



CHEMOMETRIC ANALYSIS OF RELATIONSHIPS BETWEEN BONE MINERAL DENSITY, COPPER, ZINC, MAGNESIUM AND TOTAL ANTIOXIDANT ACTIVITY IN WOMEN WITH DIFFERENT LOCALIZATION OF OSTEOPOROSIS

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ABSTRACT:

Aim: This experimental-statistical study aims to establish a relationship between serum concentrations of copper, zinc, magnesium, antioxidant activity (AOA), bone mineral density (BMD) in women with osteoporosis with different localization of the disease – hip/lumbar vertebrae.

Material/Methods: The study included menopausal and postmenopausal women. The concentration of biogenic elements in serum was determined using flame atomic absorption analysis. The results of radical scavenging activity in blood serum were obtained by experimental spectrophotometric ABTS test. Cluster analysis was used to provide new, compelling evidence of association and data comparison.

Results: Patient data, bone mineral density (BMD) and disease severity (osteopenia/osteoporosis) fell into different clusters due to differences in BMD by disease location. The data were divided into: *i*. hip and *ii*. lumbar vertebrae. We performed two hierarchical cluster analyses. In both: *i*. three identical statistically significant clusters were formed: K1(Mg/Zn/Cu); K2(AOA/T-score/age); K3(BMI/BMD/disease severity); *ii*. clear correlation was observed between BMD and disease severity. A relationship was found between BMD and RSA, AOA in patients with osteoporosis/osteopenia.

Factor analysis confirmed the clustering, forming three latent factors explaining >70% of the variance. Factor weights reveal differences in the influence of BMI and BMD: in the hip joint - positive load; in the lumbar vertebrae - negative. The graphic representation shows the specific position of zinc/age/AOA variables.

Conclusion: In the femur, age is associated with AOA, and in the lumbar vertebrae, with AOA and zinc. This proves the specific role of zinc: in the first case, it is associated with the mineral composition - copper/magnesium, and in the second - zinc/AOA.

Keywords: cluster analysis; bone density; hip and lumbar vertebrae; serum; biogenic elements; radical scavenging activity.

INTRODUCTION

Osteoporosis is a global health problem for menopausal and postmenopausal women. With age, plasma antioxidants significantly decrease and increasing oxidative stress alters the bone remodeling process, causing an imbalance between osteoclasts and osteoblasts and leading the skeletal system to the pathogenesis characterized by low bone mass [1].

With a reduced concentration of antioxidants in the body, chain radical processes begin with lipids, proteins and DNA molecules, resulting in aggressive oxygen species (ROS) and nitrogen species (RNS). The systemic imbalance between oxidants and reducers, the so-called oxidative stress, leads to irreversible changes and loss of function of molecules, cells and organs [2]. Oxidative stress disrupts bone remodeling and reduces bone density [3]. Antioxidant activity is increased in women with osteoporosis. This is thought to be a response of bone marrow stem cells to the higher concentration of oxidants by increasing antioxidant activity in patients compared to a control group of women without osteoporosis [4]. The reason for this is the fact that during the oxidative destruction of Cu, Zn-SOD, the protein is degraded and copper ions are released [5, 6]. Our previous study confirmed increased serum concentrations of the trace elements copper and zinc, with the Cu/Zn ratio corresponding to the severity of the disease [7]. The released copper ions are redox active and participate in secondary radical reactions and increasing antioxidant

activity in patients with osteoporosis. Increased radicals in the body impair bone homeostasis and reduce bone mineral density (BMD) [4, 8]. Conversely, BMD is positively affected by the addition of antioxidants to the diet of postmenopausal women [9, 10, 11].

On the other hand, researchers have shown that disruption of the homeostasis of redox-active metal ions such as Cu leads to uncontrolled production of ROS and RNS, which is the cause of oxidative damage to DNA, proteins and lipids [6]. Copper is an essential trace element for various biological processes, but in excess, it is toxic [12]. Redox-inert zinc is an essential component of proteins involved in biological defense mechanisms, and its depletion can enhance DNA damage [13]. Zinc has the following indirect roles in limiting oxidative damage to the body: protection against vitamin E depletion; stabilization of membrane structure; contribution to extracellular antioxidant enzyme structure; free radical scavenger [14].

Osteoporosis depends on many factors and requires multivariate statistical analysis to study the relationships between the various clinical indicators characteristic of this disease. Therefore, in our study, we applied multivariate statistical analysis to the data obtained from 59 patients. The aim was to clarify the relationship between bone density, the level of the biogenic elements copper, zinc, magnesium, iron, calcium and the level of antioxidant activity (AOA) in newly diagnosed patients with osteopenia and osteoporosis. After clustering the data, not two, but three clusters were formed, describing three different stages of bone metabolism disruption with different intervals in the variations of the studied indicators.

But surprisingly, bone density and disease severity (osteopenia or osteoporosis) did not fall into the same cluster. Our explanation for this is the large difference in bone density in different disease sites [15]. For a more precise analysis of the patient data, it is necessary to divide them into two groups (with reduced bone density of the hip and with reduced bone density of the lumbar vertebrae) and perform a cluster analysis of each of them.

The present study aims to classify, model, and interpret a clinical dataset of patients with reduced bone density in the hip and spine in order to discover reliable relationships between parameters and specific patterns, providing a basis for better prevention and treatment.

MATERIALS AND METHODS:

The present experimental-statistical study included menopausal and postmenopausal women without treatment or therapy for osteoporosis. Other criteria for selection of the studied individuals are: no parathyroid disease, kidney disease and diabetes; no systemic intake of Ca, Cu, Zn, Mg, Fe, P, vitamin D and collagen supplements. The studied groups of individuals are from the Sofia region and are not related by blood.

After determining BMD using the DEXA method, based on the T-score result, women were divided into

four groups: with reduced bone density of the hip; with reduced bone density of the lumbar vertebrae; with normal bone density of the hip; with normal bone density of the lumbar vertebrae. For each study participant (patients and controls), an analytical determination of the serum levels of copper, zinc, magnesium and AOA was performed.

Serum concentrations of the biogenic elements calcium, magnesium, copper and zinc were determined using a flame AAC Perkin-Elmer AAnalyst 300 under the appropriate conditions for each biogenic element - serum dilution, appropriate additives, current strength of the lamp used - source of monochromatic light, concentration of the water standard for calibration, instrumental parameters.

The serum AOA was determined by spectrophotometric ABTS-test. The method is based on spectrophotometric recording of the change in the absorption of the chromophore cation-radical ABTS^{•+} used in the system as a result of free-radical processes with substances with radical-scavenging activity. As a result, the concentration of the radical in the sample, the color intensity of the solution and the measured absorbance decrease. The decrease in absorbance corresponds to the RSA of the sample and accounts for the total antioxidant capacity of the serum.

The multivariate statistical methods used are:

- Hierarchical Cluster Analysis (HCA);
- K-means Precondition Clustering;
- Factor Analysis and Principal Component Analysis (PCA).

The input data were standardized to avoid the influence of the different dimensionality of the included parameters on the classification procedures. Therefore, the input data with specific dimensions was transformed into dimensionless data with a specific normal distribution with a mean of zero and a standard deviation of ± 1 . As a measure of data similarity, the Euclidean distances between them were used, and as a procedure for connecting parameters and objects - the Word method. In the resulting dendrogram, the significance of the clusters was determined using the Sneath test - cutting off the clusters at a height of 1/3 or 2/3 of the maximum in the graph, D_{max} .

The statistical analysis was performed with the Statistica 7.0 software product.

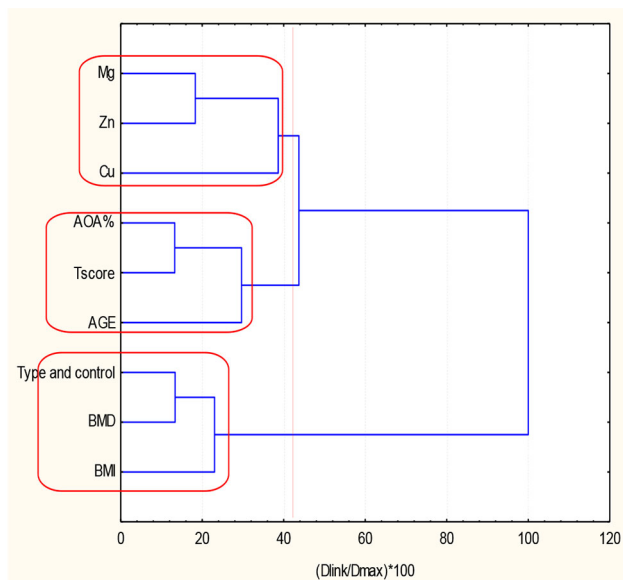
RESULTS:

In the first stage of the study, all women with measured hip BMD were included.

The output matrix for this specific case is of size [54 x 9] or 54 objects (patients and controls), described by 9 variables. Cluster analysis and principal component analysis were used to interpret the data.

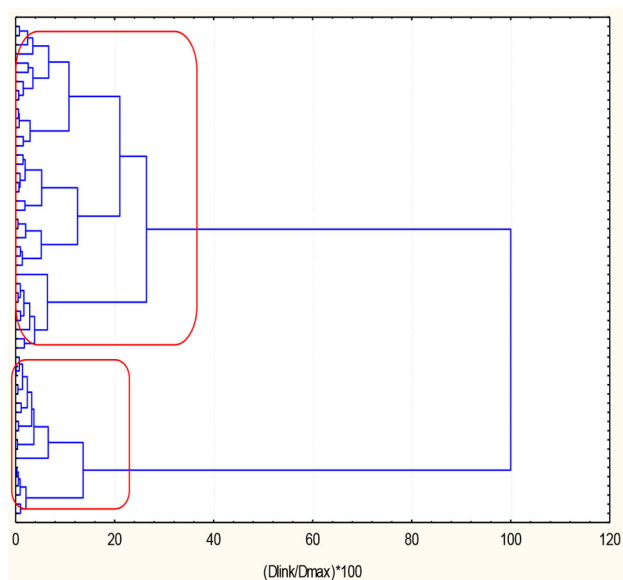
Fig. 1 presents the hierarchical dendrogram for clustering 9 variables (standardized data, squared Euclidean distance as a measure of similarity, Word's method for clustering and Sneath's test for cluster significance).

Fig. 1. Hierarchical dendrogram for clustering 9 variables 3 statistically significant clusters are formed: Cluster 1 (Mg, Zn, Cu) – this cluster illustrates the influence of mineral composition; Cluster 2 (AOA, T-score, age) – influence of AOA and age factor; Cluster 3 (BMI, BMD, type of disease and controls) – effect of body mass index and type of problem.



The following Figure 2 presents the hierarchical clustering diagram of 54 objects (patients with osteopenia and hip osteoporosis and controls).

Fig. 2. Hierarchical diagram for clustering 54 objects.



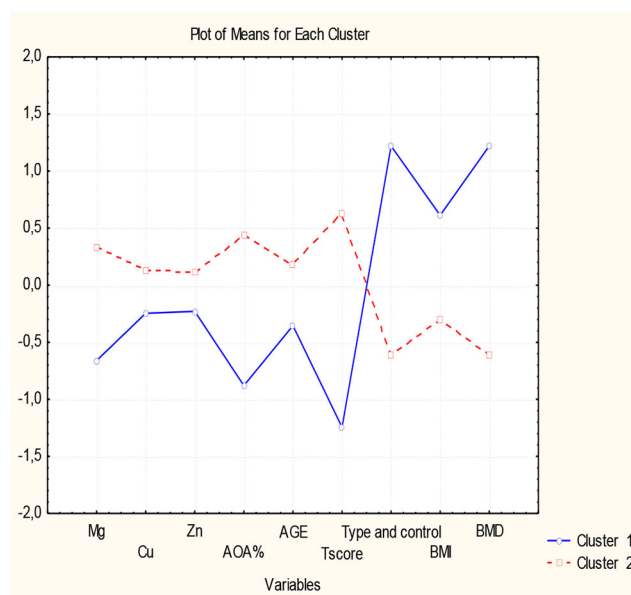
Two clusters are formed. The small cluster consists of 18 objects (numbers 37 – 54). It is formed by all objects – controls. The large cluster includes 36 objects with numbers 1 – 36 (all patients with the disease), 19 of which are coded 1 (osteopenia) and 17 with code 2 (osteoporosis).

An important stage in the study is the determination of the variables responsible for the identification of the two clusters (controls and patients). Fig. 3 presents a graph of the mean values of each variable (standardized output data) for each of the identified clusters. The specific features (descriptors) for the control cluster and the patient cluster can be easily determined.

The cluster of control subjects is characterized by low values of the components of the mineral composition (magnesium, zinc, copper), AOA, age and high values of T-score, disease code (code 3 for controls) and body mass index.

Conversely, the cluster of patients diagnosed with osteopenia or osteoporosis of the hip is characterized by high values of mineral composition components (magnesium, zinc, copper), AOA, age and low values of T-score, disease code (code 1 and 2 for patients) and body mass index. This is a logical result, suggesting that the disease affects older people with reduced BMD. Thus, we have three clusters of variables that fully correspond to the patients identified by decreased bone density in the hip. The first includes the mineral components, the second is an “age cluster”, and the third – a cluster of body mass indices and disease code.

Fig. 3. Plot of mean values (standardized output data) for each variable for each identified cluster (cluster 1 – controls, blue color; cluster 2 – patients, red color)



In the next stage of chemometric data processing, factor analysis was conducted to determine the latent factors responsible for the data structure. Table 1 presents the factor weights for identifying latent factors.

Three latent factors explain over 70% of the total variation of the system and can be interpreted as statistically significant.

The first latent factor explains over 35% of the total variance and includes high factor weights for variables related to body mass index and codes for controls and pa-

tient disease type. This factor can be conditionally called the “body mass index factor”, determining the influence of BMI and BMD on the nature of the health problem.

Table 1. Factor weights

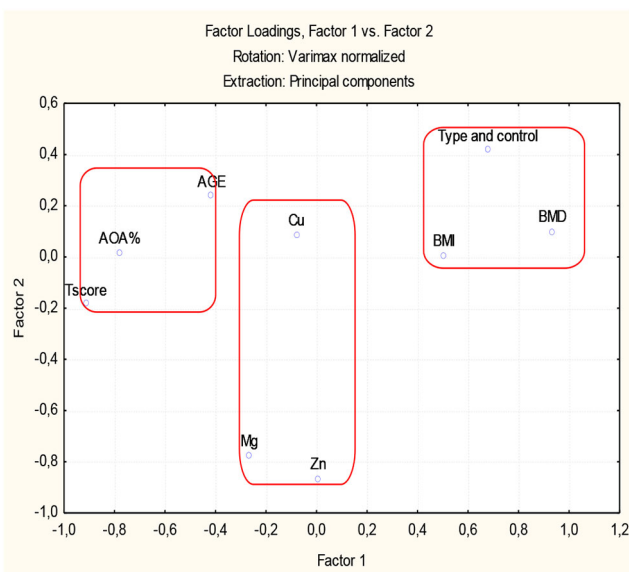
| Factor loadings (Varimax normalized) (marked loadings are > 0.7) | | | |
|--|--------------|---------------|--------------|
| Variables | Factor - 1 | Factor - 2 | Factor - 3 |
| Mg | -0.266 | -0.778 | -0.228 |
| Cu | -0.08 | -0.743 | -0.265 |
| Zn | 0.007 | -0.867 | 0.22 |
| AOA% | -0.379 | 0.015 | 0.768 |
| AGE | -0.418 | 0.242 | 0.705 |
| Tscore | -0.214 | -0.182 | 0.914 |
| Type and control | 0.778 | 0.42 | 0.113 |
| BMI | 0.703 | 0.004 | 0.496 |
| BMD | 0.933 | 0.099 | 0.148 |
| Expl.Var % | 36.4 | 20.2 | 16.8 |

The second latent factor explains over 20% of the total variation and can be conditionally called the “mineral composition factor” since it is associated with significant values of the three chemical (mineral) components in the list of variables.

The last (third) latent factor, explaining over 15% of the total variation of the system, is related to the age characteristic, the AOA and the T-score variable. It can be conditionally called the “age factor”.

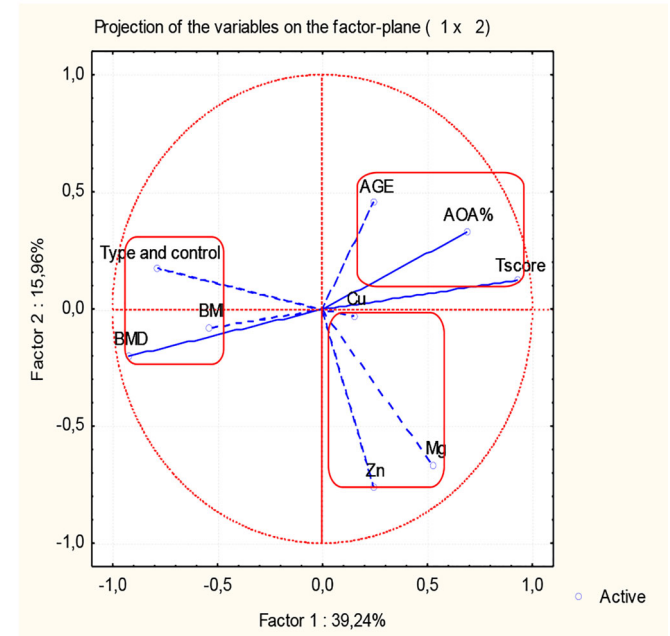
Graphically, the role of the three identified latent factors can be represented (for the factor1/factor2 plane) as follows (Fig. 4):

Fig. 4. Graph of the identified latent factors



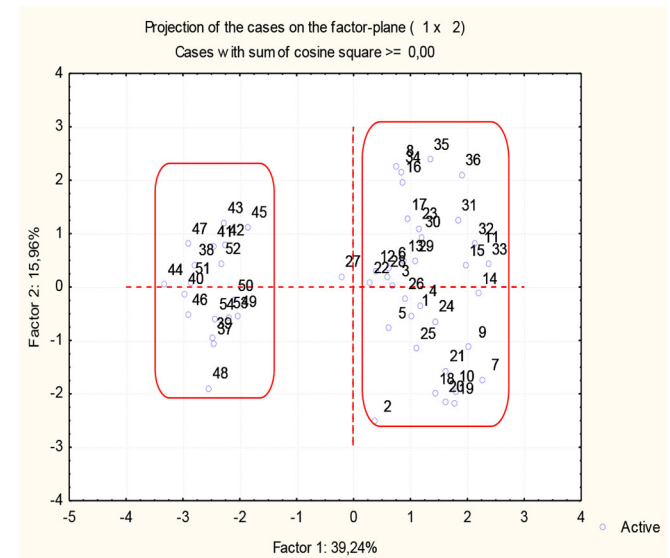
The additional conduct of the AGC to demonstrate the projections of the variables and objects in the factor 1/ factor 2 plane fully confirmed the results commented so far (Fig. 5 and Fig. 6).

Fig. 5 Projection of variables on the factor 1/factor 2 plane.



The three factors are clearly separated with the corresponding factor weights for the significant variables for each factor.

Fig. 6. Projection of objects in the same plane



The two clusters of similarity are convincingly separated – of patients with the disease (objects 1 – 36 on the right side of the graph) and of controls (numbered 37 – 54 on the left side). The only controversial object is number 27, which is very close to the patient group, but formally

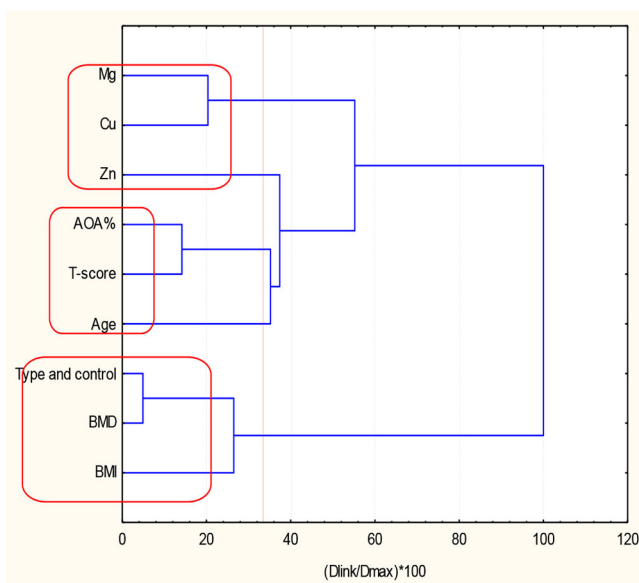
can also be attributed to the control group (although diagnosed with osteoporosis of the hip, it shows an unexpectedly high BMD value, which is closer to that of the control subjects than to those of the patient subjects).

In the second stage of the study, all women with measured lumbar spine BMD were included.

The initial matrix in this case has a dimension of 64 objects (patients with lumbar spine osteoporosis and controls), which are characterized by 9 variables (the same as in the cases of hip osteoporosis) or $[64 \times 9]$. The original data were standardized and subjected to cluster and factor (principal component analysis) analysis.

Fig. 7 presents the hierarchical dendrogram for clustering the nine variables (using a clustering algorithm, as in the hip cases).

Fig. 7. Hierarchical dendrogram for clustering 9 variables



Again, three clusters are formed with almost similar composition as in the hip cases. There is only one peculiarity – the place of zinc. Formally, it belongs to the cluster with participants AOA, age, and T-score; however, when choosing a different level of significance for the clusters, it can also be attributed to the cluster with copper and magnesium (mineral factor). Since the second option is more logical, we will use it in the interpretation. Thus, we have three clusters of variables that fully correspond to the patients identified by decreased bone density in the hip. The first includes the mineral components, the second is an “age cluster”, and the third – a cluster of body mass indices and disease code:

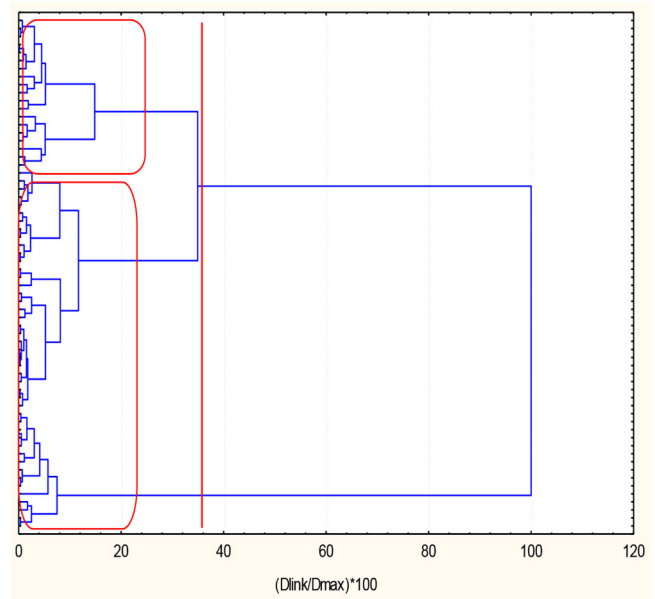
Cluster 1 (Mg, Zn, Cu) – “mineral” cluster

Cluster 2 (AOA, T-score, age) – influence of AOA and age cluster

Cluster 3 (BMI, BMD, type of disease and controls) – cluster of body mass indices and type of problem.

The following Figure 8 presents the hierarchical clustering diagram of 64 objects (patients with osteoporosis disease and controls).

Fig. 8. Hierarchical dendrogram for clustering 64 objects.

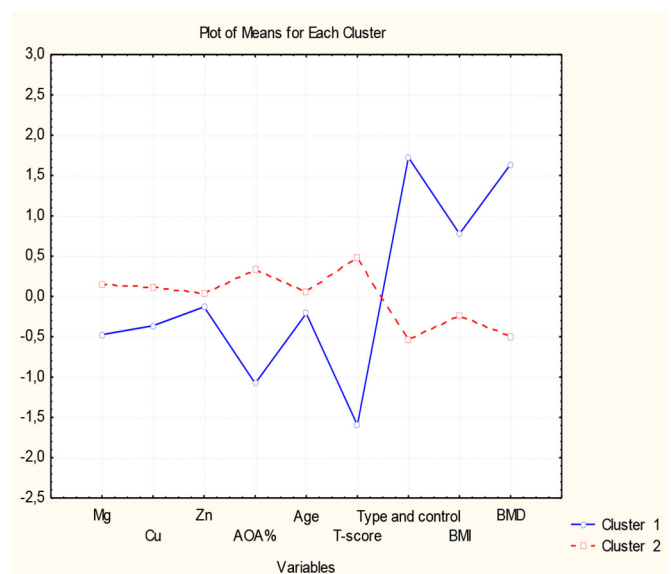


Two significant clusters are formed: A large cluster with 49 objects (object numbers 1 – 49, all with code 2 – osteoporosis); a Small cluster with 15 objects (object numbers 50-64, all coded 3 – controls).

The result is similar to that for patients with hip disease. Very good separation of controls from patients with the disease was obtained. It is logical to expect that this separation is due to the same specific factors as in cases of hip problems.

Fig. 9 presents a graph of the mean values of each variable (standardized output data) for each of the identified clusters. The specific features (descriptors) for the control cluster and the patient cluster can be easily determined.

Fig. 9. Graph of mean values (standardized baseline data) for each variable for each identified cluster (cluster 1 – controls, blue color; cluster 2 – patients, red color).



The cluster of control subjects is characterized by low values of the components of the mineral composition (magnesium, zinc, copper), AOA, age, and high values of T-score, disease code (code 3 for controls), and body mass index. Conversely, the cluster of patients diagnosed with osteopenia or osteoporosis of the lumbar spine is characterized by high values of the mineral composition components (magnesium, zinc, copper), AOA, age, and low values of T-score, disease code (code 2 for patients), and body mass index. This is a logical result, suggesting that the disease affects older people with reduced BMD.

The only minor differences with the cases for patients and controls from the “hip” sites are related to the zinc level and the age data. Here, the zinc levels for the two clusters are almost the same, and this also determines the controversial position of the “zinc” variable in the clustering of the variables. The mean values for the variable “age” in controls and diagnosed patients are very close. In the “hip” cases, controls are significantly younger than patients. In this sense, zinc and age indicators are not suitable descriptors for separating controls and patients diagnosed with vertebral osteoporosis.

In the next stage of the chemometric data processing, factor analysis was conducted to determine the latent factors responsible for the data structure. Table 2 presents the factor weights for the identified latent factors.

Table 2. Factor weights.

| Factor loadings (Varimax normalized) (marked loadings are > 0.7) | | | |
|--|---------------|---------------|--------------|
| Variables | Factor - 1 | Factor - 2 | Factor - 3 |
| Mg | 0.187 | -0.782 | 0.322 |
| Cu | 0.013 | -0.848 | -0.233 |
| Zn | 0.106 | 0.832 | 0.11 |
| AOA% | 0.048 | 0.12 | 0.722 |
| Age | -0.263 | 0.85 | 0.775 |
| T-score | 0.01 | -0.045 | 0.937 |
| Type and control | -0.908 | 0.229 | -0.027 |
| BMI | -0.542 | -0.027 | 0.142 |
| BMD | -0.931 | 0.116 | 0.029 |
| Expl.Var % | 38.5 | 19.7 | 16.2 |

Three latent factors explain almost 75% of the total variance of the system and can be interpreted as statistically significant. The first latent factor explains over 35% of the total variance and includes high factor weights for variables related to body mass index and codes for controls and patient disease type. This factor can be conditionally called the “body mass index factor”, determining the influence of BMI and BMD on the nature of the health problem.

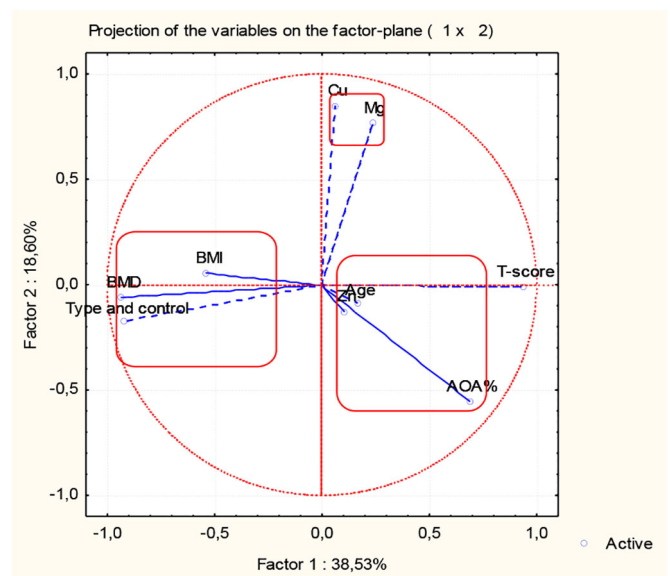
The second latent factor explains almost 20% of the total variation and can be conditionally called the “mineral composition factor” since it is associated with signifi-

cant values of the three chemical (mineral) components in the list of variables. The last (third) latent factor, explaining over 15% of the total variation of the system, is related to the age characteristic, the AOA and the T-score variable. It can be conditionally called the “age factor”.

These three hidden factors are responsible for the structure of the data in the studied system and can be summarized as “bone density”, “mineral composition” and “age”.

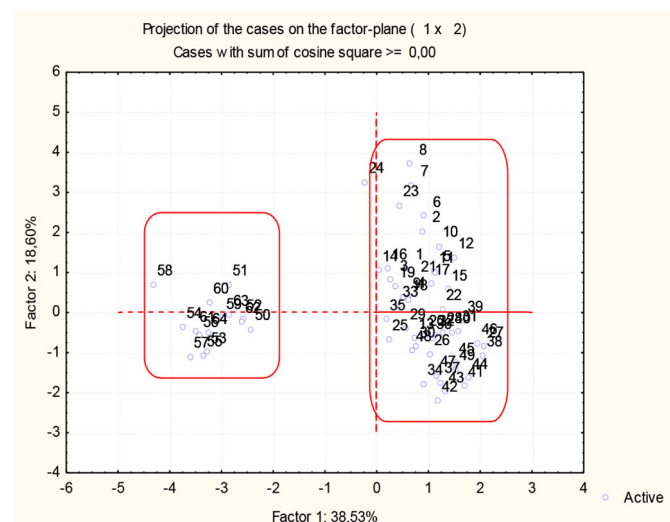
The graphical representation of the projection of the variables and objects on the factor 1/factor 2 plane (Figures 10 and 11) as a result of the principal components analysis very convincingly illustrates the results achieved with the other chemometric approaches.

Fig. 10. Projection of variables on the factor 1/factor 2 plane.



The three latent factors are clearly separated with the corresponding factor weights for the significant variables for each factor. The specific position of the variables zinc and age is also confirmed.

Fig. 11. Projection of objects in the same plane.



The two clusters of similarity are convincingly separated – of patients with the disease (objects 1 – 49 on the right side of the graph) and of controls (numbered 50 – 64 on the left side). The only controversial object is number 24, which is very close to the patient group, but formally can also be attributed to the control group (although diagnosed with osteoporosis of the spine, it shows an unexpectedly high value for copper, which brings subject 24 closer to the copper levels for controls than to those of the patient subjects).

CONCLUSIONS:

The main contributions from the two stages of the study considered – the first (women with measured hip BMD) and the second (women with measured lumbar spine BMD) can be summarized as follows:

Conclusions by variables

After hierarchical clustering of variables, three identical clusters are formed in both cases:

Cluster 1 (Mg, Zn, Cu) – “mineral” cluster; Cluster 2 (AOA, T-score, age) – influence of AOA and age cluster; Cluster 3 (BMI, BMD, type of disease and controls) – cluster of body mass indices and type of problem.

The results obtained are confirmed by the principal components analysis.

Factor analysis also confirms this clustering and forms them as three latent factors explaining over 70% of the total variance. From the obtained values of the factor weights of the identified latent factors, differences are established between the first and second cases. In the first case (femur), the “body fluid factor” that determines the influence of BMI and BMD has a positive loading, and in the second case (lumbar vertebrae), it has a negative loading. From the graphical representation of the three la-

tent factors, a specific position of the variables zinc, age, and AOA is visible. In the first case, age is associated with AOA, and in the second, it is associated with AOA and zinc. This proves the specific role of zinc, as in the first case, it is associated with the mineral composition – copper and magnesium, and in the second, a relationship between zinc and AOA is revealed. The additional conduct of principal components analysis convincingly confirms the above results by variables and objects in both cases.

Conclusions by objects

After hierarchical clustering of the objects in both cases, two clusters are formed: one comprising patients with reduced bone density and another comprising controls. The studied women are similarly convincingly separated after conducting a principal components analysis. An important stage of the study is determining the specific features (descriptors) for the control cluster and the patient cluster. They are identical in both cases, with the cluster with controls characterized by low values of mineral composition (Cu, Zn and Mg), AOA, age and high values of body mass indices (BMD and BMI), and the cluster with patients the opposite – high values of mineral composition, AOA, age and low values of body mass indices.

After performing multivariate statistical analyses in menopausal and postmenopausal women with different localization of reduced bone density and with normal bone density, we established specific correlations between the studied parameters.

A clear difference between patients and controls was deduced, and specific descriptors were identified. In the resulting models, specific parameter positions were found, which are interpreted for the first time in chemometric practice.

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