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Evaluation of zinc levels in biological samples of hypertensive patients in Valladolid, Spain

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ABSTRACT

Introduction: The risk of having heart related diseases, as well as blood vessels located in the brain and kidneys, increases when the person is hypertensive. This pathology requires additional studies for a better understanding and control of its incidence on health.

Objective: To evaluate levels of zinc (Zn) in urine and plasma of a representative sample of the population of Valladolid, Spain, in search of alterations of the metabolism of this essential metal caused by hypertension.

Method. 1502 serum and urine samples were collected to assess their zinc level in hypertensive and non-hypertensive people varying several characteristics in the population of Valladolid. The concentration of Zn was determined with the technique of mass spectrometry with inductively coupled plasma (ICP-MS).

Results. The mean Zn concentration in all biological serum samples was higher and less eliminated in the urine in non-hypertensive patients than hypertensive, untreated and hypertensive patients without treatment without renal damage with 12.83 µmol/L for serum and 2.83 µmol/g creatinine in urine, among the uncontrolled treated hypertensive patients a higher concentration of serum Zn was shown with 12.69 µmol/L and 3.18 µmol/g creatinine in urine than with the group of controlled hypertensive patients.

Conclusions. Hypertension alters the distribution of Zn in the body, causing hypertensive individuals to have a lower serum concentration and eliminate more in the urine.

KEYWORDS

Hypertension, Attention, Zinc.

INTRODUCTION

Hypertension is the consequence of having high blood pressure, normal systolic/diastolic pressure values are ≤120/80 mmHg, and values ≥140/90 mmHg indicate hypertension[1]. Tobacco use, overweight, excessive alcohol intake, sedentary lifestyle, and high salt and fat consumption increase people's risk of suffering high blood pressure[2].

In Spain, 68 deaths out of every 100,000 are attributed to cardiovascular diseases and diabetes, the prevalence of high blood pressure in adults over 25 years is 27.7% in men and 18.6% in women, 238 deaths per 100,000 people in Europe, and the prevalence of high blood pressure is 33.1% in men and 25.6 % in women[3].

The essential elements are those absolutely necessary for the metabolic and biochemical processes that occur in the body[4,5]. They participate as components of enzymatic systems being part of enzymes as cofactors or as activators[4]. There are five essential elements that may be related to cardiovascular diseases, these are: Mn, Cr, Cu, Cd and Zn. The imbalances in the internal concentration of these elements may have an influence on the incidence of cardiovascular diseases such as hypertension, experimental evidence indicates that these elements are associated with this type of disease[4]. Other essential elements related to the reduction of cardiovascular disease risk are Ca, Mg, Co, Li, V, Si, and Fe[6].

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Zinc is an essential element of the human body and is present in small quantities. We eat it through food, especially through animal products such as shellfish. Some vegetables may have approximate zinc levels of 2 ppm, and beef, fish and poultry meat approximately 29 ppm[7]. The bioavailability of vegetable zinc is much lower than in animal products[5].

Zinc is an essential nutrient necessary for the functioning of more than 300 enzymes such as alcohol dehydrogenase, alkaline phosphatase, carbonic anhydrase, leucine aminopeptidase, superoxide dismutases, and DNA and RNA polymerases. Involved in processes such as cell growth and division, in the metabolism of nucleic acids, proteins, carbohydrates, lipids and membranes[7,5]. A very important function of zinc is to maintain the nucleic acid structure of genes with the so-called zinc fingers[7].

Studies in humans and animals have shown that high blood pressure causes changes in zinc metabolism and affects its distribution among intracellular compartments[8].

Clinical and laboratory data indicate that zinc participates in the regulation of blood pressure and in the pathogenesis of hypertension. In cases of arterial hypertension the levels of zinc in the serum, lymphocytes and bones decrease, while these increase in the heart, erythrocytes, kidneys, liver, adrenal glands and spleen[9,10].

Several clinical and experimental studies have confirmed that absorption in the gastrointestinal tract and urinary excretion of zinc increase when there is primary arterial hypertension[11]. If it is assumed that zinc influences blood pressure, then intensified urinary excretion can be a mechanism of pressure regulating response, in this case, an increase in gastrointestinal absorption is a compensation for a zinc deficit, which ends up causing an increase in pressure and activating a regulatory response. The use of blood pressure medications and diuretics also alter the urinary excretion of zinc, reduces its concentration in erythrocytes and increases it in leukocytes[10].

Zinc plays a double role in the risk of cardiovascular disease because it has been associated with both beneficial and toxic effects[12].

This research aims to evaluate zinc levels in biological samples of hypertensive and non-hypertensive individuals in Valladolid, Spain.

METHOD

Population studied

To carry out this study, there was a database of 1502 individuals from the city of Valladolid, Spain, the data were obtained by the Faculty of Biological Sciences of the University of Valencia. The individuals were selected from the coverage area of the Río Hortega University Hospital (214,445 inhabitants). In the first phase of information collection, standardized questionnaires were carried out on a random sample of 20% of the population between 15 and 96 years old, from whom information on cardiovascular risk was collected; and in the second phase, a new questionnaire was sent and interviews and biological samples were scheduled. The number of participants corresponds to a representative sample of the general population. All participants gave their written consent to participate in the study 24 hours before taking blood and urine samples. The population is made up of 50.2% women and 49.8% men, who in 2003 (year the samples were taken) were between 21 and 96 years old.

Study procedure

Serum and urine zinc levels were evaluated in patients who were:

1) Hypertensive and non-hypertensive.
2) Non-hypertensive and untreated hypertensive patients.
3) Non-hypertensive and untreated hypertensive patients without kidney damage.
4) Controlled and uncontrolled treated hypertensives

In all cases, in addition to the zinc samples, a series of data were obtained that allow us to analyze other types of variables in the incidence of concentration between groups such as: central obesity, diabetes, kidney damage, hypercholesterolemia, smokers, etc.

OR (Odds Ratio) were calculated for raw and adjusted hypertension based on urine zinc levels.

Zinc measurement in biological samples

The zinc concentration in the biological samples was measured with the inductively coupled plasma mass spectrometry technique (ICP-MS). The equipment used was the Agilent 7500CE ICP-MS. Serum zinc detection limits are 4.22 to 17.34 µmol/L, and urine limits <0.08 µmol/g creatinine.

Statistic analysis

In order to perform an adequate analysis, the population was stratified into several groups and parametric (ANOVA) and non-parametric (Kruskal-Wallis) tests were used according to the distribution of the variables to determine significant differences between the groups. Binary logistic regressions were performed to determine the risk of hypertension based on predictive variables such as the concentration of zinc in urine, adjusting it for tobacco consumption, age, and sex. The values of $p < 0.05$ were considered statistically significant. The analyzes were performed using the SPSSv17 software.

Ethical aspects

All procedures were performed in accordance with the principles of the declaration of Helsinki, the study was approved

by the Commission of Ethics in Experimental Research of the University of Valencia (CEIC - CEBA or UVEG when complying with all the provisions of the commission's regulations , Law 14/2007 on Biomedical Research and International Ethical Guidelines-CIOMS, 2002) and by the Headquarters of the Center where the study was conducted, all patients were informed of the objectives to evaluate zinc in biological samples and signed the approval requested.

RESULTS

1) Hypertensive and non-hypertensive.

Of the total of 1502 individuals registered in the database (table 1), 642 have hypertension and 46.3% of them are under treatment (prevalent).

The mean serum zinc concentration of non-hypertensive patients (12.83 µmol/L) is higher than that of the hypertensive group (12.47 µmol/L), although the difference is not statistically significant (p> 0.05). The average urine zinc concentration of non-hypertensive patients (2.58 µmol/g creatinine) is lower than that of the hypertensive group (2.83 µmol/g creatinine). The serum/urine concentration ratio helps confirm that hypertensive patients (20.17 µmol/L) excrete more zinc than non-hypertensive patients (26.01 µmol/L).

2) Non-hypertensive and untreated hypertensive patients.

Excluding hypertensive patients under treatment, it can be seen in table 2 that serum zinc levels remain higher in the non-hypertensive group (12.83 µmol/L). The concentrations of zinc in urine of both groups are the same but the ratio of serum/urine concentrations indicates that there is a greater urinary excretion in the hypertensive group (21.59 µmol/L).

Table 1. Hypertensive vs. non-hypertensive.

	Hypertension		level p
	No	**Yes**	
n=1502	**860**	**642**	
Hypertensive under treatment %	---	46.3	---
Systolic pressure (mmHg)	118.03 ± 0.4	147.66 ± 0.8	<0.001
Diastolic pressure (mmHg)	74.7 ± 0.3	85.06 ± 0.4	<0.001
Men %	48.3	52.8	0.045
Age (years)	44.64 ± 0.6	67.56 ± 0.6	<0.001
Central obesity %	17.3	47.6	<0.001
IMC (kg/m2)	25.06 ± 0.1	28.19 ± 0.2	<0.001
METS (kg/min)	9.23 ± 0.3	7.40 ± 0.3	0.030
Serum zinc (µmol/L)	12.83 ± 0.1	12.47 ± 0.1	0.058
Urine zinc (µmol/g creatinine)	2.58 ± 0.1	2.83 ± 0.2	0.143
Zinc Serum/Urine	26.01 ± 1.8	20.17 ± 1.5	0.202
Smokers %			<0.001
Non smokers	42.8	52.3	
Smokers	31.4	12	
Former smokers	25.8	35.7	
Cigarettes per day	13.06 ± 0.4	15.88 ± 0.7	0.031

Levels are expressed as percentages and means ± standard error.

Table 2. Non-hypertensive and untreated hypertensive patients.

	Hypertensive Incidents		level p
	No	Yes	
n=1205	860	345	
Systolic pressure (mmHg)	118.03 ± 0.4	149.14 ± 1	<0.001
Diastolic pressure (mmHg)	74.7 ± 0.3	87.34 ± 0.5	<0.001
Men %	48.3	55.1	0.019
Age (years)	44.64 ± 0.6	63.88 ± 0.9	<0.001
Central obesity %	17.3	40.9	<0.001
IMC (kg/m2)	25.06 ± 0.1	27.97 ± 0.2	<0.001
METS (kg/min)	9.23 ± 0.3	7.82 ± 0.4	0.135
Serum zinc (µmol/L)	12.83 ± 0.1	12.43 ± 0.2	0.237
Urine zinc (µmol/g creatinine)	2.58 ± 0.1	2.58 ± 0.1	0.876
Zinc Serum/Urine	26 ± 1.8	21.59 ± 2.2	0.546
Smokers %			<0.001
Non smokers	42.8	49.6	
Smokers	31.4	15	
Former smokers	25.8	35.5	
Cigarettes per day	13.06 ± 0.4	16.98 ± 1.1	0.012

Levels are expressed as percentages and means ± standard error.

3) Non-hypertensive and untreated hypertensive patients without kidney damage.

Excluding hypertensive patients under treatment and those with renal damage, it is observed in table 3 that serum zinc levels remain higher in the non-hypertensive group (12.82 µmol/L). The concentrations of zinc in urine of both groups are the same but the ratio of concentrations of zinc serum/urine indicates that there is greater excretion in the hypertensive group (21.74 µmol/L).

4) Controlled and uncontrolled treated hypertensives

Comparing the controlled and uncontrolled hypertensive groups (table 4), serum and urine zinc levels are higher in the uncontrolled hypertensive group (12.69 µmol/L and 3.18 µmol/g creatinine respectively), and the ratio of serum/urine zinc concentrations indicate that uncontrolled hypertensive patients (17.93 µmol/L) eliminate more zinc than those controlled (19.42 µmol/L).

5) Odds Ratio

Table 5 shows the OR for hypertension based on tobacco habit and zinc levels in urine. The risk of hypertension for smokers is 3.20 times higher than that of non-smokers (95% CI 2,385-4,303). The OR of hypertension for individuals who have zinc concentrations in urine above the median is 0.95 (95% CI 0.741-1.214); adjusted for smoking status increases to 1.04 (95% CI 0.802-1.344); adjusted for age and sex increases to 1.30 (95% CI 0.943-1.778); adjusted for age, sex and smoking status increases to 1.35 (95% CI 0.978-1.865); and adjusted for age, sex, central obesity and smoking status increases to 1.43 (95% CI 1,026-1,982). The more variables we use for adjustment, the ratio of zinc excretion to hypertension is higher.

DISCUSSION

In this study, zinc levels of a representative sample of the population of Valladolid, Spain were evaluated. The main objective of the investigation was to determine if hypertension

Table 3. Non-hypertensive and untreated hypertensive patients without kidney damage.

	Hypertensive incidents without kidney damage		level p
	No	Yes	
n=1150	840	310	
Systolic pressure (mmHg)	118.04 ± 0.4	147.85 ± 0.9	<0.001
Diastolic pressure (mmHg)	74.74 ± 0.3	86.99 ± 0.6	<0.001
Men %	48.8	54.5	0.049
Age (years)	44.63 ± 0.6	63.06 ± 0.9	<0.001
Central obesity %	17.3	38.7	<0.001
IMC (kg/m2)	25.08 ± 0.1	27.85 ± 0.2	<0.001
METS (kg/min)	9.27 ± 0.3	8 ± 0.4	0.186
Serum zinc (µmol/L)	12.82 ± 0.1	12.43 ± 0.2	0.309
Urine zinc (µmol/g creatinine)	2.59 ± 0.1	2.59 ± 0.1	0.883
Zinc Serum/Urine	25.84 ± 1.8	21.74 ± 2.4	0.571
Smokers %			<0.001
Non smokers	42.6	51.1	
Smokers	31.5	14.7	
Former smokers	25.9	34.2	
Cigarettes per day	13.02 ± 0.4	17.22 ± 1.1	0.009

Levels are expressed as percentages and means ± standard error.

can alter the concentrations of this essential metal in the serum and urine of the population studied. In this investigation we observed that although no statistically significant differences were found between the means of the concentrations, individuals with hypertension have decreased serum zinc levels and increased urinary excretion, as in the investigations of several authors[13,14]. Having elevated serum zinc levels is inversely proportional to the prevalence of acute myocardial infarction[15]. This variation has been explained as a mechanism of defense of the organism to reduce the pressure, since there is evidence that the excess zinc caused by a high gastrointestinal absorption, typical of hypertension, can cause an increase in blood pressure[16] which needs to be compensated with increased urinary excretion, but at the same time this alters homeostasis and can cause a deficit that worsens hypertension because it reduces the response of hypotensive factors[17]. These findings suggest that the role of zinc in blood pressure control is not a simple process, but is involved in many systems at different physiological levels[18].

Other factors that alter zinc levels are age, type 2 diabetes and obesity[19] and since advanced age, diabetes and obesity are characteristic of the hypertensive population, the alterations found cannot only be attributed to the disease[20]. The variation of zinc levels in the body can cause a deficit that increases the probability that obesity, hypertension and type 2 diabetes appear together[21], this deficit also increases oxidative damage in tissues, especially in the structure and function of endothelial cells[22], since it is known that zinc acts as a protector against oxidative damage because it is present in enzymes with antioxidant activity such as Zn/Cu SOD that attack free radicals regulating oxidative stress by breaking down superoxide radicals into oxygen and hydrogen peroxide[23,24].

When we exclude hypertensive patients under treatment and individuals with kidney damage from the analysis to eliminate the effect of diuretic drugs on zinc levels, the differences between serum and urine concentrations of the groups are getting smaller, but the tendency to eliminate More zinc is

Table 4. Controlled and uncontrolled treated hypertensives.

	Hypertension		level p
	Controlled	Not controlled	
n=297	105	192	
Systolic pressure (mmHg)	125.09 ± 1	157.37 ± 1.3	<0.001
Diastolic pressure (mmHg)	75.68 ± 0.8	86.12 ± 0.9	<0.001
Men %	60	44.8	0.008
Age (years)	70.92 ± 1.3	72.34 ± 0.9	0.345
Central obesity %	47.1	59.9	0.023
IMC (kg/m2)	27.47 ± 0.4	29 ± 0.3	0.004
METS (kg/min)	6.65 ± 0.5	7.03 ± 0.4	0.544
Serum zinc (µmol/L)	12.2 ± 0.3	12.69 ± 0.2	0.243
Urine zinc (µmol/g creatinine)	3.04 ± 0.6	3.18 ± 0.4	0.833
Zinc Serum/Urine	19.42 ± 3.5	17.93 ± 2.6	0.733
Smokers %			0.044
Non smokers	45.5	60.7	
Smokers	9.9	7.9	
Former smokers	44.6	31.4	
Cigarettes per day	14.78 ± 1.4	14.31 ± 1.4	0.306

Levels are expressed as percentages and means ± standard error.

Tabla 5. OR for hypertension calculated for urine zinc levels over the median.

Model	N	β	Sig.	OR	IC 95%	
Model 1	1037	1.16	<0.001	3.20	2.385	4.303
Model 2	1056	-0.05	0.676	0.95	0.741	1.214
Model 3	1036	0.04	0.776	1.04	0.802	1.344
Model 4	1056	0.26	0.110	1.30	0.943	1.778
Model 5	1036	0.30	0.068	1.35	0.978	1.865

Model 1: raw OR smoker status.
Model 2: raw OR zinc urine.
Model 3: adjusted OR zinc urine + smoking status.
Model 4: adjusted OR zinc urine + age + sex.
Model 5: adjusted OR zinc urine + age + sex + smoking status.

maintained and is reflected in the serum/urine zinc ratio indicator, which is lower for the hypertensive group.

The results found among the controlled and uncontrolled hypertensive groups, although not significant, indicate that individuals with uncontrolled hypertension are removing more zinc than the controlled ones, this may indicate that the loss of zinc is one of the possible causes of lack of control of their disease[25].

Raw and adjusted OR for hypertension calculated based on urinary excretion allow us to observe that there is a correlative relationship between zinc levels in urine and hypertension, and that excessive zinc removal from the body is another risk factor to consider. Although the increase in blood pressure can be multi-causal and the most well-known risk factors such as age, sex, obesity and tobacco use used in logistic regression adjustments can act as confounding factors. , in this case they have managed to clarify that there is a risk of hypertension if it increases urinary zinc excretion, which is consistent with other research where it has been shown that certain factors during hypertension are linked to the high presence of zinc in different organs of the body[26].

The loss of homeostasis varies the intracellular and extracellular levels of this essential trace element for the functioning of the organism, damaging structures, favoring oxidative damage processes that cause accelerated aging and altering physiological functions that consequently end up raising blood pressure[27,15]. As several investigations suggest the role of zinc in the regulation of blood pressure is very complex and multilevel, so both an excess or a deficit can be a cause and effect of hypertension, so it is important to maintain the balance of this essential metal in the organism[28,29].

According to different investigations, alterations in zinc levels are due to the sum of several factors such as sex, age, and the presence of diseases such as hypertension, diabetes, asthma and obesity[30,19,31]. For this reason, it is necessary to continue investigating the variations in zinc levels for each of the factors that can affect it.

In the same way as zinc, the balance of other essential elements can be altered by factors such as age, the presence of diseases or exposure to pollutants such as tobacco, so it is also important to investigate the variation of the levels of these elements depending on exposure to air pollutants, heavy metal waters or other toxic substances, or food grown in areas of contaminated soils, in order to better understand how they affect not only intrinsic factors of individuals but environmental factors.

CONCLUSIONS

Finally, it is concluded that hypertension alters the distribution of zinc in the body causing hypertensive individuals to have a lower concentration in serum and eliminate more in the urine, this as the body's defense mechanism to regulate blood pressure. There are other factors such as age, sex, and the presence of diseases such as obesity and type 2 diabetes that also affect serum and urine zinc levels, although the data obtained did not show significant differences between the results. a clear trend in the relationship of hypertension and different factors with zinc levels.

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