Urban and rural area differences in the interaction between oxidative process elements in human femoral bone

Mikołaj Dąbrowski^{1,2} · Anetta Ziola-Frankowska³ · Łukasz Kubaszewski^{1,2} · Piotr Rogala¹ · Marcin Frankowski⁴

Received: 30 May 2018 / Accepted: 24 August 2018 / Published online: 30 August 2018

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Abstract

Elements in the human body come from contaminated food, water, and air from the living area. Bones are a marker of long-term exposure to elements and show a relationship between them. The aim of the study was to analyze the correlation between the contents of Zn, Cu, Fe, Mo, Cr, Ni, Ba, Sr, and Pb in the proximal femoral head (cancellous bone) and femoral neck (cortical bone) in rural and urban populations. The study included 96 patients who were operated on for total hip replacement (THR), acquired in a surgical procedure with atomic absorption spectrometry, and the content of Zn, Cu, Fe, Mo, Cr, Ni, Ba, Sr, and Pb was evaluated. In rural areas, significant negative correlations were observed for Mo/Cr, Mo/Cu, and Ni/Fe, and positive correlations were observed for Fe/Zn and Pb/Zn. In urban areas, a negative correlation was found for Pb/Mo. Pb and Ni increased with age only in villagers, and Zn and Sr decreased with age in urban citizens. Ba decreased with age in people from rural areas. The correlation showed variances mainly in molybdenum, nickel, and oxidative elements between rural and urban populations.

Keywords Rural · Urban · Trace elements · Environmental factors · Femoral bone

Introduction

The sources of elements in the human body are contaminated food, water, and air from the living area (Berglund et al. 2000). Air pollution is higher in cities compared to rural areas (Gonzalez-Reimers et al. 2014). The metal content of the soil

depends on the particular type of industry in the area: Pb, Zn, Ni, Cu, Fe, and As in smelter and metal industries; Mn and Cd in the textile industry; and Cr in the leather industry (Kabir et al. 2012).

Previous studies of the content of metals in the human bone have shown the influence of such factors as gender, smoking, physical activity, alcohol consumption, and air pollution (Lanocha-Arendarczyk et al. 2015, Ziola-Frankowska et al. 2015a, b, 2017). The study of Ziola-Frankowska et al. showed higher Pb, Cr, and Ni content in smokers, higher concentrations of Pb, Ni, and Cu in people who consume alcohol, and also higher Pb, Cu, Zn, and Ni concentrations in men (Ziola-Frankowska et al. 2015b). In addition, Hg content of the femoral neck with the increase of body mass index (BMI) has been demonstrated (Ziola-Frankowska et al. 2017). Another study showed that content of Al in the femoral head and neck was strictly dependent on type of medicines taken, contact with chemicals at work, differences in body anatomy, and sex (Ziola-Frankowska et al. 2015a).

It should be underlined that the slow metabolism of bones causes them to be markers for long-term exposure to elements, including heavy metals (Zaichick et al. 2011). Cancellous bone has faster turnover than cortical bone and is associated with place of residence (Boonen et al. 1997). The content and correlations between the rings depend on the location of bone

Responsible editor: Philippe Garrigues

✉ Mikołaj Dąbrowski
md@twi.net.pl

✉ Anetta Ziola-Frankowska
anettazf@amu.edu.pl

¹ Department of Spondyloortopaedics and Biomechanics of the Spine, W. Dega University Hospital, Poznan University of Medical Sciences, 28 Czerwca 1956 135/147, 61-545 Poznan, Poland

² Department of Orthopaedics and Traumatology, W. Dega University Hospital, Poznan University of Medical Sciences, 28 Czerwca 1956 135/147, 61-545 Poznan, Poland

³ Faculty of Chemistry, Department of Analytical Chemistry, Adam Mickiewicz University in Poznan, Umultowska 89b, 61-614 Poznan, Poland

⁴ Faculty of Chemistry, Department of Water and Soil Analysis, Adam Mickiewicz University in Poznan, Umultowska 89b, 61-614 Poznan, Poland

sampling along the bone area. It is suggested to select bone tissue as a tissue for monitoring inorganic contaminants and standardize the method of sampling in order to allow comparison of results between studies (Lazarus et al. 2018).

Differences in the femoral bone correlation of metals between persons living in urban and rural areas can show the degree of environmental pollution and the influence of metals on the human musculoskeletal system (Budis et al. 2014). Toxicity of environmental pollutant mechanism is associated with inflammation, oxidative stress, metabolic disorders, and epigenetic mechanism. The pollutions disrupt the homeostatic status and lead to adverse health effects. This perturbation of homeostatic balance can be most noticeable in older adults (Fougère et al. 2015). The production of free radicals is a process in which metals, such as Fe, Cu, Cr, and Co, are involved, transferring electrons between metals and substrates (Matés et al. 2008). The physiological oxidative state in the cell can be interrupted by the uncontrolled formation of free radicals leading to DNA modification and lipid peroxidation (Valko et al. 2007). The experimental study showed that the accumulation of iron leads to the production of reactive oxygen species (ROS) which stimulates the differentiation of osteoclasts and iron-induced osteopenia in mouse model (Wang et al. 2018). The literature reports the toxicity of Cr^{3+} , Fe^{3+} , Ni^{2+} , and Mo^{3+} and their impact on cell viability in vitro (Terpilowska and Siwicki 2018). There are a few pieces of information about the correlation between these elements and their influence on human systems. Moreover, the studies of these trace elements are important because they are used alone and in combination in diet supplements and they are component of biomaterials implanted in medicine.

Given that previous research mainly concerned quantitative analysis, the aim of this study was to identify the differences between urban and rural areas in the concentrations of Zn, Cu, Fe, Mo, Cr, Ni, Ba, Sr, and Pb in the proximal femoral head (FH) (cancellous bone) and femoral neck (FN) (cortical bone) of the hip joint affected by osteoarthritis.

Materials and methods

The study material included parts of the femoral bone obtained during surgical operation on for total hip replacement (THR). Biological samples were taken from patients living in Wielkopolska Region of Poland. Biological samples were collected from 96 patients, including 57 women, of whom 18 were residents of villages and 39 of cities, and 39 men, of whom six were residents of villages and 33 of cities. The mean age of the women study population was 64.5 ± 14.2 years (range = 25–87 years) and for men it was 63.2 ± 10.2 years (range 42–91 years). Inhabitants of cities were significantly older than inhabitants of rural areas (65.5 ± 12.6 vs 57.8 ± 13.3 , $p < 0.05$). A history of disease did not affect the outcome

of the study. There is no major industry concentration in this region. Detailed and accurate information about characteristics of patients and femoral bone samples are presented in the studies by Ziola-Frankowska et al. (2015a, b).

The study was approved by the Bioethical Committee (permit no. 172/4) of the University of Medical Sciences in Poznan (Poland). All patients included in the study provided written informed consent prior to participation. The femoral bone was collected intraoperatively from the patients during hip replacement procedure. The samples were taken from two anatomic regions of each type of resected fragment in situ with an orthopedic oscillating saw: the FH and FN. The bone samples were taken without articular capsule and without articular cartilage. After excision, the biological samples were frozen at -20°C in polyethylene containers.

The frozen bone samples were freeze-dried using a lyophilizer (Lyovac GT2e; Steris, Germany) for 24 h. Then, a known mass 0.5 g of the sample was weighed and placed in a Teflon bomb Mars 5 Xpress microwave oven (CEM, USA). Next, the 10-mL volume of suprapure nitric acid (V) (Merck, Germany) was added to each sample and allowed to stand for 8 h to slow mineralization. After that, the samples were mineralized in a microwave oven using a modified EPA method 3051 (Frankowski et al. 2013). The post-mineralization extract was placed into flasks and filled with 50-mL demineralized water. It should be underlined that extracts of bone samples after digestion were clear and colorless or slightly yellow, with no visible sediment and fat residues.

The concentrations of Mo, Cr, Zn, Pb, Cu, Ni, Fe, Ba, and Sr in mineralized samples were determined using inductively coupled plasma atomic emission spectrometry (ICP-AES) Jobin Yvon, 170Ultrac (Jobin Yvon, France) with laterally viewed plasma. The samples were nebulized using a concentric Meinhard nebulizer. The analytical conditions of ICP-AES were used: RF power 1200 W, plasma gas flow 12 L/min, auxiliary gas flow 0.4 L/min, nebulizer (carrier) gas 0.6 L/min, sample flow rate 1.0 mL/min, cleaning time 30 s, replicates – 3, and emission lines of Zn: $\lambda = 213.8$ nm, Cu: $\lambda = 224.7$ nm, Fe: $\lambda = 259.9$ nm, Mo: $\lambda = 204.6$ nm, Cr: $\lambda = 205.5$ nm, Ni: $\lambda = 231.6$ nm, Ba: $\lambda = 455.4$ nm, Sr: $\lambda = 407.8$ nm, and Pb: $\lambda = 220.3$ nm. During analysis, the calibration curve method was applied. The standard deviation did not exceed 5% for the results of average of the content determined for all analytical lines applied for the each element. The accuracy of the performed procedure was controlled by analysis of the Standard Reference Material 1400 Bone Ash (National Institute of Standard and Technology (NIST)) using ICP-AES analytical technique. The recoveries for analyzed elements varied from 94.6 to 109%.

The statistical analysis was performed with Statistica PL v.12.0 (StatSoft, Tulsa, USA) software. Moreover, the Spearman's rank correlation between selected elements occurring in different parts of the hip joint (femoral neck and

femoral head bone) and epidemiological data, including age, sex, and place of residence (urban and rural area), was performed. The p values < 0.05 were considered statistically significant. The chemometric analysis to evaluate variables from the independent assumption showing the mutual relations between the analyzed factors was performed by applied principal component analysis (PCA).

Results and discussion

Molybdenum and nickel

The analysis of the correlation findings in terms of place of residence showed variances mainly in molybdenum and nickel.

In rural areas, the correlation of Mo with Cr content was significant negatively correlated (Tables 1 and 2). In further gender group analysis, a similar correlation was found both in females in the FH (Table 3) and in men in the FN (Table 6).

In the group analysis of the place of residence, a statistically significant negative correlation of Mo/Cu was found in the group of rural people in the FH (Table 2). In further gender group analysis, a correlation was found mainly in women in rural areas (Table 3). The same correlation in the FN was more negative for women (cities = -0.32 , villages = -0.37) than men (cities = 0.07 , villages = -0.28) (Tables 5 and 6). A significantly positive correlation of Mo/Zn was found in the FH of men in urban areas (Table 4). In other groups' interaction, Mo/Zn was negative, but the values did not exceed the level -0.27 .

There was also a negative correlation between the content of Mo/Pb in the FN in the urban population (Table 1). In further gender analysis, the correlation in the city was higher in men than in women (-0.44 vs -0.28). This difference according to sex was also noticeable in men from rural areas although it was not statistically significant (Table 6).

The content of Mo in the analyzed femur bone decreased with age mainly in rural areas (Tables 1 and 2). Also in villages, in females' femoral head, the correlation coefficient of Mo with age was statistically significant opposite to the men (Table 3).

There were no significant interactions, and their differences depended on the sex and place of residence for Mo/Fe (range = -0.27 to 0.26), Mo/Ni (range = -0.29 to 0.17), Mo/Sr (range = -0.18 to 0.21), and Mo/Ba (range = -0.3 to 0.33).

The values of the correlation coefficients of Ni/Cr in the FN were positive and similar in urban and rural populations, although they were statistically significant only in the first group (Table 1). In addition, further gender analysis showed significantly higher values for women both in urban and rural areas (Table 5).

Increased Ni content in the femur with age was demonstrated in rural areas (Tables 1 and 2). Especially in the group of men living in rural areas, the correlation coefficient was very high (FN = 0.88 , FH = 0.94).

Also, we observed that the correlation of Ni/Ba was negative only in rural areas in men (Tables 4 and 6). A negative tendency of Ni/Zn correlation was noted, although low and statistically insignificant. Correlation values were similar only in men in the FH (cities = -0.42 , villages = -0.46).

The correlation of Ni/Fe content of the FN was significantly positive only in rural areas (0.47) and was independent of sex (Tables 5 and 6). Correlation was not found in the FH, although the value of male dependency (-0.76) was notable. Even though no statistically significant correlation was found, the results may not be fully reliable due to the small number ($n = 6$).

Oxidative process elements

In our study, we also checked the possible correlation between metals responsible for oxidative process. The Cr/Fe

Table 1 Spearman correlation coefficients for metals found in femoral neck in according place of residence

Neck	Mo	Cr	Zn	Cu	Ni	Fe	Sr	Ba	Pb	Age
										Cities
Mo	x	0.19	-0.13	-0.15	-0.02	0.01	-0.01	-0.02	-0.35*	-0.01
Cr	-0.33	x	-0.04	0.25*	0.31*	0.38*	-0.07	-0.09	-0.15	0.02
Zn	-0.18	-0.10	x	-0.03	-0.06	-0.11	0.33*	0.16	0.17	-0.25*
Cu	-0.25	0.39	-0.32	x	0.48*	0.27*	-0.10	-0.23	-0.12	0.15
Ni	-0.08	0.35	-0.38	0.86*	x	0.03	0.09	-0.19	-0.03	-0.09
Fe	-0.18	0.36	-0.36	0.54*	0.47*	x	-0.19	-0.17	-0.31	0.00
Sr	0.05	-0.08	0.56*	-0.35	-0.17	-0.24	x	0.27*	0.15	-0.32*
Ba	0.17	-0.04	0.36	-0.07	-0.09	-0.05	0.46*	x	0.15	-0.14
Pb	-0.19	-0.23	0.46*	0.22	0.03	-0.06	0.08	-0.04	x	0.02
Age	-0.21	-0.31	0.03	0.33	0.33	-0.19	-0.27	-0.32	0.46*	x
										Villages

^a Statistically significant correlation

correlation was positive in each group and significant in the FN and FH of women from cities (Tables 3 and 5). In men, the Spearman coefficient of Cr/Fe was lower, at a maximum of 0.33. In villages, Cr decreased with age in the FN of women and increased with age in the FH of men. The Cr/Zn correlation was negative only in the FN of men (Table 6).

Interesting observations arise from the analysis of Cu content, namely, its content in the femur increased with age (although not statistically significant) only in the rural population (villages: FH = 0.32, FN = 0.33 vs cities: FH = 0, FN = 0.15). The Spearman coefficient of Cu/age was significantly higher for men living in rural areas (Tables 4 and 6). The correlation of Cu/Cr was highly positive independent of the place residence, and slightly higher values were found in men, with the lowest for women living in cities (FN = 0.18). Also, the Cu/Fe interaction was significant only in the FN, and the value was higher in rural areas both in women and in men (Table 1).

We also found a high correlation of Cu/Ni in the FN (villages = 0.86 vs cities = 0.48). However, the correlation in the FN was higher in the rural population, while in the FH, the values were similar but statistically significant in the case only of urban areas (Table 2).

The Fe/Zn content in rural areas was positive in the FH and negative in the FN (Tables 1 and 2). A negative correlation of Zn/Cu was found in the FN of men living in villages (Table 6) and cities in both types of bone (Tables 4 and 6). In women, those elements did not interact significantly. It should be underlined that we observed a tendency of Zn to decrease with age in femoral head; the most visible was in men from rural areas (−0.37) and the least in men from cities (0.02).

In the case of Fe, in rural areas, we found a negative correlation of metal with age in the FN of women and the FH of men (−0.26 and −0.66, respectively). Moreover, the FH of women demonstrated increased Fe content with age (rural = 0.37, urban = 0.48), and no correlation was found in other groups.

Barium and strontium

Men in urban areas showed a significant decrease in Sr content in the FN with age, which was most visible in the FN in men from urban areas (Table 6). Sr/Fe correlation was negative regardless of the place of residence of men in the FN (Table 6). In other groups, the Sr/Fe correlation was insignificant (maximum 0.2). The Ni/Sr correlation was not determined by sex or area, and Spearman coefficient values were low (range = −0.2 to 0.29). For interactions of Sr/Cr and Sr/Cu, we did not obtain significant value in the FN of men from rural areas, and in other subgroups, it did not show absolute values above 0.2. Zn/Sr correlation was significantly positive, although the lowest values were found in the FN of women (rural = 0.27, urban = 0.33) and the highest in the FH in cities (men = 0.61, women = 0.58).

We showed a positive correlation of Ba/Sr regardless of the place of residence, but much higher correlation coefficients were found in women (Tables 3 and 4). Interesting results were obtained in relation to Ba in the femoral bone of males from villages. Negative correlations with oxidative metals were found, including statistically significant ones, and the highest coefficients were obtained for Ba/Cr and Ba/Cu (Tables 4 and 6). For urban areas, the correlation coefficients of Ba/Mo, Cr, Zn, and Cu did not exceed 0.3, except for the correlation Ba/Fe, which was not determined by sex or area, and Spearman coefficient values were low (range = −0.24 to 0.14). We found a Ba/Zn correlation in women from cities (Table 3). It is worth mentioning that the Ba content in the bones decreased with age in both men and women.

In rural areas, the absolute values of correlation coefficients were higher than those of urban residents (although statistical significance was not demonstrated) and ranged from −0.54 to −0.31 in rural areas and −0.15 to 0.17 in urban areas.

Table 2 Spearman correlation coefficients for metals found in femoral head in according place of residence

Head	Mo	Cr	Zn	Cu	Ni	Fe	Sr	Ba	Pb	Age
										Cities
Mo	x	0.05	0.15	−0.14	−0.07	0.15	0.01	0.01	0.02	0.14
Cr	−0.49 ^a	x	−0.08	0.38 ^a	0.11	0.38 ^a	−0.09	0.06	−0.21	0.13
Zn	−0.11	0.08	x	−0.12	−0.14	0.01	0.59 ^a	0.43 ^a	0.09	−0.16
Cu	−0.53 ^a	0.62 ^a	−0.09	x	0.45 ^a	0.22	−0.06	−0.13	−0.06	0.00
Ni	−0.23	0.32	−0.18	0.36	x	−0.15	−0.03	0.08	−0.14	−0.15
Fe	−0.21	0.26	0.41 ^a	−0.02	−0.14	x	−0.11	0.02	0.26	0.20
Sr	0.13	−0.09	0.37	−0.21	−0.15	0.17	x	0.40 ^a	0.06	−0.19
Ba	−0.03	0.04	0.33	−0.26	−0.19	−0.15	0.43 ^a	x	0.12	−0.02
Pb	0.03	0.03	0.01	−0.02	0.01	−0.02	−0.09	0.02	x	0.07
Age	−0.40	0.09	−0.20	0.32	0.46 ^a	0.15	−0.19	−0.41 ^a	0.03	x
										Villages

^a Statistically significant correlation

Table 3 Spearman correlation coefficients for metals found in femoral head in women in according place of residence

Head	Mo	Cr	Zn	Cu	Ni	Fe	Sr	Ba	Pb	Age
Women										Cities
Mo	x	0.02	0.04	−0.17	0.17	0.11	−0.13	−0.01	0.21	0.09
Cr	−0.49 ^a	x	−0.07	0.35 ^a	0.17	0.39 ^a	−0.10	0.08	−0.25	0.15
Zn	0.17	−0.11	x	−0.13	0.07	−0.04	0.58 ^a	0.45 ^a	−0.09	−0.18
Cu	−0.69 ^a	0.58 ^a	−0.11	x	0.32 ^a	0.04	−0.09	−0.23	−0.19	0.12
Ni	−0.19	0.33	−0.37	0.24	x	−0.27	0.15	0.13	0.02	−0.14
Fe	−0.28	0.30	0.34	0.13	0.18	x	−0.07	0.00	−0.07	0.48 ^a
Sr	0.16	−0.09	0.54 ^a	−0.24	−0.20	0.09	x	0.46 ^a	−0.22	−0.25
Ba	0.08	0.19	0.32	−0.03	−0.25	−0.24	0.63 ^a	x	−0.04	−0.10
Pb	0.01	0.07	0.05	0.07	0.00	0.16	0.04	0.06	x	0.05
Age	−0.51 ^a	0.07	−0.29	0.20	0.29	0.37	−0.40	−0.45	0.16	x
Villages										

^a Statistically significant correlation

Lead

A significantly positive correlation between age and the concentration of Pb in the FN was found in the rural population (Table 1). We found other interactions in men in the rural group in both types of sample: Pb/Zn, Pb/Cr Pb/Cu Pb/Ni, Pb/Fe, Pb/Ba, and Pb/Sr (Tables 4 and 6).

Chemometric analysis

PCA showed a difference between urban and rural populations for the first factor for Mo, Ni, Cu, Cr, Zn, and Ba (Figs. 1 and 2). The second factor describes the difference between urban and rural of Zn only in the FH and Sr (Figs. 1 and 2).

In the PCA, the elements can be divided into two groups: Ni and Cu in the FN and additionally Cr in the FH, as a first factor, to take the opposite values for

villages and cities. The second group includes Sr, Ba, and Zn as a second factor to take opposite values for villages and cities, which is particularly visible in the FH (Figs. 1 and 2). Gender-based analysis confirms the division into the above groups; in particular, in the FH, Pb variation can be observed in relation to the second factor between cities and villages (Figs. 3 and 4).

Previous studies have described the existence of heavy metals in several regions of Poland. Jurkiewicz et al. evaluated the same content of Ca, P, Mg, P, Fe, Zn, Cu, Pb, Cd, As, and Ag in the FHs of inhabitants of southern Poland (Silesia, Cracow) and middle Poland (Lodz) (Jurkiewicz et al. 2004). Specimens from different regions differed in Pb and Cd content, illustrating the differences in environmental pollution exposure. Budis et al. found no statistically significant residence-related differences in the concentrations of Sr, Mn, or Fe (Budis et al. 2014).

Table 4 Spearman correlation coefficients for metals found in femoral head in men in according place of residence

Head	Cr	Zn	Cu	Ni	Fe	Sr	Ba	Pb	Age
Men									Cities
Mo	0.11	0.47 ^a	−0.05	−0.27	0.26	0.21	0.07	−0.10	0.16
Cr	x	−0.12	0.49 ^a	0.09	0.33	−0.03	0.03	−0.19	0.06
Zn	0.14	x	−0.31	−0.42 ^a	0.11	0.61 ^a	0.29	0.16	0.02
Cu	0.94 ^a	0.03	x	0.47 ^a	0.30	−0.03	−0.06	−0.12	−0.02
Ni	0.58	−0.46	0.74	X	−0.10	−0.18	0.06	−0.08	−0.10
Fe	−0.09	0.54	−0.39	−0.76	x	−0.10	0.04	0.05	−0.02
Sr	−0.14	0.37	−0.21	0.03	0.20	x	0.32	−0.04	−0.03
Ba	−0.94 ^a	−0.31	−0.94 ^a	−0.58	0.14	0.03	x	0.04	0.17
Pb	−0.13	−0.13	−0.42	−0.42	0.65	0.13	0.39	x	0.25
Age	0.43	−0.37	0.58	0.94 ^a	−0.66	0.31	−0.49	−0.39	x
Villages									

^a Statistically significant correlation

Table 5 Spearman correlation coefficients for metals found in femoral neck in women in according place of residence

Neck	Mo	Cr	Zn	Cu	Ni	Fe	Sr	Ba	Pb	Age
Women										Cities
Mo	x	0.18	−0.03	−0.32 ^a	0.10	0.05	0.16	0.18	−0.28	−0.21
Cr	−0.25	x	0.16	0.18	0.38 ^a	0.52 ^a	0.00	−0.04	−0.14	−0.07
Zn	−0.18	−0.01	x	0.21	0.01	−0.02	0.33 ^a	0.13	0.01	−0.27
Cu	−0.37	0.49 ^a	0.06	x	0.43 ^a	0.40 ^a	−0.06	−0.31	0.24	0.07
Ni	−0.06	0.52 ^a	−0.22	0.83 ^a	x	0.23	−0.15	−0.25	0.06	−0.10
Fe	−0.29	0.36	−0.25	0.62 ^a	0.55 ^a	x	0.07	−0.20	−0.08	0.04
Sr	0.24	0.20	0.27	0.06	0.11	−0.16	x	0.39 ^a	−0.19	−0.26
Ba	0.06	0.31	0.39	0.17	0.00	−0.04	0.45	x	−0.22	−0.15
Pb	−0.18	−0.10	0.34	0.01	−0.01	−0.15	−0.19	0.06	x	0.20
Age	−0.22	−0.43	0.23	0.14	0.10	−0.26	−0.32	−0.31	0.61 ^a	x
Villages										

^a Statistically significant correlation

Chromium, molybdenum, zinc, iron, and diabetes

Interestingly, the correlation noted in regard to Mo/Cr is negative in persons living in rural areas. In this study, five patients (two women and three men) were diagnosed with diabetes, and most (four patients) lived in the city. Similar negative correlations were observed in the hair study population living in an urban population group in a large industrial center of southwest Poland (Chojnacka et al. 2005). Molybdenum plays a role in blood glucose level. Sodium molybdate prevented hyperinsulinemia in rats (Güner et al. 2001). Ajibola et al. showed that a significant increase of plasma glucose was significantly correlated with decreases of Cr and Zn, with significant increases of molybdenum compared to the control (Ajibola et al. 2014). This can confirm the fact that in inhabitants of Lower Silesia (Poland), diabetes and impaired fasting glucose were more common in men and the rural population (Zatońska et al. 2017).

The chromium, especially a water-soluble complex Cr, and niacin are co-factors for insulin and glucose tolerance. The content of Zn and Cr decreased in blood and scalp hair of diabetic patients of both genders (Kazi et al. 2008). Zn is utilized in the beta cells of the pancreas to release of insulin. Supplementation of Zn can lead to improvement in diabetics (Maanvizihi et al. 2014). Urinary Zn is associated with diabetes risk (Feng et al. 2015). In metabolic syndrome, Zn is increased in erythrocytes and decreased in urine (Freitas et al. 2017). Mo could reduce the concentration of Zn in both the liver and muscle (Van Ryssen 1994). In this study, the antagonism of Mo/Cu was demonstrated. In another study, antagonistic interaction of Mo/Cu was associated with progress of diabetes complications (Flores et al. 2011). There was no difference in Zn/Fe correlation in diabetics (Badran et al. 2016). In another study, it was showed that increased levels of Cu, Fe, and Cu/Zn ratio and decreased levels of Zn correlated with the increased value of HbA1c in diabetics (Atari-Hajipirloo et al. 2016).

Table 6 Spearman correlation coefficients for metals found in femoral neck in men in according place of residence

Neck	Mo	Cr	Zn	Cu	Ni	Fe	Sr	Ba	Pb	Age
Men										Cities
Mo	x	0.14	−0.14	0.07	−0.11	−0.06	−0.18	−0.30	−0.44 ^a	0.22
Cr	−0.48 ^a	x	−0.30	0.37 ^a	0.26	0.17	−0.13	−0.20	−0.19	0.09
Zn	−0.27	−0.33	x	−0.27	−0.14	−0.26	0.35 ^a	0.16	0.30	−0.19
Cu	−0.28	0.34	−0.58	x	0.51 ^a	0.18	−0.18	−0.15	0.20	0.23
Ni	−0.29	0.16	−0.39	0.95 ^a	x	−0.22	0.29	−0.15	−0.04	−0.12
Fe	0.27	0.21	−0.94 ^a	0.70	0.52	x	−0.46 ^a	−0.14	−0.02	0.02
Sr	0.03	−0.52	0.89 ^a	−0.46	−0.21	−0.83 ^a	x	0.11	0.30	−0.43 ^a
Ba	0.33	−0.88 ^a	0.26	−0.49	−0.39	−0.20	0.26	x	0.04	−0.07
Pb	−0.35	−0.48	0.88 ^a	−0.28	−0.10	−0.70	0.76	0.39	x	0.04
Age	−0.33	0.21	−0.09	0.75	0.88 ^a	0.14	0.14	−0.54	0.03	x
Villages										

^a Statistically significant correlation

Fig. 1 A graphic illustration of Principal Components Analysis of contents of elements in femoral neck. Projection of the variables on the factor plane of the first two principal components for place of residence

Molybdenum and endocrine disease

It has been shown that in older women, Mo is released from the bones along with the increasing demineralization of bones with age. A potential Mo mechanism of action is the effect on the hormonal system by disruption of sex hormones and,

indirectly, on bone health (Lewis et al. 2016). A connection with men's endocrine system has also been found, showing interactions between Mo and low Cu or Zn and an inverse association between Mo and semen quality (Meeker et al. 2008). Potential deficiency of Zn and Mo can lead to esophageal cancer in some populations (Ray et al. 2012). In our

Fig. 2 A graphic illustration of Principal Components Analysis of contents of elements in femoral head. Projection of the variables on the factor plane of the first two principal components for place of residence

Fig. 3 A graphic illustration of Principal Components Analysis of contents of elements in femoral head of women and men. Projection of the variables on the factor plane of the first two principal components for place of residence

study, we observed several correlations between Mo and other metals, both positive and negative, which can confirm the role of this element in endocrine disease.

Oxidative stress process and Fe and Cu supplementation

In Upper Silesia, a significant correlation of 0.83 in cancellous bone and 0.51 in cortical bone (Brodziak-Dopierala et al.

2009) was found. However, Jurkiewicz et al. provide completely opposite data from Silesia (-0.57) (Jurkiewicz et al. 2004). Our data oscillate between -0.03 and -0.12 in the urban population and -0.36 in the rural population in the FN similarly with data from knee joint (Roczniak et al. 2017). There was a negative correlation of Zn/Cu in the blood of patients with diabetes and rheumatoid arthritis (Badran et al. 2016; Ullah et al. 2017). An imbalance of Zn/Cu content is linked with diabetes and diabetic complications (Hamasaki

Fig. 4 A graphic illustration of Principal Components Analysis of contents of elements in femoral neck of women and men. Projection of the variables on the factor plane of the first two principal components for place of residence

et al. 2016). The study showed a higher Zn/Cu ratio in serum in patients with knee osteoarthritis in comparison to controls (Yazar et al. 2005). Level of Cu in patients with osteoarthritis can be a marker of inflammation and oxidative stress. Similar correlations of elements involved in oxidative processes in cardiovascular metabolic diseases and osteoarthritis can be explained by the oxidative stress in both diseases.

Additionally, urban road dust was significantly enriched with Cr, Zn, and Fe compared to rural road dust (Apeagyei et al. 2011). Obesity among women is more common in rural areas than in cities (Stepaniak et al. 2016). In this study, there was no difference in the correlation of Fe with other metals like Zn, Cu, Cr, and Mo, depending on BMI as a factor. Correlation between the serum Cu concentration and age was not found

(Strecker et al. 2013). According to the age factor, in the bones, correlation between Cu content and the age is not demonstrated, although higher correlation coefficients of Cu/age can be seen in villagers.

Polish study showed a Zn/Fe correlation in the FH from patients living in city, for example -0.58 in Cracow and 0.06 in Silesia (Jurkiewicz et al. 2004) and 0.3 in Upper Silesia (Brodziak-Dopierala et al. 2009). In urban populations, hair samples demonstrated a small negative correlation (-0.05) (Chojnacka et al. 2005). In our study, Fe/Zn correlation in the FH was 0.41 in rural areas and 0.01 in urban areas; in the FN (a long-time marker turnover trace elements), correlation was negative for villagers (-0.36) and city-dwellers (-0.11). This may indicate disturbances in the course of these elements, regardless of the place of residence. In addition, studies on herbs demonstrated a higher Fe content in the rural population. Zn and vitamin A interact in regulating absorption of Fe (Graham et al. 2012). The population of pregnant women in urban areas less frequently exceeded consumption norms for vitamin A than in rural areas ($p < 0.05$) (Bojar et al. 2012). It is traced to a deficiency of Zn in the diet, which can lead to Fe deficiency (Graham et al. 2012).

An Australian study showed a positive correlation of Fe/Zn in premenopausal women (Lim et al. 2015). The explanation of this interaction may be zinc supplementation provided to upregulate hepcidin leading to decreased Fe absorption, while increased Fe uptake influences the level of Zn transporters and disturbs Zn action. Studies indicate that Zn/Fe interaction is dependent on the level of metals and their ratios (Bjørklund et al. 2017).

Only one study showed Fe/Cu correlation in the FH between 0.27 and 0.36 in industrialized Polish cities (Lodz, Cracow, Silesia). In this study, a higher significant correlation was related to the FN in villagers (0.54). Suliburska et al. reported lower consumption of Cu in the diet of villagers (Suliburska et al. 2012). The assessment showed that the Cu/Fe ratio was similar in the maternal vein with obesity and in controls, while significant differences were found in the Zn/Cu ratio, which was associated with oxidative stress (Al-Saleh et al. 2006).

Brodziak et al. showed no Fe/Cr correlation in industrial inhabitants of the Upper Silesia region (Brodziak-Dopierala et al. 2009). In our study, we found a positive correlation between the place of residence and type of bone. There is no evidence of Cr deficiencies in humans. Cr may disturb Fe absorption, decreasing the Fe reserve and linking to diabetes and heart disease (Prescha et al. 2014). However, supplementation of Cr did not influence the Fe level, independent of gender (Bjørklund et al. 2017). Those elements connect with oxidative stress but also sex, age, diet, physical condition, and pathological situation.

Nickel and oxidative balance

The contents of Cr and Ni in the femoral bone determine gender, smoking, and air pollution in the patient's place of

residence (Brodziak-Dopierala et al. 2011). Inhabitants of the Upper Silesian industrial area had much higher correlation of Ni/Cr compared to our results (Brodziak-Dopierala et al. 2009; Brodziak-Dopierala et al. 2011), which can be associated with smoking. In Poland, significantly more smokers are found among the residents of villages (Połtyn-Zaradna et al. 2016). Recent studies confirm the antioxidant properties of low concentration of Cr by activating enzymes that reduce Ni toxicity (Terpilowska and Siwicki 2018). A study of the endometrium in smoking women showed increases of endometrial content of Cd and Pb but not Ni (Rzymyski et al. 2014). In this study, the correlation was lower and fluctuated between 0.11 and 0.38 . The results are lower probably because the average number of cigarettes smoked was the lowest in western Poland (Lipowicz 2015). Additional Cr, Ni, and Pb contents in rook eggshells were higher in urban areas than in rural areas, suggesting pollution with these elements in cities (Orłowski et al. 2014). Similarly, the correlation was related to Ni/Cu as found by studies of Brodziak et al. (0.79 – 0.87) (Brodziak-Dopierala et al. 2009; Brodziak-Dopierala et al. 2011). In this study, the correlation was lower and fluctuated between 0.45 and 0.48 in urban residents and between 0.36 and 0.86 in rural residents, which may indicate a slight difference between the village and the city in pollution in the area of the study (Great Poland Voivodeship).

Another aspect of Ni and Fe may contribute to lipid peroxidation and oxidative stress (Terpilowska and Siwicki 2018). Ni is probably absorbed through transport with interaction of Fe found in the hemoglobin and participates in oxygen transport (Zambelli et al. 2016). In our study, Fe/Ni correlation was significantly positive in the FN of men and women from rural areas. This may be due to the fact that in Poland, people living in cities have more risk factors for atherosclerosis than those living in rural areas (Mierzecki et al. 2014).

According to Ni and Zn, interaction may stabilize the RNA structure, DNA, and ribosomal conformation and is an enzyme activator. Antagonistic actions Ni/Zn may result: Zn may cause Ni-induced toxicity in the liver. Ni–Zn supplementation led to decreased osteons (Martiniaková et al. 2009). Our study showed negative Ni/Zn correlation mainly in men, and the values were higher in rural areas, with the exception of the FH of men from villages. Low variation in exposure to nickel pollution between cities and villages in Wielkopolska may indicate higher nickel exposure in rural areas. This hypothesis can confirm the results of Ni accumulation with age only in men from rural areas.

Barium competes with calcium

Ba has a larger ionic radius than Ca and Sr, and incorporation of Ba may have similar effects as Sr on the formation of smaller and stronger bone minerals. Lower content of Ba had an influence on osteoporotic fractures, but this effect did

not show in deficiency of Sr or Zn. Aaseth et al. suggested that low Ba content may increase risk fracture, and Ba supplements may potentially have an effect on the treatment of osteoporosis (Aaseth et al. 2012). Some studies have shown lower BMD in rural women than urban women, although other data indicate no statistically significant differences in BMD between urban and rural populations (Filip and Zagórski 2001). Our study showed a positive Sr/Ba correlation regardless of place of residence. Ba may have a beneficial effect on bone strength like Sr. Ba competes with Ca, replacing it in chemical and physiological processes, particularly regarding the action of adrenal neurotransmitters (Kravchenko et al. 2014). The Ba content in the air is higher in cities, and its source is industrial pollution. The content of Ba in the bone decreases with age, as we confirmed in this study, and it is associated with the loss of bone mass in which the element accumulates. However, this decrease is lower in cities (minimum -0.15) compared to rural areas (-0.54). The greatest number of significant correlation coefficients was observed in rural areas. Synergic reactions of pharyngeal tonsils for boys from rural regions concerned Ba/Cr (0.91) (Nogaj et al. 2011). The most probable cause is exposure to Ba by pollution of the urban environment. In the case of facial bone, the level of Ba increased with the age of the subjects. Ba increased with age in bone and teeth (Fischer et al. 2014). In our study, Ba content decreased with age most statistically significantly in the FH of rural residents.

Strontium

Budis et al. showed a positive Fe/Sr correlation in the compact and cancellous bone in a predominantly urban population (Budis et al. 2014). In this study, Fe/Sr was significantly negative in the FN of men in urban and rural areas. In women, no significant correlation was observed between Sr or Fe in blood and BMD (Unfer et al. 2007). In men (prostatic gland), a statistically significant negative Zn/Sr correlation and positive Fe/Sr correlation were found (Zaichick and Zaichick 2014). Positive Sr/Zn correlation independent of place of residence agrees with our results (Zaichick et al. 2011). Moreover, previous research showed that Sr and Zn concentrations in bone decrease with age (Wang et al. 2008). In this study, these correlations were found only in the FN of the urban population, which may be related to the loss of bone mass with age.

Lead

A previous study showed that Pb increases with age, especially in the case of higher Pb exposure in the past (Bjermo et al. 2013). Our study showed that Pb increases in the FN with age only in villagers. This is probably related to a lower incidence of osteoporosis in the rural population.

Conclusions

We showed significant dissimilarity between people living in cities and in villages in terms of the five elements: Ni, Mo, Cr, Cu, and Zn. Ni and Pb increased and Ba decreased with age only in villagers. Sr decreased with age only in people living in cities. Mo/Cr correlation was negative in villagers. Mo/Pb correlation was higher in men than in women. We found highly positive Cu/Ni correlation in the FN. Differences in correlation of metal content in femoral bone between urban and rural populations can influence environmental factors (pollution) and age. In villagers, Fe/Zn correlation in the FH was more positive and negative in the FN; one of the reasons may be higher Fe content in the rural population. Trace mineral micronutrients like Fe, Zn, Cu, Mo, and Cr are essential for regulating inflammatory pathways. The contents of metals and their correlations in various tissues can therefore be treated as a marker of oxidative stress (as a long-term marker in bone), whereas there is no evidence of the effect of supplementation on oxidative stress. Positive correlation of Ni/Fe was significant in the FN of villagers independent of sex, and Ni/Zn correlation was found only in urban females in the FH.

Funding This project was partly financed by the National Science Center in Poland (MINIATURA 1 2017), under grant agreement no. DEC-2017/01/X/NZ5/00308.

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