Accepted manuscripts are the articles in press that have been peer reviewed and accepted for publication by the Editorial Board of the Vojnosanitetski Pregled. They have not yet been copy edited and/or formatted in the publication house style, and the text could still be changed before final publication.

Although accepted manuscripts do not yet have all bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: article title, the author(s), publication (year), the DOI.

Please cite this article THE RELATIONSHIP BETWEEN INSULIN RESISTANCE, BONE MINERAL DENSITY AND FRACTURE RISK IN POSTMENOPAUSAL WOMEN

Authors Danijela Bazić Sretenović*, Mirjana Veselinovć*, Ivan Čekerevac*, Tamara Nikolić Turnić*, Anja Azanjac*, Aleksandra Koricanac†, Aleksandra Tomić Lučić*, Vojnosanitetski pregled (2021); Online First April, 2021.

UDC:

DOI: https://doi.org/10.2298/VSP210216041B

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appear in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.
THE RELATIONSHIP BETWEEN INSULIN RESISTANCE, BONE MINERAL DENSITY AND FRACTURE RISK IN POSTMENOPAUSAL WOMEN

Authors:

Danijela Bazić Sretenović*, Mirjana Veselinovć*, Ivan Čekerevac**, Tamara Nikolić Turnić†, Anja Azanjac***, Aleksandra Koricanac†, Aleksandra Tomić Lučić***

*University of Kragujevac, Serbia, Faculty of Medical Sciences, Department of Internal Medicine
※Clinic for Internal medicine, University Clinical Center Kragujevac, Kragujevac, Serbia
†Clinic for Pulmonology, University Clinical Center Kragujevac, Kragujevac, Serbia
⁂University of Kragujevac, Serbia, Faculty of Medical Sciences, Department of Clinical Pharmacy
‡Department of Internal Medicine, General Hospital Kraljevo, Serbia

Correspondence to:
Aleksandra Tomic Lucic, Full Professor, MD Ph.D.
Department of Internal medicine, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia;
Clinic for Internal medicine, University Clinical Center Kragujevac, Kragujevac, Serbia;
Address: Svetozara Markovica str. 69, 34000 Kragujevac, Serbia;
Phone: +381648065112; E-mail address: atomiclucic@gmail.com

All authors confirmed that the material has not been published or submitted for publication elsewhere.
INTRODUCTION
Skeletal muscle is a vital tissue that supports body posture and is also the primary glucose uptake site after a meal. Skeletal muscle is significantly related to insulin resistance\(^1\). The connection between bone strength or mineral bone density and insulin resistance is very complex\(^2\). According to the study, when the inflammatory response is inadequate, as in the case of aging muscles, acellular fat droplets and adipocytes tend to accumulate, so the development of insulin resistance may be the inflammatory response of the muscles\(^3\). This results in the secretion of different cytokines, chemokines, and adipocytes, which affects insulin resistance\(^1,3\).

The World Health Organization has defined natural menopause as the least twelve consecutive months of amenorrhea, not physiologic and pathological causes. According to statistics, the mean age of natural menopause is 51 years in industrialized nations, compared to 48 years in low and non-industrialized nations\(^1\). With the average life span extended to 70 years, most women will spend more than one-third of their life beyond the menopausal transition. Besides, the proportion of menopausal women is rising since the aging population is expanding rapidly.

A significant number of studies, on the other hand, studies discuss the impact of reduced muscle mass on bone mineral density and the consequences that result from them, in the first place, a higher incidence of osteoporotic fractures\(^4\). It is known that muscle mass and osteoporosis, and metabolic disorders are closely related. However, data on the association of muscle properties, bone mass, and insulin resistance are lacking\(^5\). Besides, few of them talk about the association of bone mineral density, muscle mass, and insulin resistance in postmenopausal women, especially in women in Serbia.

The key goal of this study was to determine the effects of insulin resistance on bone mineral density and fracture risk and evaluate the relationship between muscle properties (muscle mass, muscle strength, and physical performance) and bone mineral density and insulin resistance in postmenopausal women in Serbia.

METHODS

Ethical concerns
The protocol, as well as the study procedures, were approved by the ethics committee, the Clinical Center in Kragujevac (number 01/17-3765), and the Faculty of Medical science, University of Kragujevac (number 01-15581/3-6) from November 2017 to June 2018.

**Study design**

The study was conducted at the Clinical Center Kragujevac, the reference healthcare institution for osteodensitometry in the region of central Serbia. The study was designed as a clinical, non-interventional, observational, cross-sectional study and included 66 women over 65 years of age who were selected through random sampling. Participants were divided into two groups and based on the HOMA-IR limit values as used in the study by Nikolic et al. 6. The cut-off value for participants from the group "Low HOMA-IR" was <2, and for those from the group "High HOMA-IR," the values of insulin resistance were > 2. Among the study participants were 44 women with osteoporosis (T score <2.5) and 22 women with normal bone mineral density or osteopenia (T score ≥-2.5, without fracture data).

**Inclusion and exclusion criteria**

The inclusion criteria were confirmed as a menopause of at least five years based on no menstruation. None of the participants had the following diseases that affect bone mineral density such as hyperthyroidism, hyperparathyroidism, renal failure, malabsorption syndrome, chronic colitis, multiple myeloma, leukemia, chronic arthritis, DM, or previous use of therapy that interfere with bone metabolism (e.g., glucocorticoids, heparin, warfarin, thyroxin, and estrogen). Also, the exclusion criteria were cigarette smoking, alcohol intake, BMI> 30kg/m^2, and <19kg/m^2, respectively. Before joining the study, all participants confirmed their participation in it with their own signatures.

**The insulin resistance**

Index expressed as HOMA-IR was calculated using the following equation, as described by Matthews et al.: HOMA-IR=[glucose (mg/dL)×insulin (μU/mL)]/405 for each participant^7. Due to its simplicity and calculation, the most commonly used technique in clinical practice but also in epidemiological studies for the assessment of insulin resistance was the homeostatic test (HOMA-IR)^7.

**Osteodensitometric, anthropometric, and body composition measurements**
Bone Mass Density (BMD; g/cm²) was measured on the lumbar spine (LS) in the region L1-L4 and total hip in all participants. The measurement was done with a densitometer with X-ray energy absorption (DXA) (QDR 4500, Hologic Model Discoveri Inc., Waltham, MA). Participants did not wear metal items (for example, clips, belts, brassieres, jewelry) and shoes. There were instructed to be motionless during the scan. Daily standardized quality control of DXA instruments was performed using the manufacturer's phantom spine before the start of the study. The definition of osteopenia and osteoporosis was made using the World Health Organization (WHO) -2.5 < T-score < -1 and T-score -2.5, respectively. Body weight and height were obtained from the mean of three measurements. The accurate and precise values of these body composition parameters were also estimated from the DXA scan of the total body, which included BMC (bone mineral content), LM (lean mass), and FM (fat mass).

Following the manufacturer's guidelines, all scans were obtained and analyzed by the same experienced operator. Muscle strength was measured using the handgrip test (HGT) dynamometer and is closely related to the muscle strength of the lower extremities. In our study, the Jamar dynamometer was used, which is small, portable, and easy to handle. It was considered a reduced muscle strength HGT <16kg. To measure physical performance, we use the walk's speed test at a distance of 4 m (gait speed-GS). Physical ability is considered to be reduced when the gait speed is <0.8m / s for 4m.

Fracture risk

FRAX algorithm was used to calculate the probability of major osteoporotic fractures and hip fracture ((www.Sheffield.ac.Uk/FRAX/), using data specific to our country. FRAX Index 1 represented the probability of a major osteoporotic fracture (clinical fracture of the spine, forearm, hip, or shoulder), while FRAX Index 2 represents the probability of hip fracture.

Statistical analyses

IBM SPSS version 20 (IBM Company, Armonk, NY) was used for all statistical analyses. The outcome variables used were BMD of the whole body and at skeletal sites. The sample size was calculated using G*Power software version 3.1, and 66 subjects were required for a 90% power and 5% for the t-test. The cases and controls were distributed between two groups. The values of all variables for the whole body and regional sites were presented as mean (M) – standard deviation (SD). Comparison of mean values
between two groups of subjects, those with osteoporosis and those with normal bone mineral density/osteopenia, are classified according to their spine, bones, and BMD of the entire body, as well as weight, height, BMI, LM, FM, total weight and body fat. Correlation analyses of the whole body, regional sites BMD, and T-scores with the independent variables such as weight, LM, FM, and BMD were performed to obtain the Pearson's correlations. We use stepwise multiple linear regression analysis to obtain determinants/predictors for the outcome variables. All p-values were reported significant at 0.05 or less\textsuperscript{16}.

RESULTS

Comparison of Anthropometric parameters between High HOMA-IR and Low HOMA-IR Groups

The average values and standard deviations/standard errors of means of the examined parameters according to the level of HOMA-IR are shown in Table 1. Body mass index, waist size, Lean Mass, Fat mass, Total mass, and Lean+BMC were significantly different in Low-HOMA-IR and High-HOMA-IR groups (p<0.05). Other tested parameters were not significantly different in these groups (Table 1).

Baseline anthropometric and demographic characteristics of the study population

The average age of participants was 71.20±4.72 years, with the range being 65 to 83. For women with normal bone mass/osteopenia, the mean age was (±SD) 70.91 ± 4.97 years, while the mean age for women with osteoporosis was 71.34 ± 5.09 (Table 2).

Correlation analysis between Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and BMD and Muscle Parameters and between Body Composition Parameters, Bone Mineral Density (BMD)
In the study population, regarding their BMD values, LM was shown to have a higher degree of positive correlation with BMD on the lumbar spine (\( \beta = 0.418, p<0.001 \)) but also had a significant effect on the hip (\( \beta = 0.416, p<0.01 \)). In contrast, FM showed a high degree of positive correlation with both BMD at the hip (\( \beta = 0.473, p<0.001 \)) and the lumbar spine (\( \beta = 0.480, p<0.001 \)).

In this study, the results showed a significant degree of a positive correlation between HGT and bone mineral density of the hip (\( \beta = 0.331, p<0.01 \)) and spine (\( \beta = 0.243, p<0.05 \)), whereas GS was only correlated with bone mineral density on the hip (\( \beta = 0.268, p<0.05 \)). (Table 3).

A positive correlation was confirmed between HOMA-IR and fat mass (\( \beta = 0.322, p<0.05 \)) and total mass (\( \beta = 0.287, p<0.05 \)). However, there was no correlation between HOMA-IR and lean mass (\( \beta = 0.163, p > 0.05 \)). (Table 4). A significant degree of positive correlation was obtained between HOMA-IR and body mass index (\( \beta = 0.381, p<0.01 \)) and waist circumference (\( \beta = 0.405, p = 0.001 \)). A high degree of positive correlation was also observed between HOMA-IR and bone mineral density on the spine (\( \beta = 0.362, p = 0.01 \)) and the T score of the spine (\( \beta = 0.359, p = 0.01 \)). Besides, a correlation was also shown between HOMA-IR and hip bone mineral density (\( \beta = 0.264, p<0.05 \)) and T score hip (\( \beta = 0.305, p<0.05 \)). In the study, no correlation was confirmed between insulin resistance and muscle strength, measured by handgrip, and physical performance measured by gait speed (Table 4).

Univariate linear regression model of analysis between HOMA-IR and BMD parameters, DXA scores, and Blood markers in postmenopausal women

Univariate regression analysis with HOMA-IR as the dependent variable showed marginally significant associations between HOMA-IR and lumbar spine BMD (\( p = 0.055 \), stand. beta coefficient = 0.311), which means that an increase of HOMA-IR will lead to an increase of values of BMD of the spine (Table 5). Also, univariate regression analysis confirmed the association between HOMA-IR and changes of T-score of the spine (\( p = 0.009 \), stand. beta coefficient = 0.387) (Table 6). Regarding to the significance of blood markers as a predictors, we statistically confirmed the significance of Insulin level (\( p = 0.000 \), stand. beta coefficient = 0.241), Glucose level (\( p = 0.000 \), stand. beta coefficient = 0.241),
0.350) and inversely associated with marginally significance of fT4 levels (p = 0.071, stand. beta coefficient = -0.027) (Table 7).

Considering that the association between other tested parameters and HOMA-IR appears to be statistically insignificant in univariate linear regression analysis, other variables are not recognized as a predictor of changing HOMA-IR values in postmenopausal women (Tables 5-7).

**Comparison of Anthropometric parameters between women with osteoporosis and women with normal to osteopenic bone mass**

No significant difference was observed (p = 0.935) in age between women with osteoporosis (M = 69.5) and women in group with normal bone mass/osteopenic (M = 70). All participants were postmenopausal. The subjects' mean BMI was 26.11kg / m² and ranged from 15.6 to 35.6 kg /m². The mean BMI for women with normal BMD/osteopenia is 15% higher (28.57 kg/m²) than in women with osteoporosis (24.88kg/m²) (p<0.001). The group of women with normal BMD/osteopenia has an 18% higher body mass (p<0.001), 13% more LM (p<0.001), and even 30% more FM (p<0.001). This group of women has about 9% more LMI (p=0.003) and about 25% more FMI (p=0.001). HOMA-IR had a mean of 1.92 in the subjects and ranged from 0.2 to 6.7. HOMA-IR values were 1.56 in the subjects with osteoporosis and 2.68 in the group with normal BMD / osteopenia (Table 3).

**DISCUSSION**

The association between muscle properties, bone mineral density, and insulin resistance in this study was evaluated based on body composition parameters, muscle strength, and physical performance. Based on these parameters, we provide clinical evidence that body composition changes, muscle strength, and physical performance are associated with decreased bone mineral density. Also, adipose tissue accumulation and an increase in total mass are closely related to insulin resistance. Finally, we confirmed the association between bone mineral density and insulin resistance in postmenopausal women in Serbia.
Fat mass is a significant source of proinflammatory cytokines that mediate bone metabolism, and postmenopausal women tend to accumulate visceral fat. Some authors reported in their studies the independent effect of fat mass on BMD over estrogens, insulin, and leptin\textsuperscript{16,18}. It was also observed that the relative contribution of body composition parameters to BMD depends on gender, ethnicity, and age\textsuperscript{19}.

Ho-Pam et al.\textsuperscript{8}, in their study, state that lean mass and fat mass are significant precursors to bone mineral density. Our study results are consistent with the fact that a positive correlation was obtained between lean mass and fat mass and BMD on the hip and spine. Several studies have suggested a positive correlation between HGT and BMD in elderly people\textsuperscript{18}, whereas some studies have suggested the opposite\textsuperscript{19}. Our study is consistent with the study that revealed a significant positive correlation between muscle strength and BMD. The results showed that the handgrip test (HGT) had a high degree of positive correlation with the BMD of the hip and a significant positive correlation with the BMD of the lumbar spine. Although multiple physiological and psychological factors influence gait speed (GS), this is the most useful clinical practice test. It showed to be a significant predictor of health events in the elderly\textsuperscript{20}. Gait speed (GS) had the highest degree of positive correlation with hip BMD, which confirms that maximum gait speed can be a useful and specific test for predicting bone status in older postmenopausal women\textsuperscript{21}.

In the present study, lean mass, muscle strength, and physical performance were not associated with insulin resistance. In contrast, adipose tissue and bone mineral density on the hip, and especially on the spine, were significantly associated with insulin resistance: women with higher adipose tissue showed higher insulin resistance levels. Therefore, our study implies that the reduction of lean mass accompanied by its damage and the accumulation of adipose tissue contributes to insulin resistance development. Study results are in line with results reported by Hye-Sun Park et al. These authors state in their research that lean mass reduction with muscle damage and fat accumulation has a close positive relationship with developed insulin resistance\textsuperscript{22}. The relationship between BMD and insulin resistance has been studied in different populations, and mixed results have been obtained. Kalamari M. et al. in a study involving Caucasian postmenopausal women, a statistically significant positive association between hip bone mineral density and insulin resistance was demonstrated\textsuperscript{2}, which is consistent with our study results. The main predictors in changing the metabolic profile in postmenopausal women are lumbar spine BMD, T score of the
spine, fT4, insulin, and glucose levels. Study results are according to the results of the study Srikanthan et al. They confirmed the association between insulin resistance and strength femoral neck and suggested that obesity and hyperinsulinemia may not be bone-protective. They add just that to the growing body of evidence that points to the importance of measuring bone strength relative to load in assessing and understanding fracture risk. This is consistent with our results, which indicate that although it has been found that there is a positive correlation between insulin resistance and BMD, there is no correlation between insulin resistance and fracture risk. This means that women with higher insulin resistance levels and higher bone mineral density do not have a lower fracture risk.

Several studies have investigated the correlation between muscle parameters, fat accumulation, and insulin resistance. With aging, muscle mass is lost, muscle damage and fat accumulation occur. Specifically, the infiltration of muscle tissue by fat leads to the activation of apoptotic cells and the release of inflammatory cytokines and adipokines, leading to the development of insulin resistance. On this basis, the idea that local inflammation in the muscle followed by the accumulation of fat by secretion of cytokines and adipokines instead of a decrease in muscle strength and physical performance may have a more important role in the production of insulin resistance. In this regard, our results may provide clinical evidence to support the results of other studies.

CONCLUSION

These results suggest that lean mass and fat mass significantly affect BMD and muscle strength, and physical performance. Besides, a decrease in lean mass, muscle damage, and fat buildup has been associated with a higher incidence of insulin resistance in postmenopausal women. Finally, bone mineral density on the hip, and especially on the spine, was associated with the onset of insulin resistance. However, there is no correlation between insulin resistance and fracture risk. These results significantly contribute to understanding the changes that occur in the body with aging in these women.
Basic Anthropometric Characteristics of study population divided into Low-HOMA-IR and High-HOMA-IR groups.

| Parameters               | Groups         | N   | Mean       | Std. Deviation | Std. Error Mean | p values  |
|--------------------------|----------------|-----|------------|----------------|-----------------|-----------|
| Age (years)              | low-HOMA-IR   | 44  | 70.89      | 4.84           | 0.73            | 0.812     |
|                          | high-HOMA-IR  | 18  | 71.83      | 4.81           | 1.13            |           |
| Body height (cm)         | low-HOMA-IR   | 44  | 160.36     | 6.62           | 1.00            | 0.199     |
|                          | high-HOMA-IR  | 18  | 159.33     | 7.50           | 1.77            |           |
| Bodyweight (kg)          | low-HOMA-IR   | 44  | 64.45      | 9.77           | 1.47            | 0.071     |
|                          | high-HOMA-IR  | 18  | 72.56      | 14.80          | 3.49            |           |
| Body mass index (kg/m²)  | low-HOMA-IR   | 44  | 25.061     | 3.52           | 0.53            | 0.046     |
|                          | high-HOMA-IR  | 18  | 28.133     | 4.91           | 1.16            |           |
| Waist size (cm)          | low-HOMA-IR   | 44  | 77.64      | 11.41          | 1.72            | 0.008     |
|                          | high-HOMA-IR  | 18  | 92.28      | 19.57          | 4.61            |           |
| Lean mass (kg)           | low-HOMA-IR   | 44  | 3395.06    | 372.98         | 156.85          | 0.005     |
|                          | high-HOMA-IR  | 18  | 3573.09    | 583.04         | 137.43          |           |
| Fat mass (kg)            | low-HOMA-IR   | 44  | 2411.89    | 636.12         | 196.65          | 0.035     |
|                          | high-HOMA-IR  | 18  | 2981.78    | 994.23         | 234.87          |           |
| Total mass (g)           | low-HOMA-IR   | 44  | 62335.07   | 894.45         | 135.87          | 0.011     |
|                          | high-HOMA-IR  | 18  | 69759.96   | 1495.45        | 352.33          |           |
| Body fat (%)             | low-HOMA-IR   | 44  | 38132.66   | 587.67         | 189.56          | 0.483     |
|                          | high-HOMA-IR  | 18  | 41600.56   | 781.45         | 184.45          |           |
| Handgrip test (kg)       | low-HOMA-IR   | 43  | 12.40      | 9.14           | 1.39            | 0.954     |
|                          | high-HOMA-IR  | 17  | 14.29      | 8.31           | 2.01            |           |
| Gait speed (m/s)         | low-HOMA-IR   | 44  | 0.378      | 0.17           | 0.03            | 0.736     |
|                          | high-HOMA-IR  | 18  | 0.360      | 0.16           | 0.04            |           |
| Hip BMD (g/cm²)          | low-HOMA-IR   | 43  | 0.693      | 0.09           | 0.01            | 0.557     |
|                          | high-HOMA-IR  | 18  | 0.728      | 0.10           | 0.02            |           |
| Lumbar spine BMD (g/cm²) | low-HOMA-IR   | 44  | 0.756      | 0.10           | 0.01            | 0.179     |
|                          | high-HOMA-IR  | 18  | 0.825      | 0.13           | 0.03            |           |
The cut-off value for HOMA-IR was 2; Independent T-Test confirmed statistical differences for normally distributed data with the level of significance of 0.05;

HOMA-IR - Homeostatic model assessment - insulin resistance; BMD LH - Bone mineral density left hip; BMC - Bone mineral content.

**Comparison of Anthropometric parameters and Dual/Energy X/Ray absorptiometry (DXA) in a woman with normal BMD/osteopenia and a woman with osteoporosis.**

Table 2.

| Parameters                  | Woman with normal BMD/osteopenia (n=22) | Woman with osteoporosis (n=44) | p value |
|-----------------------------|----------------------------------------|-------------------------------|---------|
| Mean±SD                     |                                        |                               |         |
| Age (years)                 | 70.91±4.97                             | 71.34±5.09                    | 0.935   |
| Weight (kg)                 | 74.77±9.47                             | 63.41±11.25                   | 0.000   |
| Height (cm)                 | 161.77±4.68                            | 159.20±7.61                   | 0.096   |
| Body mass index (kg/m²)     | 28.57±3.47                             | 24.88±3.99                    | 0.000   |
| HOMA-IR*                    | 2.684±1.98                             | 1.566±1.13                    | 0.005   |
| Lean mass (g)               | 37513.73±4128                          | 33168.40±3979                 | 0.000   |
| Fat mass (g)                | 30973.18±6613                          | 23859.95±7593                 | 0.000   |
| Total mass (g)              | 72986.69±9162                          | 61197.15±10600                | 0.000   |
| Body fat (%)                | 42.10±4.98                             | 38.14±6.91                    | 0.020   |
| BMD LH (g/cm²)              | 0.78±0.06                              | 0.66±0.07                     | 0.000   |
| BMD Spine (g/cm²)           | 0.89±0.08                              | 0.72±0.07                     | 0.000   |
| Bone mineral content (g)    | 1790.69±227                            | 1510.26±272                   | 0.000   |
| Lean+ Bone mineral content (g) | 42013.52±4282                       | 37337.20±4269                 | 0.000   |
HOMA-IR - Homeostatic model assessment - insulin resistance; BMD LH - bone mineral density left hip.

**Correlation between bone mineral density (BMD) and Muscle Parameters**

Table 3.

| Parameters         | Hip BMD (g/cm²) | Spine BMD g/cm² |
|--------------------|-----------------|-----------------|
|                    | □ (SE) P-value  | □ (SE) P-value  |
| Lean mass (g)      | 0.416 0.01      | 0.418 0.001     |
| Fat mass (g)       | 0.473 0.000     | 0.480 0.000     |
| Handgrip test (kg) | 0.331 0.007     | 0.243 0.049     |
| Gait Speed (m/s)   | 0.268 0.031     | 0.232 0.061     |

The values are expressed as a Person correlation coefficient. The statistical significance is presented as *p<0.05; ** p<0.01; ***p<0.001
Correlation between Body Composition Parameters, Bone Mineral Density (BMD), and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR).

Table 4.

| Parameters                                    | \( \beta \) (SE) | HOMA-IR P-value |
|----------------------------------------------|------------------|-----------------|
| Lean mass (g)                                | 0.163            | 0.213           |
| Fat mass (g)                                 | 0.322            | 0.012*          |
| Total mass (g)                               | 0.287            | 0.026*          |
| Body mass index (kg/m\(^2\))                | 0.381            | 0.003**         |
| Waist circumference (cm)                     | 0.405            | 0.001**         |
| Hip BMD (g/cm\(^2\))                        | 0.264            | 0.043*          |
| Spine(L1-L4) BMD (g/cm\(^2\))               | 0.362            | 0.005**         |
| T score Hip                                  | 0.306            | 0.019*          |
| T score Spine                                | 0.359            | 0.005**         |
| Handgrip test (kg)                           | 0.031            | 0.815           |
| Gait Speed (m/s)                             | 0.121            | 0.356           |
| FRAX Index 1                                 | -0.070           | 0.588           |
| FRAX Index 2                                 | -0.111           | 0.389           |

The values are expressed as a Person correlation coefficient. The statistical significance is presented as *p<0.05; **p<0.01; ***p<0.001.

FRAX Index 1 - the probability of a major osteoporotic fracture (clinical fracture of the spine, forearm, hip, or shoulder); FRAX Index 2 - the probability of hip fracture.
Univariate linear regression analysis between HOMA-IR and hip BMD, femoral neck BMD and lumbar spine BMD.

Table 5.

| Variables                  | Unstandardized Coefficients | Std. Error | Standardized Coefficients | t   | Sig. | 95.0% Confidence Interval for B |
|----------------------------|-----------------------------|------------|---------------------------|-----|------|---------------------------------|
|                            | B                           |            | Beta                      |     |      | Lower Bound | Upper Bound |
| Hip BMD (g/cm²)            | 0.602                       | 3.315      | 0.036                     | 0.181 | 0.857 | -6.036 | 7.239     |
| Femoral neck BMD (g/cm²)   | 0.544                       | 3.128      | 0.032                     | 0.174 | 0.863 | -5.719 | 6.807     |
| Lumbar spine BMD (g/cm²)   | 4.334                       | 2.211      | 0.311                     | 1.960 | 0.055* | -.093  | 8.762     |

HOMA-IR- Dependent variable; Predictors: (Constant), Lumbar spine BMD (g/cm²), Femoral neck BMD (g/cm²), Hip BMD (g/cm²);

β- standardized β-coefficient; Sig- significance level; B-coefficient of the model.
Univariate linear regression analysis between HOMA-IR and T and Z score (hip and spine) and Fracture risk (FRAX 1 and 2).

Table 6.

| Variables          | Unstandardized Coefficients | Std. Error | Standardized Coefficients | t     | Sig. | 95.0% Confidence Interval for B |
|--------------------|-----------------------------|------------|---------------------------|-------|------|-------------------------------|
|                    | B                           | Beta       |                           |       |      | Lower Bound | Upper Bound |
| T score (hip)      | .136                        | .066       | .095                      | .924  | -2.732 | 3.005                      |
| Z score (hip)      | .578                        | .274       | .680                      | -2.218 | 3.373 |
| T score (spine)    | .588                        | .387       | .429                      | .009* | -2.156 | 3.332                      |
| Z score (spine)    | -.234                       | -.154      | -.169                     | .867  | -3.011 | 2.544                      |
| FRAX-1             | .073                        | .287       | .594                      | .555  | -.172 | .317                       |
| FRAX-2             | -.027                       | -.062      | -.114                     | .910  | -.509 | .454                       |

Dependent Variable: HOMA-IR, Predictors: (Constant), T and Z score (hip and spine), Fracture risk (FRAX Index 1 and 2 / FRAX Index 1 - the probability of a major osteoporotic fracture (clinical fracture of the spine, forearm, hip or shoulder); FRAX Index 2 - the probability of hip fracture); $\beta$ - standardized $\beta$-coefficient; Sig - significance level; B - coefficient of the model.
### Table 7.

| Variables          | Unstandardized Coefficients | Standardized Coefficients | t  | Sig.  | 95.0% Confidence Interval for B |
|--------------------|-----------------------------|---------------------------|----|-------|---------------------------------|
|                    | B                           | Std. Error                | Beta |       | Lower Bound | Upper Bound |
| Vitamin D (ng/ml)  | -.002                       | .002                      | -.015 | -1.021 | .313             | -.006       | .002       |
| Somatotropin (ng/ml) | -.011                       | .010                      | -.015 | -1.143 | .259             | -.031       | .009       |
| IGF (ng/ml)        | .000                        | .001                      | -.005 | -1.367 | .715             | -.002       | .001       |
| TSH (mlU/l)        | .029                        | .021                      | .019  | 1.407  | .166             | -.013       | .071       |
| fT4 (pg/ml)        | -.013                       | .007                      | -.027 | -1.852 | .071             | -.028       | .001       |
| TgAt (IU/ml)       | .095                        | .000                      | .010  | .717   | .477             | .000        | .000       |
| TPOAt (IU/ml)      | .078                        | .000                      | -.007 | -1.486 | .630             | .000        | .000       |
| PTH (pg/ml)        | -.001                       | .001                      | -.011 | -1.767 | .447             | -.003       | .001       |
| Insulin (ulU/ml)   | .248                        | .004                      | .925  | 65.560 | .000**           | .241        | .256       |
| Glucose (mmol/l)   | .414                        | .032                      | .186  | 13.112 | .000**           | .350        | .477       |

**Dependent Variable:** HOMA-IR, **Predictors:** (Constant), Glucose (mmol/l), Vitamin D (ng/ml), Somatotropin (ng/ml), TPOAt (IU/ml) – anti-thyroid peroxidase antibodies, TSH (mlU/l) - thyroid-stimulating hormone, fT4 (pg/ml) - free thyroxine, TgAt (IU/ml), IGF (ng/ml) - insulin growth factor, Insulin (ulU/ml), PTH (pg/ml) - parathyroid hormone.

β - standardized β-coefficient; Sig - significance level; B-coefficient of the model.
REFERENCES

1. *DeFronzo RA, Tripathy D*. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care 2009;32; 2:S157-63.

2. *Kalamari M, Leek F, Wang NX, Koh HR, Roy NC, Cameron-Smith D et al*. Association of Insulin Resistance with Bone Strength and Bone Turnover in Menopausal Chinese-Singaporean Women without Diabetes. Int. J. Environ. Res. Public Health, 2018, 15, 889.

3. *Sciorati C, Rigamonti E, Manfredi AA, Rovere-Querini P*. Cell death, clearance and immunity in the skeletal muscle. Cell Death Differ 2016;23:927-37.

4. *Hamrick MW*. The skeletal muscle secretome: an emerging player in muscle-bone crosstalk. Bone key Rep 2012;1:60.

5. *Shanbhogue V.V, Finkelstein J.S, Bouxsein M.L, Yu EW* Association between insulin resistance and bone structure in nondiabetic postmenopausal women. J. Clin. Endocrinol. Metab. 2016, 101, 3114–3122.

6. *Nikolić S, Ćurić N, Mijović R, Ilinčić B, Ben D*. Significance and role of homeostatic model assessment in the evaluation of glucose regulation mechanisms. Med Pregl 2017; LXX (5-6): 155-161.

7. *Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC*. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28:412-9.

8. *Ho-Pham LT, Nguyen ND, Lai TQ, Nguyen TV*. Contributions of lean mass and fat mass to bone mineral density: a study in postmenopausal women. BMC Musculoskeletal Disorders. 2010. DOI:10.1186/1471-2474-11-59.

9. *Jiang Y, Zhang Y, Jin M, Gu Z, Pei Y, Meng P*. Aged-Related Changes in Body Composition and Association between Body Composition with Bone Mass Density by Body Mass Index in Chinese Han Men over 50-year-old. PLoS ONE. 2015; 10(6).

10. *Roberts HC, Denison Hj, Martin HJ, Patel HP, Syddall H, Cooper C, et al*. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardized approach. Age and Ageing. 2011; 40(4): 423–429.
11. Mathiowetz V. Comparison of Rolyan and Jamar dynamometers for measuring grip strength. Occup Ther Int. 2002; 9(3): 201–209.

12. Beaudet C, Rolland Y, Cruz-Jentoft AJ, Bauer JM, Sieber C, Cooper C et al. Assessment of muscle function and physical performance in daily clinical practice. Calcif Tissue Int. 2019. DOI:10.1007/s00223-019-00545-w

13. Hars M, Biver E, Chevalley T, Herrmann F, Rizzoli R, Serge Ferrari et al. Low lean mass predicts incident fractures independently from FRAX: a prospective cohort study of recent retirees. JBMR. 2016; 31(11): 2048–2056. DOI:10.1002/jbmr.2878

14. Lippuner K, Johansson H, Kanis JA, Rizzoli R. FRAX assessment of osteoporotic fracture probability in Switzerland. Osteoporosis Int. 2010; 21(3): 381–9. DOI:10.1007/s00198-009-0975-1

15. Liu PY, Ilich JZ, Brummel-Smith K, Ghosh S. New insight into fat, muscle, and bone relationship in women: determining the threshold at which body fat assumes a negative relationship with bone mineral density. Int J Prev Med. 2014; 5(11): 1452–1463.

16. Ijuin M, Douchi T, Matsuo T, Yamamoto S, Uto H, Nagata Y. Difference in the effects of body composition on bone mineral density between pre-and postmenopausal women. Maturitas. 2002; 43(4): 239–244.

17. Schaap LA, Koster A, and Visser M. Adiposity, muscle mass, and muscle strength in relation to functional decline in older persons. Epidemiol Rev. 2013; 35:51–65.

18. Kim S.W, Lee H.A, Cho E.H. Low handgrip strength is associated with low bone mineral density and fragility fractures in postmenopausal healthy Korean women. J Korean Med Sci. 2012; 27(7): 744-747.

19. Bayramoglu M, Sozay S, Karatas M, Kilinc S. Relationships between muscle strength and bone mineral density of three body regions in sedentary postmenopausal women. Rheumatol Int. 2005; 25(7): 513-517.

20. H. Lundin, M. Sääf, L.-E. Strender1, S. Nyren, S.-E. Johansson1, H. Salminen. Gait speed and one-leg standing time each add to the predictive ability of FRAX. Osteoporos Int. 2017; 28: 179–187.
21. Sakazaki T, Koike T, Yanagimoto Y, Oshida Y. Association between gait speed and bone strength in community-dwelling postmenopausal Japanese women. Environ Health Prev Med. 2012; 17(5): 394–400.

22. Park HS, Lim JS, and Lim SK. Determinants of Bone Mass and Insulin Resistance in Korean Postmenopausal Women: Muscle Area, Strength, or Composition? Yonsei Med J 2019;60(8):742-750

23. Srikanthan P, Crandall C.J, Miller-Martinez D, Seeman T.E, Greendale G.A, Binkley N. et al. Insulin resistance, and bone strength: Findings from the study of midlife in the United States. J. Bone Miner. Res. 2014, 29, 796–803.

24. Chapman NM, Chi H. Dietary fat inflames CD4+ T cell memory in obesity. Cell Metab 2017;25:490-2.

25. Mauro C, Smith J, Cucchi D, Coe D, Fu H, Bonacina F, et al. Obesity-induced metabolic stress leads to biased effector memory CD4+ T cell differentiation via PI3K p110δ-Akt-mediated signals.Cell Metab 2017;25:593-609.

Received on February 16, 2021.
Accepted March 23, 2021.
Online First April, 2021.