/gHb)	49.7 ± 9.8	49.4 ± 10.9	50.1 ± 10.8	49.6 ± 9.9
		Urine		
Fe (μmol/24h)	1.9 ± 0.6	1.8 ± 0.8	1.9 ± 0.7	1.8 ± 0.8
Zn (μmol/24 h)	5.2 ± 2.0	7.7 ± 2.8*	7.3 ± 2.3*	7.6 ± 2.7*
Cu (μmol/24h)	1.0 ± 0.4	1.0 ± 0.4	1.0 ± 0.3	1.1 ± 0.4

N-number of subjects, I-baseline, II-after 3-months treatment with hypotensive monotherapy, III-after 1 month treatment with optimal mineral diet (Diet) or without dietary recommendations (Control), *-significant differences with stage I, **Significant differences with Diet group in stage III.

Moreover, our findings suggest that a combination of hypotensive monotherapy with a diet containing optimal mineral levels restores mineral homeostasis and has protective effects on glucose metabolism.

The results obtained in the present work suggest that the interaction between zinc and hypotensive drugs has a pharmacokinetic basis, and may be caused by the inhibition of the kidneys' zinc reabsorption, resulting in zincuria[9,15]. In this study, we observed increased zinc excretion in the urine following antihypertensive treatment. Most patients used diuretics (38%) and calcium channel blockers (31%) and it seems that these classes of drugs may have the greatest impact on zinc status disorders in patients. In clinical and experimental reports, it has been found that some diuretics may affect zinc reabsorption and increase zinc levels in urine, while decreasing the concentration of this mineral in serum and in ery-

Table IV. Daily intake of selected nutrients and energy supply.

Parameters	Stages			
	I	II	III	
	N = 45	N = 45	Diet N = 27	Control N = 18
Energy (kcal)	1972.8 ± 860.2	1898.4 ± 923.2	1890.2 ± 911.2	1870.4 ± 875.8
Fat (% energy)	37.5 ± 10.2	36.8 ± 11.2	34.5 ± 10.9	36.0 ± 11.8
Protein (% energy)	14.2 ± 5.8	13.8 ± 5.2	14.5 ± 4.2	14.6 ± 5.7
Carbohydrate (% energy)	48.3 ± 12.2	49.1 ± 13.0	50.7 ± 10.5	48.9 ± 13.0
Fe (mg)	9.7 ± 3.9	9.8 ± 4.2	10.8 ± 3.3	10.0 ± 3.5
Zn (mg)	9.2 ± 3.1	9.2 ± 3.2	11.0 ± 2.0*	9.3 ± 3.4**
Cu (mg)	0.9 ± 0.4	0.9 ± 0.4	1.1 ± 0.4	0.9 ± 0.3

N-number of subjects, I-baseline, II-after 3- months treatment with hypotensive monotherapy, III-after 1 month treatment with optimal mineral diet (Diet) or without dietary recommendations (Control), *-significant differences with stage I, **Significant differences with Diet group in stage III.

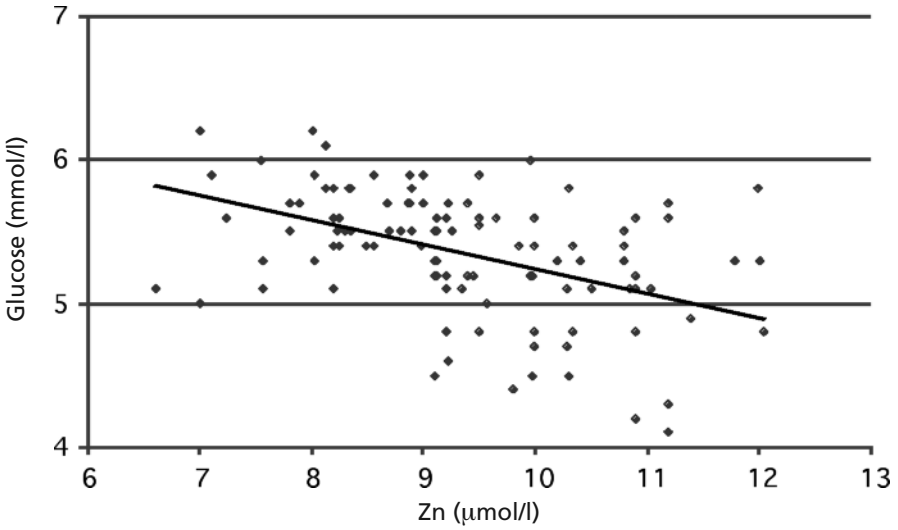

Figure 1. Correlation between zinc and glucose level in serum (stage I-III). Spearman correlation R = –0.42, $p < 0.05$

throcytes[9,15]. In the most recent clinical study[12], the treatment with diuretics can increase zinc excretion by suppressing the reabsorption of zinc through renal tubules. In that work, it was found that diuretics increase the excretion of zinc, even in patients receiving zinc preparations. The authors suggest that diuretics can lead to a deficiency of zinc in the body. In our study, the combination of hypotensive treatment and an optimal-mineral diet prevented the decrease of zinc in the patients, but zinc excretion in urine remained at a similar level. The other evidence[9] suggested that the use of ACE inhibitors and angiotensin II receptor antagonists also had the potential to reduce zinc levels in hypertensive patients.

Over 30% of our patients received calcium channels blockers, and in some studies it has been found that this kind of hypotensive drug may influence mineral status. Mainous et al[16] found that calcium antagonists may act as an iron chelating agent and decrease the ferritin level in serum in hypertensive patients. It is known[17] that ferritin is an inflammation marker and that some calcium channel blockers show anti-inflammatory activity. However, those authors did not evaluate the inflammation status of the patients. In our work, iron status, ferritin level, and C-reactive protein level (an inflammation marker) in serum did not change significantly after the antihypertension treatment.

We did not observe any significant changes in either iron or copper status, nor in other parameters dependent on the iron level in the body, such as ferritin levels and CAT activity, or copper-ceruloplasmin and SOD activity.

On the basis of the results of SOD and CAT activity in the subjects at every stage, it seems that antioxidant status did not significantly change during the treatment. However, it was observed that SOD activity was slightly related to zinc concentration in the serum. Some studies indicate that SOD activity is associated with zinc status, and that the measurement of serum extracellular superoxide dismutase activity may be useful as a marker for zinc status in humans[18]. In other clinical studies, it has been found that, following antihypertensive treatment with β-blockers, ACE inhibitors, diuretics, and calcium channel blockers, in combination or in monotherapy, the activity of SOD and CAT increased in hypertensive patients[19]. In experimental researches, it has been found that the inhibition of angiotensin II receptors decreased oxidative stress and increased the activity of antioxidant enzymes in rats[20]. We could not confirm these previous findings, which may be the result of differing subject selection, experimental stages, and duration of the research.

It should be noted that disorders in zinc homeostasis caused by hypotensive drugs may have a wide range of negative effects in the body. It is known that zinc deficiency can predispose to glucose intolerance and insulin resistance[21]. We found an association between zinc and glucose levels in the serum of patients. This could be caused by a connection between the zinc and glu-

cose metabolisms. It is known that zinc plays a major role in the synthesis and action of insulin. Zinc is also a component of many enzymes, and is involved in the synthesis, storage, and release of insulin[22]. It is worth noting that, in the present study, the use of a diet containing an optimal mineral supply prevented the negative effect of antihypertensive drugs on zinc status and glucose metabolism. The relation between the higher intake of zinc and the lower fasting glucose level in serum was also observed in the cohort studies[23,24].

Conclusions

Our study group was relatively small and does not allow the impact of the different antihypertensive drug classes on the mineral balance in patients to be shown. However, we indicate the fact that antihypertensive therapy is associated with significant metabolic impairment, which in chronic antihypertensive therapy may have future implications.

Our results suggest that antihypertensive treatments should include monitoring of mineral status, and that the zinc balance of patients on long-term therapy with hypotensive drugs may benefit from an optimal-mineral diet.

Acknowledgements

This research was supported by grant from the National Science Centre, Poland (2669/B/P01/2011/40).

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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