International Journal of Pharmaceutical and Medical Research
Volume – 3 Issue – 5 October 2015
Website: www.woarjournals.org/IJPMR *ISSN: 2348-0262*

Zinc and Paroxysmal Atrial Fibrillation

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Abstract: ***Introduction:*** ***Studies show in recent years that many micro- and macroelements are related to the clinical course of atrial fibrillation. There are no current data on zinc status in the development of the disease.*** ***Aim:*** ***To study the plasma concentrations of zinc in the clinical manifestation of paroxysmal atrial fibrillation and seek changes in them after restoration of sinus rhythm.*** ***Materials and methods:*** ***The indicator was studied in 33 patients (17 men, 16 women; mean age 60.03±1.93 years) with paroxysmal atrial fibrillation and 33 controls (17 men, 16 women; mean age 59.27±1.72 years) without evidence of rhythm disorder to date. Plasma levels of the element were determined in patients three times: immediately after hospitalization (initial values), twenty-four hours and twenty-eight days after restoration of sinus rhythm, and in controls – once. Regularization of rhythm was achieved with propafenone. A direct colorimetric method was used to determine the indicator.*** ***Results:*** ***Patients were hospitalized between the second and the twenty-fourth hour after the onset of the arrhythmia. The initially measured concentrations did not differ significantly from controls (15.63±0.62 vs 16.46±1.25 µmol/L, p=0.55). No difference was also found at the twenty-fourth hour and on the twenty-eighth day after restoration of sinus rhythm (15.31±0.70 vs 16.46±1.25 µmol/L, p=0.42; 15.70±0.63 vs 16.46±1.25 µmol/L, p=0.58, respectively).*** ***Conclusion:*** ***In patients with paroxysmal atrial fibrillation the plasma zinc concentrations did not show any deviation from controls with no evidence of the arrhythmia to date. There were no significant differences in both the clinical manifestation of the rhythm disorder as well as after restoration of sinus rhythm. The lack of dynamics in the values of the indicator gives a good reason to believe that zinc has no relation to the manifestation and recurrence of the disease.***

Keywords: atrial fibrillation, sinus rhythm, zinc

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia and its incidence increases significantly with age. In the population aged between 55-60 years it is 0.5% to almost 18% in those over 85 years [1]. Despite the ongoing anti-recurrence treatment, AF usually has a progressive course. In treatment-naïve patients relapse is observed in 50% of cases by the end of the first year, and in treated patients – in about 10% of the cases [2]. Over time the relapses multiply, the duration of episodes increases and the arrhythmia becomes resistant to treatment. The created to date drugs do not show the necessary efficiency. The main reason for this is probably insufficient knowledge of the pathogenesis of the disease [3].

The mechanisms involved in the initiation and retention of AF are of special research interest in recent years. More and more studies are directed at paroxysmal AF (PAF), as it represents about 25% of all cases of AF, and the risk of stroke in PAF is not less than that in persistent and permanent AF [4], [5].

Studies show in recent years that many micro- and macroelements are related to the clinical course of atrial fibrillation. For example, reduction of the levels of ferritin results in reduction of AF relapses [6]. The systemic exposure of the organism to iron selectively reduces CaV1.3-mediated ICa,L and is associated with the development of the arrhythmia [7]. Studies to date show that the occurrence of the rhythm disorder correlates with the serum levels of magnesium. Its intravenous application reduces significantly post CABG AF [8], [9]. It also affects the conversion of AF paroxysms to sinus rhythm [10]. The copper status in patients with AF is also changed. Reduced serum copper levels and reduced activity of the major multi-copper oxidase ceruloplasmin is observed in them [11], [12]. The absence of selenium in its turn is a prerequisite for the development of oxidative damages in the atrial myocardium that are relevant to the structural and electrical remodeling of the atria [13], [14].

It is well known that the balance of micro- and macroelements in the human body is well regulated and shortages of some elements lead to changes in others. For example, zinc inhibits the resorption of copper. There is an antagonist relationship between iron and zinc [15]. These facts logically determine the need for an in-depth study of the zinc status in patients with AF. There are no studies to date on zinc in PAF.

2. Aim

To study plasma concentrations of zinc in the clinical expression of PAF and seek changes in them after restoration of sinus rhythm.

3. Materials and Methods

3.1. Study design

Object of clinical interest in the study were only PAF patients with an occurrence of the disorder <48 hours prior to hospitalization. The start of the rhythm disorder was accurately determined based on the medical history in which patients clearly indicate the emergence of "palpitations" continuing until hospitalization. The diagnosis "atrial fibrillation" was accepted only after it was objectified by ECG. In the absence of contraindications mentioned elsewhere, propafenone was administered to restore sinus rhythm [16], [17]. After the discontinuation of the arrhythmia the patients were monitored for a minimum of 24 hours and subsequently discharged from hospital. They were followed up for 28 days (4 weeks) after restoration of sinus rhythm. Two control examinations were carried out – on the seventh and twenty-eighth day after regularization of the rhythm for signs of recurrence of the rhythm disorder.

The following inclusion criteria were used to select the patients for the study:

1. Restored sinus rhythm after administration of propafenone in the prescribed for it scheme [16], [17];
2. Absence of recurrence of the arrhythmia by the end of the study;

Exclusion criteria:

1. Cardiovascular diseases: coronary artery disease; heart failure; inflammatory diseases of the heart; congenital heart diseases; moderate or severe acquired valvular disorders; cardiomyopathies;
2. Other diseases – renal or hepatic failure; diseases of the central nervous system; inflammatory and/or infectious diseases in the past three months; neoplastic or autoimmune diseases; chronic lung diseases; diseases of the endocrine system (with the exception of type 2 diabetes mellitus, non-insulin dependent); diseases of the gastrointestinal tract;
3. Hormone replacement therapy, pregnancy, systemic administration of analgesics and other drugs that could affect the absorption and metabolism of iron; obesity with BMI>35.

The same exclusion criteria were applied to form the control group. Blood samples were taken three times – immediately after hospitalization in the ward (baseline values), twenty-four hours and twenty-eight days after restoration of sinus rhythm. Controls were tested once.

3.2. Study population

33 patients were selected sequentially for the study (17 men, 16 women; mean age 60.03±1.93 years) with an occurrence of PAF<48 hours prior to hospitalization. 33 controls were also selected (17 men, 16 women; mean age 59.27±1.72 years).

The study was conducted in the Intensive Cardiology Department of First Cardiology Clinic at the University Hospital "St. Marina "- Varna for the period October 2010 – May 2012 after approval by the Research Ethics Committee (№35/29.10.2010) at the same hospital and in accordance with the Declaration of Helsinki [18]. The participants were included in the study after previously signing the informed consent for participation.

3.3. Sample collection and storage

Zinc concentrations were examined in plasma obtained from peripheral venous blood. Blood samples were collected in heparin vacutainer (VACUETTE/4.0 ml/Li Hep) and immediately centrifuged at 2000g for 10 min. The resulting plasma was immediately pipetted, frozen at –20°C and kept under the same conditions for up to 3 months.

Re-freezing of samples was not allowed in conducting the study.

3.4. Laboratory procedures

Plasma zinc concentrations were determined by a direct colorimetric method without deproteinizaton. The reagent used was by Sentinel Diagnostics, Italy in full compliance with the manufacturer guidelines. The basis of the methodology is the reaction between plasma zinc and a specific complexant, during which a color compound is formed, which intensity is proportional to the plasma zinc concentration. It was determined by end-point spectrophotometry at 560 nm.

3.5. Regimen of propafenone

Restoration of sinus rhythm was achieved after administration of the drug propafenone. The drug was administered in the prescribed for it scheme with a total duration of 24 hours [16], [17]. After restoration of sinus rhythm until the end of the study (28 days after restoration of rhythm) all patients received a maintenance dose of p.o. propafenone of 150 mg three times daily.

3.6. Statistical analysis

We used descriptive statistics to calculated the means, standard deviations, relative shares and central tendency (Mo = mode).

The testing of the hypothesis for equality of means and indicators for relative share was done by Student's t-test. A two-sided t-test was used in our study for independent (unpaired) samples at a level of significance of $p = 0.05$. Values of $p < 0.05$ were used to confirm the hypothesis that the difference between the means was statistically significant.

4. Results

4.1. Characteristics of study participants

There was no statistically significant difference between the patient and control group regarding the number of respondents, mean age and gender structure ($p > 0.05$) (Table. 1). The frequency of accompanying diseases, dyslipidemia, their ongoing treatment, bad habits and BMI were also not different ($p > 0.05$) (Table. 1).

Table 1. Demographic and clinical characteristics of study participants

	Patients with PAF	**Control group**	**P values**
Number of participants in the group	33	33	p=1
Mean age	60.03±1.93	59.27±1.72	p=0.77

(years)			
Men/Women	17/16	17/16	p=1
Accompanying diseases			
Hypertension	21 (63.64%)	24 (73.73%)	p=0.38
Diabetes mellitus type 2	1 (3.03%)	1 (3.03%)	p=1
Dyslipidemia	3 (9.09%)	1 (3.03%)	p=0.30
Medicaments for Hypertension and Dyslipidemia			
	8 (24.24%)	10 (30.30%)	p=0.58
	10 (30.30%)	7 (21.21%)	p=0.40
Beta blockers	5 (15.15%)	6 (18.18%)	p=0.74
ACE inhibitors	2 (6.06%)	1 (3.03%)	p=0.55
Sartans	1 (3.03%)	1 (3.03%)	p=1
Statins			
Metformin			
Deleterious habits			
	4 (12.12%)	7 (21.21%)	p=0.32
Smoking	4 (12.12%)	6 (18.18%)	p=0.49
Alcohol intake			
BMI (kg/m2)	23.86±2.84	23.98±2.75	p=0.86

Statistical analysis showed that the mean duration of AF until hospitalization was 8.64±1.03 hours (from 2nd to 24th hour).

4.2. Plasma zinc concentrations

Baseline zinc concentrations were not statistically significantly different from controls (15.63±0.62 vs 16.46±1.25 μmol/L, p=0.55) (Figure 1). No difference was found also on the twenty fourth hour and twenty-eighth day after restoration of sinus rhythm (15.31±0.70 vs 16.46±1.25 μmol/L, p=0.42; 15.70±0.63 vs 16.46±1.25 μmol/L, p=0.58, respectively).

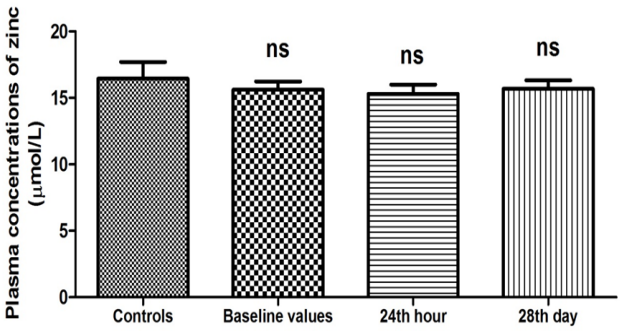

Figure 1. Plasma zinc concentrations (mmol/L) of patients with PAF and controls. (initial values - immediately after hospitalization of the patient, 24th hour - 24 hours after discontinuation of the arrhythmia; 28th day - 28 days after discontinuation of the arrhythmia; ns - statistically insignificant difference).

5. Discussion

Zinc is an essential trace element for the human organism and plays an important role in many physiological processes. It is a key regulator of the innate immune system as well as growth processes. It is vital for the functional activity of over 300 enzymes with multiple functions, incl. synthesis and degradation of protein molecules, lipids and carbohydrates, as well as gene expression [19].

The significance of zinc deficiency on human health was established in 1961 and since then the plasma levels of the element represent significant biochemical and clinical interest in the pathogenesis of many diseases [20]. The concentrations of zinc in plasma and blood are currently the best laboratory marker for assessing the zinc status and probability of zinc deficiency. Although they may have limitations on the validity and reliability in establishing light to moderate deficiency of the element, for the moment the indicator is accepted as reliable [21]. This gave us a good reason for it to be preferred in the study of our patients, and the results could be clearly interpreted.

Studies so far on the zinc levels in patients with AF are single. Object of clinical interest is primarily long-lasting AF. For example, Ghaemian et al. established hypozincemia in the chronic form of the arrhythmia [22]. Patients, however, were with significantly suppressed left ventricle ejection fraction (EF<35%), which limits the interpretation of results. A logical question arises whether zinc deficiency is a consequence of the rhythm disorder or heart failure. Decrease in the plasma concentrations of the element was measured as well in AF, occurred due to elective coronary artery bypass grafting [15]. Tubek et al. however, establish an increased incidence of AF hospitalizations with the increase in zinc intake [23].

Summarizing the data from the studies so far we can say that the presented results are contradictory. The patients have significant co-morbidity and the zinc levels were measured once, making it difficult to analyze them. In our study the plasma concentrations of the element were investigated both during the arrhythmia as well as after its interruption i.e. in sinus rhythm. Tracing the indicators over time has a serious advantage over being measured only once, as it allows to seek a correlation between the indicators and the manifestation of the rhythm disorder.

Zinc has antioxidant and anti-inflammatory properties [24], [25]. In recent years research on the intimate mechanisms of AF showed development of oxidative stress and inflammation in patients with this disease [26]-[29]. In this sense it is appropriate to assume that the trace element could be relevant to the clinical course of the arrhythmia. As it is apparent from Figure 1, however, the levels of zinc in patients with PAF were not statistically different from the controls in any of the measurements. The lack of dynamics in the values of the indicator gives a good reason to believe that zinc has no

relation to the development of the disease. It is appropriate to note that this is the first-ever clinical study researching the zinc status in the early hours of arrhythmia. The study population included only patients hospitalized until the twenty fourth hour of the rhythm disorder. Indeed, the early detection of the indicator allows not only to make a general conclusion that zinc has no relation to the pathogenesis of the disease, but also in particular that it is not a part of the initiation mechanisms. We must note, however, that taking into account the extremely short episode of the arrhythmia, the results and conclusions made could not be transferred automatically on long-lasting PAF.

Of particular interest are the data obtained twenty-four hours after interruption of the arrhythmia. In essence they reflect the status of the element immediately following the restoration of sinus rhythm. The results showed no changes in the levels of zinc, which gives grounds to assume that the micro-element has no relation to the processes associated with the persistence and recurrence of the arrhythmia (Figure 1). The values from the twenty-eighth day confirm this assumption (Figure 1).

6. Conclusion

Plasma zinc concentrations in patients with PAF did not show deviations from controls which never experienced arrhythmia episodes. No significant differences in both the clinical manifestation of the rhythm disorder and in sinus rhythm were observed. The lack of dynamics in the values of the indicator gives a good reason to believe that zinc has no relation to the appearance and recurrence of the disease.

References

[1] Lip G, Caterina R, Savelieva I et al. ESC Committee for Practice Guidelines 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. Eur Heart J. 2012;33:2719–2747.

[2] Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener HC et al. Outcome parameters for trials in atrial fibrillation: executive summary. Eur Heart J. 2007;28(22):2803-17.

[3] Mayyas F, Alzoubi KH, Van Wagoner DR. Impact of aldosterone antagonists on the substrate for atrial fibrillation: aldosterone promotes oxidative stress and atrial structural/electrical remodeling. Int J Cardiol. 2013;168(6):5135-42.

[4] Lip GY, Li FL, Hee S. Paroxysmal atrial fibrillation. QJM. 2001;94(12): 665-678.

[5] Levy S, Maarek M, Coumel P et al. Characterisation of different subsets of atrial fibrillation in general practice in France: the ALFA study, Circulation. 1999;99:3028–35.

[6] Zacharski LR, McKernan L, Metzger ME, Malone MG, Samnotra V, Bhargava A, Steiner PR, Rauwerdink CA, Ornstein DL, Cornell CJ. Remission of paroxysmal atrial fibrillation with iron reduction in haemophilia A. Haemophilia. 2010;16(5):726-30.

[7] Rose RA, Sellan M, Simpson JA, Izaddoustdar F, Cifelli C, Panama BK, Davis M, Zhao D, Markhani M, Murphy GG, Striessnig J, Liu PP, Heximer SP, Backx PH. Iron overload decreases CaV1.3-dependent L-type Ca2+ currents leading to bradycardia, altered electrical conduction, and atrial fibrillation. Circ Arrhythm Electrophysiol. 2011;4(5):733-42.

[8] Bakhsh M, Abbas S, Hussain RM, Ali Khan S, Naqvi SM. Role of magnesium in preventing post-operative atrial fibrillation after coronary artery bypass surgery. J Ayub Med Coll Abbottabad. 2009;21(2):27-29.

[9] Chelazzi C, Villa G, De Gaudio AR. Postoperative Atrial Fibrillation. ISRN Cardiology. ISRN Cardiol. 2011;2011:203179. doi: 10.5402/2011/203179.

[10] Chiladakis JA, Stathopoulos C, Davlouros P, Manolis AS. Intravenous magnesium sulfate versus diltiazem in paroxysmal atrial fibrillation. Int J Cardiol. 2001;79(2-3):287-291.

[11] Yan YQ, Zou LJ. Relation between zinc, copper, and magnesium concentrations following cardiopulmonary bypass and postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting. Biol Trace Elem Res. 2012;148(2):148-53.

[12] Negreva MN, Georgiev SJ, Penev AP, Prodanova K, Georgieva RB, Alexandrova AA. Assessment of Copper Status in Patients with Paroxysmal Atrial Fibrillation. J Cardiobiol. 2014;2(2): 5.

[13] Meschy F. Nutrition minérale des ruminants. Versaille: Quae;2010. 208 p.

[14] Yeh YH, Kuo CT, Chan TH, Chang GJ, Qi XY, Tsai F, Nattel S, Chen WJ. Transforming growth factor-β and oxidative stress mediate tachycardia-induced cellular remodelling in cultured atrial-derived myocytes. Cardiovasc Res. 2011;91(1):62-70.

[15] Meunier N, O'Connor JM, Maiani G, Cashman KD, Secker DL, Ferry M, Roussel AM, Coudray C. Importance of zinc in the elderly: the ZENITH study. Eur J Clin Nutr. 2005;59 Suppl 2:S1-4.

[16] Bellandi F, Cantini F, Pedone T, Palchetti R, Bamoshmoosh M, Dabizzi RP. Effectiveness of Intravenous Propafenone for Conversion of Recent-Onset Atrial Fibrillation: A Placebo-Controlled Study. Clin Cardiol. 1995;18: 631-634.

[17] Bianconi L, Mennuni M. Comparison Between Propafenone and Digoxin Administered Intravenously to Patients With Acute Atrial Fibrillation. Am J Cardiol. 1998;82:584-588.

[18] World Medical Association Declaration of Helsinki (2008). Ethical principles for medical research involving human subjects. 59th WMA General Assembly. Seoul.

[19] Frassinetti S, Bronzetti G, Caltavuturo L, Cini M, Croce CD. The role of zinc in life: a review. Environ Pathol Toxicol Oncol. 2006;25(3):597-610.

[20] King JC, Cousins RJ. Zinc. In: Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ, editors. Modern Nutrition in Health and Disease. 10th ed. Baltimore: Lippincott Williams and Wilkins; 2006. pp 271–85.

[21] Roohani N, Hurrell R, Kelishadi R, Schulin R. Zinc and its importance for human health: An integrative review. J Res Med Sci. 2013;18(2):144-57.

[22] Ghaemian A, Salehifar E, Jalalian R, Ghasemi F, Azizi S, Masoumi S, Shiraj H, Mohammadpour RA, Bagheri GA. Zinc and copper levels in severe heart failure and the effects of atrial fibrillation on the zinc and copper status. Biol Trace Elem Res. 2011;143(3):1239-46.

[23] Tubek S, Bunio A, Szyguła R, Krasowski G. The content of elements in rainwater and its relation to the frequency

of hospitalization for atrial fibrillation in Opole Voivodship, Poland, during 2000-2002. Biol Trace Elem Res. 2010;138(1-3):1-7.
[24] Prasad AS. Zinc: an antioxidant and anti-inflammatory agent: role of zinc in degenerative disorders of aging. J Trace Elem Med Biol. 2014;28(4):364-71.
[25] Zago MP, Oteiza PI. The antioxidant properties of zinc: interactions with iron and antioxidants. Free Radic Biol Med. 2001;31(2):266-74.
[26] Patel P, Dokainish H, Tsai P, Lakkis N. Update on the association of inflammation and atrial fibrillation. J Cardiovasc Electrophysiol. 2010;21(9):1064-70.
[27] Friedrichs K, Klinke A, Baldus S. Inflammatory pathways underlying atrial fibrillation. Trends Mol Med. 2011;17(10):556-63.
[28] Youn JY, Zhang J, Zhang Y, Chen H, Liu D, Ping P, Weiss JN, Cai H. Oxidative stress in atrial fibrillation: an emerging role of NADPH oxidase. J Mol Cell Cardiol. 2013;62:72-9.
[29] Yang KC, Dudley SC Jr. Oxidative Stress and Atrial Fibrillation: Finding a Missing Piece to the Puzzle. Circulation. 2013;128:1724-1726.