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ASSOCIATION OF INSULIN RESISTANCE WITH BONE MINERAL DENSITY AND FRACTURE RISK IN NON-DIABETIC POSTMENOPAUSAL WOMEN

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Abstract. *There is conflicting literature evidence regarding the independent effects of insulin resistance and concomitant hyperinsulinemia on bone mineral density. In addition, it is still under debate whether the net effect is favorable or unfavorable for the fracture risk. Therefore, we conducted a cross-sectional study.* ***Aim:*** *To assess the correlation between bone mineral density and fracture risk with insulin resistance and circulating insulin levels in non-diabetic postmenopausal women.* ***Materials and methods:*** *The study analyzed 84 women. The mean age of the participants was 60.54 ± 7.07 years, and the mean postmenopausal period was 11.45 ± 6.62 years. A standard oral glucose tolerance test was performed with measurement of blood glucose and insulin levels at 0 and 120 min. Dual-energy X-ray absorptiometry was used to determine bone mineral density at lumbar spine and proximal femur. Fracture risk was calculated using the Fracture Risk Assessment Tool.* ***Results:*** *We found that in non-diabetic postmenopausal women lower basal insulin levels (fasting insulin) were associated with a higher 10-year risk of major osteoporotic fracture when insulin sensitivity was preserved (HOMA-IR index < 2). Fasting insulin levels under 6.15 μIU/ml were considered high-risk regarding the fracture risk. On the other hand, higher stimulated insulin levels at 120 min (post-load insulin) were associated with a higher 10-year risk of major osteoporotic fracture at HOMA-IR index greater than 2. Stimulated insulin levels above 39.7 μIU/ml were considered high-risk regarding the fracture risk.* ***Conclusion:*** *Our results revealed a negative relationship between stimulated insulin levels at HOMA-IR index above 2 and bone integrity in postmenopausal age. On the other hand, higher basal insulin levels at HOMA-IR index lower than 2 were associated with better parameters of postmenopausal bone health.*

Key words: *insulin resistance, bone mineral density, fracture risk*

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INTRODUCTION

The hypothesis of the osteoanabolic insulin action is supported by in vitro studies and animal models [1, 2]. Additionally, it is well known, that patients with type 1 diabetes mellitus (DM) and insulin deficiency have increased skeletal fragility [1]. On the other hand, some clinical trials demonstrate that insulin resistance (IR) and concomitant hyperinsulinemia could be associated with increased bone mass [3-5]. Patients with IR and overt type 2 DM also have higher bone mineral density (BMD) [6]. However, animal

studies reveal that in IR conditions osteoblasts could become insulin resistant [7]. These data suggest that IR has an unfavorable effect on their function [7]. In addition, many clinical studies and meta-analyses report an increased fracture risk in patients with type 2 DM, regardless of their BMD [8-13].

There is an ongoing discussion about the independent effect of IR and concomitant hyperinsulinemia on bone integrity in individuals without overt DM. For example, several large population-based clinical trials demonstrate that circulating insulin or IR are positively associated with BMD in individuals both with and without DM [3, 14-16]. However, it remains unclear whether the net effect of IR is favorable or unfavorable for the fracture risk. It is hypothesized that IR could decrease the fracture risk, due to its positive correlation with BMD. On the other hand, type 2 DM is associated with an increased fracture risk, despite higher BMD. In this regard, IR may have a similar correlation with fractures. These data suggest unfavorable effects on bone quality (bone geometry, volumetric BMD, microarchitecture and bone strength), that remain undetected by dual-energy x-ray absorptiometry (DEXA) measurement of BMD.

On the other hand, additional factors, associated with insulin levels and bone integrity, should be considered in the assessment of the correlations between IR and BMD. Several clinical trials, for example, demonstrate a loss of the positive association between circulating insulin levels and BMD after adjustment for body mass index (BMI) [14, 17, 18], suggesting that IR might affect BMD indirectly (eg. through body weight). However, other studies reveal a positive correlation irrespective of BMI [3, 4, 16, 19]. These date suggest that the effect of IR on bone could be mediated regardless of BMI. Additionally, some studies demonstrate lack of association [20] or even an inverse correlation between IR and BMD [21].

The controversial literature data on the relationship between IR and bone health undoubtedly point at the need for additional investigational studies to clarify the independent effect of IR and concomitant hyperinsulinemia on bone health in the non-diabetic state.

AIM

To assess the correlations of bone density and fracture risk with insulin resistance and circulating insulin levels in non-diabetic postmenopausal women.

MATERIALS AND METHODS

In the study were included 84 women from North-Eastern Bulgaria. They were over 45 years old. The following including criteria were used: 1. women with signed informed consent. 2. women with menopause for at least 12 months. Patients were excluded from the study if they fulfilled one of the following exclusion criteria: 1. iatrogenic and premature menopause (MP) (< 40 years of age); 2. current or previous use of medications that affect bone metabolism (hormonal replacement therapy, corticosteroids, anticonvulsants, medications used for osteoporosis treatment); 3. medical history of malignancy; 4. acute or chronic inflammation; 5. thyroid and parathyroid dysfunction; 6. limited physical activity (immobilization, paralysis); 7. liver and/or kidney disease; 8. DM and/or use of antidiabetic medication.

Clinical methods

The participants underwent a structured medical interview and a thorough medical examination. Height (cm), body weight (BW) (kg) and waist circumference (WC) (cm) were measured, then BMI was calculated (BMI = kg/m^2).

Functional test

A standard **oral glucose tolerance test** (OGTT) was conducted. The test was performed in the morning after at least 8 hours of fasting, using 75 grams of glucose, dissolved in 250-300 ml of water, which was drunk by the participants in about 5 minutes. The participants were in a sitting position during the test. Blood samples were taken just before and 120 minutes after the glucose intake. Plasma glucose levels were measured by hexokinase method via Olympus and Adiva 1800. Insulin levels were measured by chemiluminescent immunoassay using an Immulite 2000 analyzer. The homeostasis model assessment (HOMA)-IR index was calculated using the formula:

$$\frac{\text{fasting serum insulin (mIU/L)} \times \text{fasting plasma glucose (mmol/L)}}{22.5}$$

Although “normal” values of HOMA-IR index appear to vary widely among different populations, several studies suggest a cut-off value of above 2 for any IR [22, 23]. Considering these data, we assumed a HOMA-IR index value below 2 for preserved insulin sensitivity.

Instrumental methods

The measurement of BMD at lumbar spine and proximal femur by DEXA was performed with Lunar Prodigy Bx-1L (GE Medical, Madison, WI, USA). According to the WHO criteria, normal bone mass was defined as having T-scores ≥ −1.0 SD at any site, osteopenia was defined as having a T-score between -1 and -2,5 SD at any site and osteoporosis was diagnosed

as having a T-score ≤ −2.5 SD at any site. Using the Fracture Risk Assessment Tool (FRAX) (https://www.sheffield.ac.uk) the 10-year risk of major osteoporotic fracture (MOF) and the 10-year risk of hip fracture (HF) were determined. Fracture risk was calculated according to the Bulgarian database, using femoral neck BMD (g/cm^2).

Statistical analysis

The data were processed with SPSS v.20.0 for Windows. Descriptive analyses were performed to determine mean values with standard deviations, minimum and maximum range of the quantitative variables. The qualitative variables were described by number of observations (n) and relative frequency distribution (in percentages). We used Student's t-test (for two groups) and One-Way ANOVA (for more than two groups) to compare the sample characteristics. Correlations were assessed by Pearson's R (for the total cohort) and Spearman's rho (for the subgroups) analyses. Partial multiple correlation analyses were applied to determine the influence of other factors on the relationship between two variables. Stepwise multiple linear regression analyses were performed to assess the influence of independent variables on a dependent variable. ROC curve analyses were used to determine insulin threshold values. For all performed analyses, statistical significance was set as $p < 0.05$ with a confidence interval of 95%.

RESULTS

We studied 84 women, aged between 46-75 years (mean 60.54 ± 7.07 years). The time since final menstrual period was between 1-24 years (mean 11.45 ± 6.62 years).

Assessment of BMD: Considering the results of the DEXA, the subjects were divided into three groups, based on the lowest BMD at lumbar spine, total neck and/or femoral neck (Figure 1).

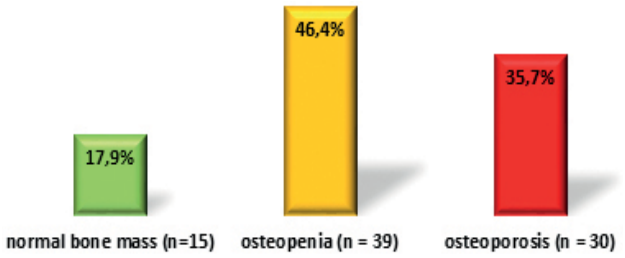


Fig. 1. Proportion of the study subjects according to bone density

The comparative analysis (One-Way ANOVA) of the baseline characteristics between the groups demonstrated significant differences in age, time since final menstrual period and body weight (BW) (Table 1).

Association of BMD with insulin levels and HOMA-IR index

It was found that in 46% of the subjects HOMA-IR index was above 2 with the highest relative proportion in the group with normal bone mass (Figure 2).

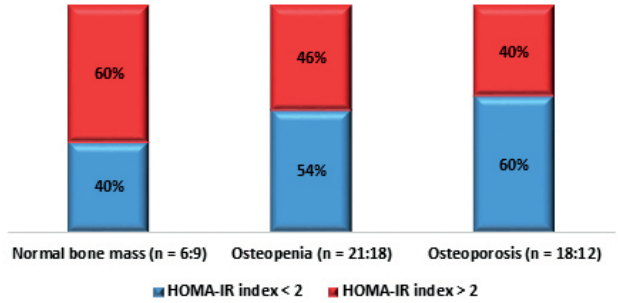


Fig. 2. Proportions of low and high HOMA-IR index in the groups stratified by BMD

Comparative analyses of BMD according to HOMA-IR index was performed in the total cohort. The re-

Table 1. Baseline characteristics between the groups stratified by BMD

	Normal bone mass (mean ± SD)	Osteopenia (mean ± SD)	Osteoporosis (mean ± SD)	p value
Age (years)	56.60 ± 6.58	60.21 ± 6.19	62.93 ± 7.59	0.015
Time since menopause (years)	7.56 ± 4.79	9.92 ± 5.72	15.03 ± 6.99	<0.001
Waist circumference (cm)	94.33 ± 9.34	91.03 ± 12.26	89.33 ± 11.15	0.387
Body weight (kg)	74.47 ± 7.65	69.92 ± 11.18	65.43 ± 12.08	0.033
BMI (kg/m^2)	27.64 ± 3.27	27.13 ± 4.01	26.49 ± 4.56	0.651
Fasting blood glucose (mmol/l)	5.64 ± 0.51	5.57 ± 0.54	5.67 ± 0.65	0.773
Blood glucose at the 120 min (mmol/l)	5.36 ± 1.08	6.06 ± 1.99	6.32 ± 1.78	0.244
Fasting insulin (μIU/ml)	10.39 ± 5.11	7.63 ± 3.52	9.12 ± 6.60	0.174
Insulin at the 120 min (μIU/ml)	51.85 ± 19.78	46.87 ± 22.27	61.30 ± 52.07	0.253
HOMA-IR index	2.66 ± 1.48	1.91 ± 0.92	2.33 ± 1.79	0.167

sults revealed a significantly higher total neck BMD when the index was above 2 (Table 2).

Table 2. Comparison of BMD between high and low HOMA-IR groups (t-test)

Skeletal area	BMD (g/cm²)		
	HOMA index < 2 (mean ± SD)	HOMA index > 2 (mean ± SD)	p value
L1-L4	1.00 ± 0.15	1.06 ± 0.15	0.106
Femoral Neck	0.81 ± 0.10	0.85 ± 0.13	0.177
Total Neck	0.88 ± 0.11	0.94 ± 0.13	0.032

Furthermore, weak positive correlations (Pearson's R) were found in the total cohort between fasting insulin and proximal femur BMD (femoral neck BMD r = 0.204, p = 0.031, total neck BMD r = 0.277, p = 0.011). Similar weak correlations were seen also regarding the HOMA-IR index (femoral neck BMD r = 0.201, p = 0.034, total neck BMD r = 0.283, p = 0.009).

The subgroup analyses of correlations (Spearman`s rho) between insulin levels and HOMA-IR index with BMD in the femoral region revealed some differences. It was found that the positive relationships remained significant only in the group with normal bone mass (fasting insulin with femoral neck BMD r = 0.627, p = 0.012; with total neck BMD r = 0.589, p = 0.021; HOMA-IR index with femoral neck BMD r = 0.642, p = 0.01; with total neck BMD r = 0.604, p = 0.014).

We assumed that the loss of correlations in subjects with osteopenia and osteoporosis could be related to differences in age, menopausal period and/or anthropometric parameters. Therefore, we performed additional partial correlation analyses. After adjustment for age and menopausal period no significant changes were found in the initially detected positive associations of BMD with fasting insulin and HOMA-IR index in the total cohort. However, these positive correlations were lost after adjustment for BW, waist circumference (WC) and BMI.

On the other hand, additional dependencies were found between BMD and insulin levels after adjustment for HOMA-IR index. A weak negative correlation between stimulated insulin levels at 120 min and femoral neck BMD (r = -0.262, p = 0.017) was revealed, but a loss of the positive relationship between fasting insulin and proximal femur BMD was detected (Figure 3).

In order to determine the independent relationship between insulin and BMD from the association between obesity and bone density, we performed a stepwise multiple linear regression analysis. The results indicated that the positive correlations of fasting insulin and HOMA-IR index with proximal femur BMD were determined by WC (β = 0.393 ± 0.001 SE, p < 0.001). However, when BW was added to the analysis, BMI was found to become negatively associated with femoral neck BMD (β = -0.451 ± 0.005 SE, p = 0.018), while BW proved to be the leading positive predictor of better bone density (β = 0.792 ± 0.002 SE, p < 0.001).

Association of fracture risk with insulin levels and HOMA-IR index

Previous fractures were found in 19% (n = 16) of the total group, distributed among women with osteopenia (n = 7, 18% of this group) and osteoporosis (n = 9, 30% of this group). There was no history of previous hip fracture in the total group. X-ray proven vertebral

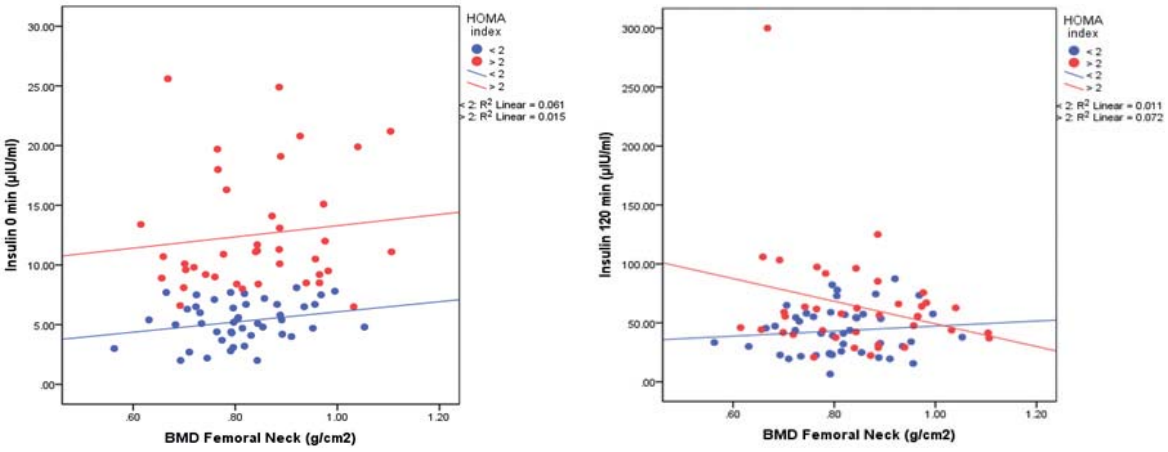


Fig. 3. Correlations between femoral neck BMD and insulin levels at low and high HOMA-IR index. The figures illustrate the loss of the positive correlation between fasting insulin and femoral neck BMD at HOMA-IR index > 2 (r = 0.122, p > 0.05) and the weak negative correlation between stimulated insulin at 120 min (post-load insulin) and femoral neck BMD at HOMA-IR index > 2 (r = -0.268, p < 0.05)

fractures were presented in 6% (n = 5) of the cases, and the rest were mainly in the region of the distal part of upper or lower limbs. Previous fractures were reported in 10.7% (n = 9) of the subjects with HOMA-IR index < 2 and in 8.3% (n = 7) of those with HOMA-IR index > 2. Regarding vertebral fractures, it was found that 1.2% (n = 1) of them were in women with HOMA-IR index < 2, and 4.8% (n = 4) were in those with HOMA-IR index > 2.

We found no significant differences (t-test) in the 10-year risk of major osteoporotic fracture (MOF) and hip fracture (HF) at HOMA-IR index below and above 2 (MOF 9.84 ± 4.83 vs 9.41 ± 4.72, p < 0.05; HF 1.69 ± 1.9 vs 1.7 ± 2.04, p < 0.05). Furthermore, no significant correlations (Pearson's R) of insulin levels and HOMA-IR index with fracture risks were revealed in the total cohort. On the other hand, correlations were seen between insulin levels and fracture risks after adjustment for HOMA-IR index. A weak negative correlation was found between fasting insulin levels and the 10-year risk of MOF (r = -0.275, p = 0.012). Nevertheless, there was a weak positive correlation between stimulated insulin at 120 min and the 10-year risk of MOF (r = 0.219, p = 0.047). Similar trends were found also in the 10-year risk of HF, although not statistically significant. The negative correlation between fasting insulin levels and the 10-year risk of MOF was found to be statistically significant at preserved insulin sensitivity (Spearman`s rho at HOMA-IR index < 2, r = -0.316, p = 0.034), whereas at HOMA-IR index > 2 this correlation remained non-significant. On the other hand, the positive correlation between post-load insulin levels at 120 min and the 10-year risk of MOF remained significant at HOMA-IR index > 2 (Spearman`s rho r = 0.321, p = 0.046), whereas at HOMA-IR index < 2 the correlation was non-significant (Figure 4). In addition, a positive correlation between the 10-year risk of HF and post-load insulin levels at 120 min was found at HOMA-IR index > 2 (Spearman`s rho r = 0.355, p = 0.026).

These results were confirmed by the additionally performed a stepwise multiple linear regression analysis, which included anthropometric parameters. At HOMA-IR index < 2 fasting insulin levels remained negatively associated with the 10-year risk of MOF (β = -0.397 ± 0.395 SE, p = 0.007). At HOMA-IR index > 2 post-load insulin levels remained positively associated with the 10-year risk of MOF (β = 0.348 ± 0.014 SE, p = 0.018), but also with the 10-year risk of HF (β = 0.303 ± 0.006 SE, p = 0.039). Additionally, these analyses demonstrated a negative association of BW with fracture risk at HOMA-IR index > 2 (for MOF β = -0.425 ± 0.055 SE, p = 0.004; for HF β = -0.443 ± 0.024 SE, p = 0.003).

Based on the performed analyses and the results, the threshold values of insulin were determined for risk assessment and prognosis. As risk values of fasting insulin regarding the 10-year risk of MOF were accepted levels under 6.15 μIU/ml (AUC = 0.772 (0.446-1.000); p = 0.011) with sensitivity and specificity of 66.7%. As risk values of post-load insulin regarding the 10-year risk of MOF were accepted levels above 39.7 μIU/ml (AUC = 0.720 (0.540-0.900); p = 0.019) with sensitivity and specificity of 66.7%.

DISCUSSION

The presented results of our research revealed several, mainly weak correlations of insulin levels and HOMA-IR index with proximal femur BMD. Moreover, some of them were modulated by additional factors. Higher basal insulin levels and HOMA-IR index

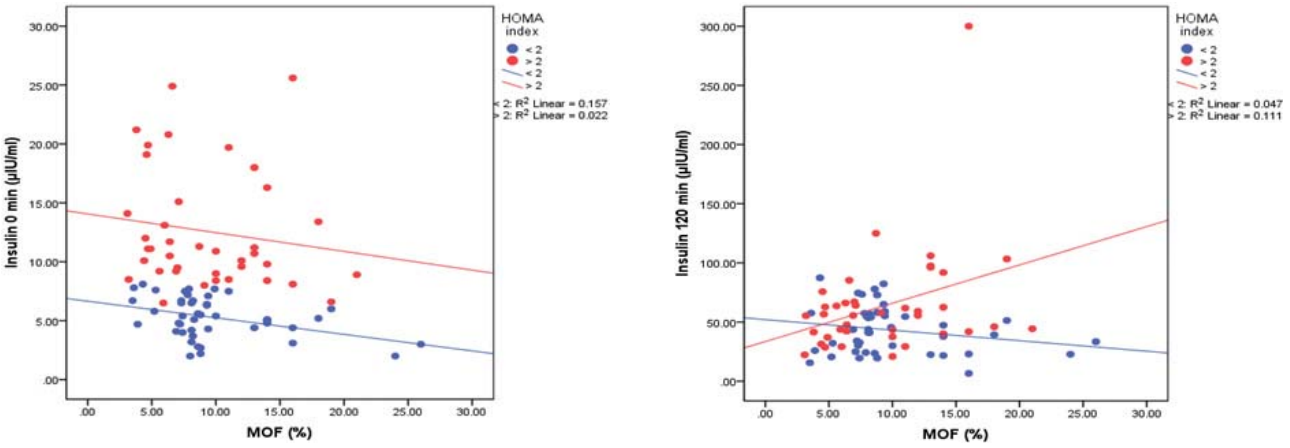


Fig. 4. Correlations between the 10-year risk of MOF and insulin levels at low and high HOMA-IR index. The figures illustrate the significant negative correlation between fasting insulin levels and the 10-year risk of MOF at HOMA-IR index < 2 and the significant positive correlation between stimulated insulin levels at 120 min and the 10-year risk of MOF at HOMA-IR index > 2

were associated with better BMD parameters. However, these relationships remained dependent on anthropometric parameters. In accordance with our results, Napoli et al. found that BMD increased with the rise of HOMA-IR index. This positive correlation between BMD and IR also lost its significance after adjustment for BMI, demonstrating that the association is influenced by body size [24]. In another study among non-diabetic postmenopausal women, Yang et al. similarly demonstrated, that IR was associated with higher cortical volumetric BMD, but the relationship with bone volume was the opposite, especially for the cortical compartment [25]. Moreover, the authors found that higher IR was associated with lower bone strength, irrespective of body size. Campillo-Sánchez et al. confirmed the negative association of IR with bone quality in nondiabetic postmenopausal women. The authors revealed an independent of BW inverse correlation of trabecular bone score (TBS) with HbA1c, insulin levels and HOMA-IR index. However, it is further clarified, that the established direct association between IR and volumetric BMD was determined by higher BW [26]. Although bone microarchitecture was not evaluated in our research, we suppose a negative relationship of bone integrity with IR and associated compensatory hyperinsulinemia. The conducted sub-analyses in our study revealed that the positive association between fasting insulin and proximal femur BMD was lost as insulin sensitivity decreased. Additionally, there was a negative correlation between post-load insulin levels and femoral neck BMD at HOMA-IR index > 2. The loss of positive association between fasting insulin and proximal femur BMD, as well as the negative correlation between stimulated insulin levels at 120 min and femoral neck BMD at HOMA-IR index greater than 2, raise the question about a loss of insulin sensitivity at the bone level in the setting of systemic IR [27, 28].

It still remains unclear, whether the fracture risk is increased or decreased in non-diabetic people with IR. Some authors found, that individuals with prediabetes had a lower fracture risk after adjustment for BMI and/or BMD [29, 30]. Other investigators did not find statistically significant difference in fracture risk of those individuals, despite the suggested increased risk by some sub-analyses [11, 12]. On the other hand, Chen et al. discovered, that there was a lower incidence of osteopenia/osteoporosis among individuals with prediabetes, but a higher incidence of fractures compared to individuals with normal glucose metabolism [31]. Our study revealed a controversial correlation between fasting and stimulated insulin with fracture risks, which was dependent on HOMA-IR index. At preserved insulin sensitivity (HOMA-index < 2) higher basal insulin levels were associated with a lower 10-year risk of MOF. On the other hand, basal insulin levels were not associated with a lower fracture risk in the setting of IR. Additionally, at HOMA-IR index greater than 2 higher stimulated insulin levels correlated positively with the 10-year risk of MOF. One of the explanation of the observed opposite relationships between basal and stimulated insulin levels with bone integrity could be related to the sensitivity of bone to insulin action at increasing levels of the hormone. In addition, with the increase of insulin resistance, other related factors, such as pro-inflammatory cytokines and oxidative stress, have also increased, which exerts an adverse effect on bone health, exceeding the anabolic effect of insulin on bone. Another explanation could be sought in IR-associated metabolic and body composition changes and their relationships with quantitative and qualitative bone characteristics. Clarification of these questions could be obtained by conducting larger longitudinal studies in the future. The necessity of such researches is indisputable, because the exact mechanisms, determining the role of insulin in bone homeostasis, remain incompletely understood. It is also unclear whether bone cells develop resistance to the insulin action, similarly to muscle and fat cells. The controversial literature data probably result from the heterogeneity of the studied populations, especially in terms of age [17, 18], ethnicity [17, 18, 20], sex, menopausal status [17, 18, 20]. An additional difference in some studies is also seen due to the inclusion of individuals with DM on antidiabetic medication [16, 17, 20, 21].

Limitations of the clinical trial

The small number of participants reduced the strength of the established relationships between bone health and the assessed clinical and laboratory parameters. On the other hand, our study did not evaluate bone microarchitecture, which is an additional determinant of bone strength. Because the study was cross-sectional, the causal associations between the evaluated bone parameters and the studied biochemical and anthropometric parameters could not be definitively determined.

CONCLUSION

Our results suggest a negative relationship between postmenopausal bone health and higher stimulated insulin levels at the setting of IR, as post-load insulin levels at HOMA-IR index greater than 2 were associated with lower BMD and higher fracture risk. Nevertheless, higher basal insulin levels at preserved insulin sensitivity were related to better parameters

of bone health, as fasting insulin levels at HOMA-IR index lower than 2 were associated with higher BMD and lower fracture risk. Based on these findings, we suppose that the relationship between insulin and bone health could be modulated by the level of insulin sensitivity. Moreover, other IR-related factors (anthropometric, metabolic, inflammatory, etc.) should be discussed, as their relationships with bone integrity could not be excluded.

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