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Effect of hypotensive therapy combined with modified diet or zinc supplementation on biochemical parameters and mineral status in hypertensive patients☆

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ABSTRACT

Background: Hypotensive therapy leads to a number of trace elements metabolism disturbances. Zinc balance is frequently affected by antihypertensive treatment.

Aim: To evaluate the effect of a hypotensive treatment, modified diet and zinc supplementation on mineral status and selected biochemical parameters in newly diagnosed hypertensive patients on monotherapy.

Methods: In the first stage, arterial hypertension in ninety-eight human subjects was diagnosed. In the second stage, antihypertensive monopharmacotherapy was implemented. In the third stage, patients were randomized into three groups and continued antihypertensive monotherapy: group D received an optimal-mineral-content diet, group S received zinc supplementation, and group C had no changes in diet or zinc supplementation. Iron, zinc, and copper concentrations in serum, erythrocytes, urine, and hair were determined. Lipids, glucose, ceruloplasmin, ferritin, albumin, C-reactive protein (CRP), tumor necrosis factor α (TNF-α), nitric oxide (NO), superoxide dismutase (SOD) and catalase (CAT) were assayed in serum.

Results: Antihypertensive monotherapy decreased zinc concentration in serum and erythrocytes and increased the level of zinc in urine, decreased CAT and SOD activity, TNF-α concentration in serum, and increased the level of NO in the serum. Zinc supply led to an increase in zinc concentration in serum, erythrocytes, and hair (in group S only). In the groups with higher zinc intake, decreased glucose concentration in the serum was observed. Significant correlation was seen between the zinc and glucose serum concentrations.

Conclusion: Hypotensive drugs disturb zinc status in newly diagnosed hypertensive patients. Antihypertensive monotherapy combined with increased zinc supply in the diet or supplementation favorably modify zinc homeostasis and regulate glucose status without blood pressure affecting in patients with hypertension.

1. Introduction

A high number of trials have provided data on the disorders of trace elements metabolism resulting from hypotensive therapy [1–4]. Treatment with angiotensin-converting enzyme inhibitors (ACE-Is) and some diuretics leads to deficits of zinc, magnesium, and potassium [5]. Disturbances in macroelement and microelement status can additionally be a reason for unfavorable changes in the metabolism of carbohydrates and lipids, and may affect enzyme activity of enzymes such as superoxide dismutase (SOD), catalase (CAT), and carbonic

Abbreviations: ACE-Is, angiotensin-converting enzyme inhibitors; AH, arterial hypertension; ARBs, angiotensin II receptor antagonists; BMI, body mass index; BP, blood pressure; CA, carbonic anhydrase; cAMP, cyclic adenosine monophosphate; CAT, catalase; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; ESR, erythrocyte sedimentation rate; GLU, glucose; HDL, high-density lipoprotein; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; LDL, low-density lipoprotein; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; SDs, standard deviations; SHR, spontaneously hypertensive rats; SOD, superoxide dismutase; TCH, total cholesterol; TG, triglycerides; TIBC, total iron binding capacity; TNF-α, tumor necrosis factor α; ZnT8, zinc efflux transporter 8

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anhydrase (CA) [6]. Beneficial effects of a diet enriched in minerals on the homeostasis of macroelement and microelement, along with hypotensive monotherapy, have been reported in some studies [1,7,8]. However, there are still only a limited number of studies that provide data on the effect of antihypertensive monotherapy on mineral status, and also on the effects of combining mineral supplementation with pharmacotherapy on biochemical parameters in patients with arterial hypertension (AH). A combination of antihypertensive pharmacotherapy with mineral supplementation or dietary intervention seems to be more effective and beneficial to the health of patients.

Zinc is a microelement frequently affected by commonly recommended antihypertensive drugs [9]. Studies on antihypertensive treatment and zinc metabolism have presented inconsistent results on correlation between serum zinc concentration and blood pressure (BP) [7,8,10–14]. Some studies have shown that high serum zinc concentration is associated with incident hypertension, however with no association between zinc intake in diet and risk of hypertension [11]. Contrary, other studies registered inverse correlation between serum Zn and blood pressure [8]. Moreover, it has been documented that zinc deficiency is the risk factor of elevated blood pressure and dietary zinc intake is inversely correlated with systolic blood pressure independently from body mass, energy intake and sodium intake [14]. Zinc regulates blood pressure and takes part in vascular tone modulation by inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) transactivation activity. Thus, Zn controls inducible nitric oxide synthase (iNOS) endothelial expression and activity [15].

The aim of our study was to evaluate the effects of hypotensive treatment combined with a higher zinc supply in the diet and supplements on the mineral status and selected biochemical parameters of newly diagnosed hypertensive patients on monotherapy. To the best of our knowledge, our study is the first human study to compare these two models of zinc supply in such a homogenous group of patients. So far, there has been an evident lack of convincing scientific evidence, which might serve as a basis for revising the recommendations regarding mineral supplementation during hypotensive pharmacotherapy.

2. Material and methods

2.1. Study patients

The study protocol was approved by the Ethics Committee at Poznań University of Medical Sciences, approval no. 86/09. The study complies with the ethical standards of the Declaration of Helsinki and its amendments. All subjects gave their written informed consent prior to their inclusion in the study.

Four hundred and twenty-five patients with no antihypertensive therapy were screened at the outpatient clinic of the Department of Internal Medicine, Metabolic Disorders and Hypertension, Poznań University of Medical Sciences, and 105 were enrolled in the study. The inclusion criteria were informed written consent; age 18–65 years; primary arterial hypertension diagnosed in accordance with the guidelines of the European Society of Hypertension 2013 and the European Society of Cardiology 2013; [16] beginning monotherapy with an antihypertensive drug; stable body weight (less than 3 kg self-reported change during the three months prior to enrollment). The exclusion criteria were any secondary form of hypertension; the use of mineral supplements within the three months prior to enrollment; lipid disorders requiring treatment in the three months prior to the trial; a history of ischemic heart disease, stroke, congestive heart failure, clinically significant arrhythmia or conduction disorders, peripheral artery or vein disease, diabetes mellitus, abnormal renal, liver or thyroid gland function, clinically significant chronic or acute inflammatory process within the respiratory, genitourinary, or digestive tract, or in the oral cavity, larynx, pharynx, or in the paranasal sinuses, or connective tissue diseases, arthritis, or malignancy; infection in the month prior to enrollment, having an pacemaker implanted; alcohol, nicotine or drug abuse; mental disorders; pregnancy, childbirth or lactation at enrollment or in the three months prior to enrollment; or any other condition that, in the opinion of investigators, would make participation in the study not in the best interest of the subject, or could prevent, limit, or confound the efficacy of the study. The occurrence of any of the exclusion criteria during the study resulted in withdrawal of the subject from the trial.

Of 425 patients examined at the outpatient clinic of the Department of Internal Medicine, Metabolic Disorders and Hypertension, Poznań University of Medical Sciences, 320 individuals were excluded from the trial due to secondary forms of hypertension (5); the use of mineral supplements within the three months prior to enrollment (22); lipid disorders requiring treatment in the three month prior to the trial (15); history of ischemic heart disease (55), stroke (18), congestive heart failure (21), clinically significant arrhythmia or conduction disorders (19), peripheral artery or vein disease (9), diabetes mellitus (44), abnormal renal (8), liver (7) or thyroid gland (11) function, clinically significant chronic or acute inflammatory process within the respiratory (2), genitourinary (3), or digestive tract (3), or in the oral cavity, larynx, pharynx, or paranasal sinuses (9), connective tissue diseases (3), arthritis (2), or malignancy (1); infection in the month prior to enrollment (26), having a pacemaker implanted (14); alcohol, nicotine or drug abuse (19); mental disorders (2); pregnancy, childbirth or lactation at enrollment or in the three months prior to enrollment (2). The 105 subjects who fulfilled all inclusion criteria and had no exclusion criteria were randomized into three groups C, D, and S of 35 subjects each. Seven subjects (5 from group C and 2 from group D) were excluded from the trial due to acute inflammatory processes within the genitourinary (2) or digestive (3) tract, and infection (2). A total of 98 subjects (61 women and 37 men) completed all three stages of the trial and were included in the statistical analysis: 30 from group C (19 women and 11 men), 33 from group D (20 women and 13 men), and 35 from group S (22 women and 13 men).

2.2. Study design

The study was designed as a prospective randomized trial and was performed in three stages. In the first stage, primary hypertension was diagnosed and antihypertensive monotherapy was begun. In the second stage, patients underwent antihypertensive monotherapy lasting three months. The subjects received diuretics; calcium antagonists (Ca-antagonists); ACE-Is; angiotensin II receptor antagonists (ARBs); or β-blockers. After three months of monotherapy, patients were divided using a randomization list into three equinumerous groups: C (control group), D (diet group) and S (supplementation group). In the third stage, which lasted 30 days, subjects from all groups received the same antihypertensive drug as in the second stage and either an optimal-mineral-content diet (group D), zinc supplementation (group S), or continued drug use with no change in diet and no mineral supplementation (group C). Patients from group D received an optimal-mineral-content properly balanced diet enriched in food with high zinc content prepared individually for each patient by a qualified dietician. Patients from group S received zinc supplementation as one capsule containing 15 mg of Zn taken orally once a day in the morning, two hours after antihypertensive drug administration with no change in diet, through all 30 days of the third stage of the trial. Zinc supplementation was chosen in group S due to significantly lower serum, erythrocyte, and urine zinc concentration in stage II of the study, and in account of the results of our previous study, [17] which showed disturbed zinc homeostasis after antihypertensive monotherapy.

Antihypertensive drug administration was comparable between groups and between stages II and III. The number of patients receiving particular antihypertensive monotherapy is shown in Table 1. During the study, patients were asked to not use dietary supplements and not to change their lifestyle or level of physical activity. All patients consulted