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ORIGINAL ARTICLE

The influence of Visfatin, RBP-4 and insulin resistance on bone mineral density in women with treated primary osteoporosis

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Abstract

Introduction The impact of the two adipokines, visfatin and retinol-binding protein 4 (RBP-4) on bone mineral density (BMD) has been analysed in various studies with conflicting results. Visfatin is highly expressed in visceral fat with stimulatory effect on osteoblast proliferation and inhibition on osteoclast formation, while RBP-4 acts as a transporter protein for retinol, associated with changes in insulin sensitivity, independent of obesity, with no consensus on its effect on bone metabolism. We evaluated the relationship between serum concentrations of visfatin, RBP-4, markers of insulin resistance and current BMD in treated postmenopausal osteoporosis (PO).

Methods Demographics, previous treatment, metabolic status, anthropometry, serum Alkaline phosphatise (ALP), visfatin, RBP-4, the HOMA IR (homeostatic model assessment of insulin resistance) index and BMD were evaluated in 61 subjects with PO. Statistical analysis used SPSS v. 25.0, with a level of significance $\alpha = 0.05$. Regression models were constructed to evaluate the relationship between adipokines and BMD, adjusting for covariates.

Results In multilinear regression analysis, the strongest predictor for current BMD was a previous BMD, followed by ALP and age. RBP4 and HOMA IR were significant predictors, while visfatin had no significant effect. A significant correlation between body mass index (BMI) and BMD at the femoral neck was observed. ALP was negatively correlated with BMD and visfatin positively with RBP4.

Conclusions Data indicate a positive relationship between BMD and RBP-4, an inverse relationship between markers of insulin resistance, bone turn-over and current BMD. No significant effect of visfatin on BMD was observed.

Keywords Bone mineral density · Adipokines

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Introduction

Osteoporosis is a systemic bone disease characterized by skeletal fragility resulting in increased risk of fracture causing diminished quality of life and significant health care costs [1]. Certain factors such as oestrogen deficiency and related bone-loss in the case of postmenopausal women or low body mass index have been considered risk factors for osteoporosis [2, 3].

Adipose tissue is considered to be an important oestrogen reservoir in postmenopausal women due to the ability to aromatize androgen precursors into oestrogens [4]. However, the relationship between body mass index (BMI), bone mineral density (BMD) and fracture risk has been controversial. Although obese postmenopausal women were previously assumed to be protected against fracture, there is nonetheless growing evidence that has challenged this hypothesis [5–7].

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Moreover, data from the Glow study report a site-specific pattern of fractures, obese women being at increased risk of ankle, lower leg and humerus fractures and at reduced risk for wrist and hip fractures [8]. In this matter, the meta-analysis of prospective cohort studies suggested that obesity in adults significantly reduces the risk of hip fractures [9]. Sogaard et al. [10] reported similar results, overweight and obese subjects having lower risk of hip fracture compared to individuals with a normal BMI. However, in a large Canadian cohort study on adults above 50 years old, it is shown that increasing fat mass was associated with a small initial increase in femoral BMD, reaching a plateau around a BMI of 30 kg/m^2 [11]. Another recent study in Asian adults reported that being overweight, but not obese, may be protective against hip fracture [12]. For vertebral fracture risk and BMI, a meta-analysis of prospective studies found no significant association between BMI and risk of vertebral fracture in women, except when adjusted for BMD [13].

Since BMI is not a precise measure of adipose tissue, there is a particular focus on the relationship between visceral/abdominal adiposity and lower BMD [14–16]. Obesity has been demonstrated to cause a low-grade chronic inflammation state, triggering and releasing several adipokines [17]. Among these, visfatin is an adipokine highly expressed in visceral fat and has a stimulatory effect on human osteoblast proliferation and inhibitory effect on osteoclast formation [18–22]. Furthermore, a recent study using murine models demonstrates that visfatin has anti-clasteogenetic effects by interfering with bone marrow macrophage (BMM)-derived osteoclastogenesis, suggesting a potential therapeutic target to treat in Osteoporosis [23].

The studies regarding the impact of this adipokine on BMD have conflictual results, with no clear relationship proven so far.

Another newly identified adipokine is retinol-binding protein 4 (RBP-4) which acts as a transporter protein for retinol and has been associated with insulin resistance and changes in insulin sensitivity independent of obesity [24], but whether RBP-4 is related to osteoporosis/osteopenia or not has not yet been fully established.

The aim of our study was to investigate the relationships between serum concentrations of visfatin, RBP-4, markers of insulin resistance and current bone mineral density in postmenopausal treated osteoporosis.

Material and methods

The sample size consisted of (61) subjects recruited from the Clinical County Hospital, Endocrinology Department, Tirgu Mures and Medical Rehabilitation Hospital, Baile Felix, Romania. The inclusion criteria were: postmenopausal female patients diagnosed with Osteoporosis treated for at least a year before the evaluation with oral or intravenous bisphosphonates, monoclonal antibodies (Denosumab) or recombinant protein form of parathyroid hormone (Teriparatide). Osteoporosis was diagnosed based on bone mineral density T score of − 2.5 DS (standard deviations) or lower, measured by dual-energy X-ray absorptiometry (DXA) at the mean lumbar spine (L1–L4), and bilateral femoral neck. Repeated BMD measurements had to be performed on the same machine each time in order to accurately identify BMD changes over time.

Exclusion criteria: secondary osteoporosis associated with other endocrine diseases such as prolonged exposure to elevated levels of glucocorticoids (endogenous or exogenous), hypogonadism including premature ovarian failure (menopause < 40 years), primary or tertiary hyperparathyroidism due to severe kidney failure; untreated overt hyperthyroidism, acromegaly; non-endocrine secondary osteoporosis: bone marrow related disorders, gastrointestinal disorders, active tumour; immobilization; patients with mental illness or inability to give written consent; patients without treatment or treated for less than a year; patients who do not present repeated BMD evaluations on the same machine.

For subjects who had the above-mentioned inclusion criteria and have agreed to take part in the study, the next step involved anthropometric measurements: height (cm), weight (kg), BMI (kg/m^2) and abdominal circumference (cm). Serum biochemical parameters of bone metabolism included total calcium (Normal values (NV) 8.8–10.0 mg/dl), alkaline phosphatase, (ALP) (NV 40–150 IU/L), lipid metabolism: total cholesterol (NV < 200 mg/dl), triglycerides (NV < 150 mg/dl), HDL-cholesterol (NV > 50 mg/dl), blood glucose (NV < 100 mg/dl), serum creatinine (NV 0.6–1.0 mg/dl) to estimate glomerular filtration rate (eGFR) using CKD-EPI (chronic kidney disease epidemiology collaboration) equation.

For peripheral biomarkers measurement blood was collected in an EDTA collection tube, centrifuged at 1500*g* for 15 min, aliquoted and stored at − 80 °C until analysed. For insulin and visfatin measurements, the ELISA technique was used on DSX automated ELISA analyser (Dynex Technologies, USA).

Insulin was evaluated using Insulin ELISA sandwich kit (DRG Instruments, Germany); the analytical sensitivity: 1.76 µUI/ml, and coefficients of variations (CVs) < 2.6% for intra-assay precision and < 3.0% for inter-assay precision. The HOMA IR index (homeostatic model assessment of insulin resistance) was calculated using the formula (blood glucose (mg) x insulin (IU/l))/405, interpreted as: < 2 normal, > 2 possible insulin resistance, > 2.5 increased probability of insulin resistance, > 5 average in diabetic patients).

For visfatin and RBP 4, Sigma-Aldrich ELISA protocols were used. For visfatin quantification, four-fold prediluted samples were used in a competitive ELISA protocol,

according to manufacturer's instructions. In the first step, the microwells were coated (after overnight incubation at 4 °C) with the anti-visfatin antibody, while the sample and standards were pretreated with biotinylated visfatin. In a second step, the samples and standards added to the plate competed with endogenous visfatin for binding to the visfatin antibody. The final concentration of visfatin was calculated after the interpolation on the calibration curve. The analytical performances for visfatin were: minimum detectable concentration of 0.778 ng/ml, intra-assay CV < 10% and inter-assay CV < 15%.

For RBP4 quantification, 1000-fold prediluted samples were used, in order to fit in the linearity of the reaction curve. After overnight incubation of samples and standards in precoated wells and three additional incubation steps (with biotinylated detection antibody, streptavidin, and colorimetric substrate) the absorbance of each sample was interpolated on the best-fit calibration curve. The minimum detectable concentration for RBP4 was 0.1 ng/ml with intra- and inter-assay CV below 10%.

Imagistic investigations: plain X-ray of the spine to assess vertebral fractures in patients at risk and DXA scan with current BMD g/cm^2.

A number of covariate variables were also taken into account, such as age, age at menopause onset, age at the time of the diagnosis and years between menopause onset and osteoporosis diagnosis defined as diagnostic delay; smoking status, presence of fragility fractures; type of anti-osteoporotic treatment and total treatment duration (months) with the following drugs: Ibandronic acid, Alendronic acid or Risendronic acid, Strontium Ranelate; Denosumab or Teriparatide.

Statistical analysis

M.O Excel was used for data collection. Normal distribution of the data was assessed by the Shapiro-Wilk test. Spearman correlation was used to study the relationship between adipokine values and the metabolic and bone profile. Regression models were constructed to assess the relationship between the adipokines, age, treatment, previous BMD evaluations bone profile (independent variables) and the current BMD at lumbar spine and femoral neck. Both manual and automatic modelling were used, the latter, using a boosting approach, the forward stepwise method, information criterion for entry/removal, inclusion with P values less than 0.05, and removal with P values greater than 0.1 All statistical analyses were performed using the SPSS v 25.0 with a level of significance $\alpha = 0.05$.

The study was approved by the local Ethics Committee, written consent was obtained from all participants before any study procedure.

Results

Subjects with postmenopausal osteoporosis were stratified into two groups according to BMI, in normal BMI ($n = 23$) vs overweight and obese group ($n = 38$). Table 1 shows the main characteristics of the study participants. In the obese and overweight group our female subjects had significantly higher cholesterol levels and triglycerides levels compared to subjects with normal BMI. We also observed that female subjects in the overweight and obese group had significantly lower insulin sensitivity compared to those with normal BMI. The estimated glomerular filtration rate was notably lower in the overweight and obese group compared to normal BMI group. Regarding fragility fractures, 54% of subjects ($n = 33$) had at least one fragility fracture during their lifetime, among subjects with normal BMI, 36.4% ($n = 12$) vs 63.6% ($n = 21$) in the obese and overweight group.

We found a negative correlation between ALP and Lumbar BMD g/cm^2 ($r = -0.291$, p −0.04), ALP and visfatin ($r = -0.302$, p −0.02), and a positive correlation between ALP and RBP-4 ($r = 0.307$, p −0.02). We also noticed a significant correlation between BMI and BMD (g/cm^2) at left and right femoral neck ($r = 0.398$, p −0.02; $r = 0.516$, $p < 0.001$).

In regression analysis using current Lumbar BMD (g/cm^2) as dependent variable, the significant predictive factors were previous BMD ($\beta = 0.610$, $p < 0.001$), RBP-4 levels ($\beta = 0.266$ $p = 0.026$), ALP levels ($\beta = -0.436$, $p = 0.001$) and Strontium Ranelate treatment ($\beta = 0.307$, $p = 0.027$), the model explaining 71% of the variation ($r^2 = 0.71$ $p < 0.01$).

When introducing HOMA IR index as an independent factor, the model explains 76.5% of the lumbar BMD variation with age, BMI, Denosumab, Strontium Ranelate treatment, ALP, previous BMD and HOMA IR index as significant predictors.

The model including visfatin as an independent variable explained 62% of the lumbar BMD variation, along with previous BMD and ALP as significant predictors (r^2 − 0.662, $p < 0.001$).

The model combining all variables analysed explains 89.9% of the current lumbar BMD, with the strongest predictors being previous lumbar BMD, ALP, previous treatment with strontium ranelate and denosumab, RBP4, treatment duration and HOMA IR index, with visfatin having a small non-significant effect (Table 2).

Using the automatic linear modelling for boosting accuracy, the strongest predictors remain previous BMD (importance 0.5), smoking (importance 0.12) and ALP (importance 0.08) (Fig. 1) with an accuracy of 50.7%.

Table 1 General characteristics of the study group

Mean or median	Normal BMI $N=23$	SD or interquartile range	Overweight and obese $N=38$	SD or Interquartile range	*P* value
Age (years)	65.69	9.66	67.58	5.80	0.266
Menopause age (years)	48.35	3.86	48.29	3.93	0.770
Age at diagnosis (years)	60.70	8.51	60.68	6.65	0.887
Diagnostic Delay (years)	12.35	8.81	12.39	6.26	0.737
Treatment duration (months)	37	10–64	36	−9.75–26.25	0.659
Waist (cm)	**84.1**	**11.2**	**99.2**	**9.9**	**0.001**
BMI (Kg/sqm)	**22.6**	**21.2–23.9**	**28.8**	**26.6–30.1**	**0.001**
Cholesterol, mg/dl	**192.83**	**33.47**	**212.67**	**46.93**	**0.031**
Triglycerides, mg/dl	**83.50**	**49.75–117.25**	**108.50**	**45.81 + 171.18**	**0.012**
HDL, mg/dl	60.50	44.07–76.92	54.22	32.06–76.36	0.653
LDL, mg/dl	116.17	34.93	137.92	37.43	0.220
Alkaline phosphatase, U/L	74.50	24.5–124.5	91.00	8.75–173.25	0.230
Total calcium, mg/dl	9.64	0.52	9.62	0.45	0.783
Glycaemia, mg/dl	93.41	15.16	96.57	11.63	0.215
eGFR, mil/min/1.73 m^2	**83.10**	**54.47–111.72**	**68.85**	**43.42–94.27**	**0.046**
RBP 4, µg/ml	13.12	9.27–16.96	15.26	9.49–21.11	0.129
Visfatin, ng/ml	13.77	9.74–17.80	13.96	10.42–17.49	0.315
HOMA-IR	**3.20**	**0.96–5.43**	**5.47**	**2–8.93**	**0.020**

Bold symbol was used for statistically significant differences

Table 2 Regression analysis results

Lumbar BMD g/cm^2 (dependent variable)			
Predictors	*B*	*p*	95% CI
Age (years)	−0.390	0.043	−0.766 to 0.013
Menopause age (years)	0.193	0.151	−0.075 to 0.461
Diagnostic delay (years)	0.182	0.315	−0.182 to 0.546
Smoking (Y/N)	0.141	0.216	−0.087 to 0.370
BMI (kg/m^2)	0.177	0.090	−0.030 to 0.384
Treatment duration (months)	0.219	0.133	−0.071 to 0.510
Bisphosphonates (months)	−0.024	0.859	−0.301 to 0.252
Strontium ranelate (months)	0.304	0.014	0.067–0.541
Denosumab (months)	0.274	0.033	0.024–0.524
Teriparatide (months)	−0.068	0.502	−0.275 to 0.138
Fragility fracture (Y/N)	0.190	0.091	−0.033 to 0.414
Alkaline phosphatase (U/L)	−0.421	0.001	−0.649 to −0.194
Previous BMD (g/cm^2)	0.654	<0.001	0.448–0.859
RBP 4, (ng/ml)	0.257	0.012	0.062–0.452
HOMA IR	−0.205	0.072	−0.430–0.020
Visfatin (ng/ml)	0.018	0.877	−0.219–0.255
Model (r^2)	0.899	<0.001	

Discussion

The current study aimed to investigate the effect of various adipokines and markers of insulin sensitivity on BMD in postmenopausal osteoporotic subjects with at least 1 year of treatment. The results showed that both RBP-4 and HOMA IR index, but not visfatin are significant predictive factors for BMD.

After adjusting for age, BMI, treatment, ALP and previous BMD, our subjects with postmenopausal osteoporosis, HOMA-IR index were inversely related to lumbar BMD, suggesting that insulin resistance might not be a protective factor. Paradoxically, subjects with T2DM where insulin resistance is a hallmark, have higher BMD independent of BMI; thus, the consequences of increased insulin levels on bone mineral density are not entirely clear [25, 26].

In a recent study published by Shanbhogue et al., in the case of non-diabetic postmenopausal women, insulin resistance was associated with smaller bone size but increased volumetric BMD [27]. Previously, Srikanthan et al. reported a negative association between insulin resistance and femoral neck strength [28].

Regarding the relationship between BMD and RBP-4, after adjusting for confounders, RBP-4 was positively related to lumbar BMD. A recent study published by Zhou et al. in a cohort of diabetic patients above 50 years old, reported higher levels of RBP-4 in T2DM subjects with normal BMD compared to osteopenia/osteoporosis group. They also found a positive association between serum RBP-4 and (lumbar, femoral neck, hip) BMD after adjustments for bone related factors, in osteopenia/osteoporosis group compared to normal BMD group. Moreover, it was speculated that in diabetic subjects RBP-4 might have a potential role in bone

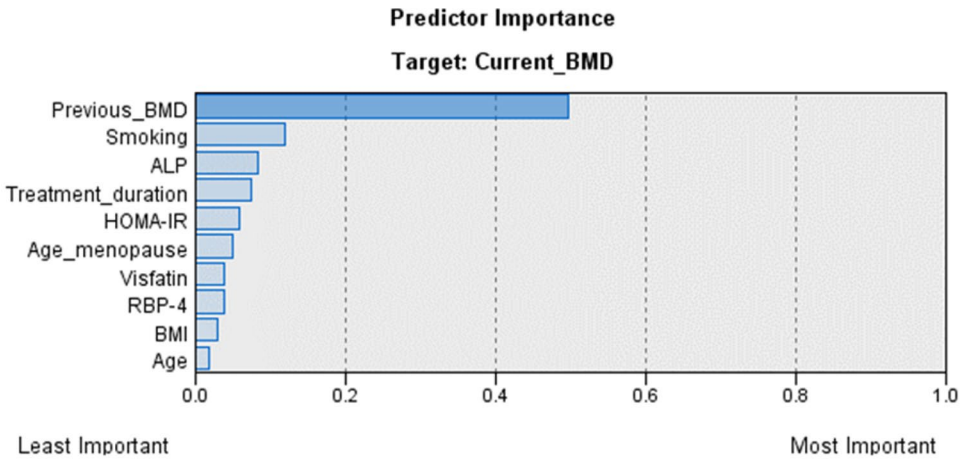

Fig. 1 Automatic Linear modelling

mass maintenance [29]. Rico et al. reported similar results; in their study, RBP-4 levels were lower in osteoporotic elderly subjects as well [30]. Although, in our cohort study, we did not have patients with DM, in regression analysis we found that RBP-4 was significantly related to lumbar BMD.

We found no significant association between visfatin and BMD. Although there is no convincing data to support a correlation between visfatin levels and BMD in Chinese or Iranian postmenopausal women, in a study published by Tohidi et al. a correlation between bone turnover markers and circulating visfatin levels in postmenopausal women was found [20, 31]. In our study, we also report a correlation between circulating levels of ALP as a marker of nonspecific bone resorption and visfatin levels.

Interestingly, a more recent study on one of the polymorphisms in visfatin gene (rs2110385) and BMD among obese adults showed that among different genotypes (GG, GT, TT), subjects with TT genotype had significantly higher lumbar BMD and T score, whereas those with GT genotype had higher hip BMD [32]. Giving the fact that genetic polymorphism of visfatin gene was not assessed in the Romanian population, future research should involve genotyping the visfatin gene in our cohort in order to comprehend the relationship between visfatin and BMD in postmenopausal osteoporosis.

We consider a limitation of our study the cross-sectional design, which does not enable the evaluation of the effect of adipokine levels on BMD change over time. Furthermore, for evaluation of BMD which is a quantitative measurement, it is important to evaluate the quality of BMD, as well as the bone microarchitecture. Another limitation is the low number of patients treated with Teriparatide (as a potent anabolic agent). The lack of measurements of calcium metabolism markers, PTH, vitamin D and more specific bone turnover markers are also limitations worth to be mentioned.

Because of the cross-sectional design, we could not assess fracture risk and evaluate its relationship between BMI and BMD. However, in our sample, subjects with normal BMI had a lower frequency of fragility fractures compared to the overweight and obese group. BMI was correlated to BMD but only for the femoral neck (both left and right) suggesting that increased BMI might be protective for hip as previous reports have hypothesized, with the underlying assumption that an increased mechanical load on the bone stimulates bone mass increase to accommodate to the greater load [33]. Further longitudinal studies are needed to clarify the relationship between BMI, BMD and fracture pattern risk in postmenopausal osteoporosis.

Conclusions

In summary, the current study demonstrated that there is an inverse relationship between markers of insulin resistance, bone turnover and current BMD in postmenopausal osteoporosis and a positive one with RBP-4, with visfatin having no significant effect. A great number of covariates should be taken into account when studying effects on BMD, with previous anti-osteoporotic medication having an important role as proven in the present study. Thus, to better understand the role of RBP-4, insulin resistance and bone metabolism, further longitudinal studies are needed, including fracture risk assessment, as the bone and fat interface might be a target for treatment and/or prevention of osteoporosis.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standards All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written consent was obtained from all participants before any study procedure.

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