Endokrynologia Polska
Tom/Volume 63; Numer/Number 6/2012
ISSN 0423–104X

Adiponectin and resistin in relationship with skeletal status in women from the RAC-OST-POL study

Adiponektyna i rezystyna a stan szkieletu u kobiet uczestniczących w badaniu RAC-OST-POL

Wojciech Pluskiewicz[1], Piotr Adamczyk[2], Bogdan Marek[3], Aleksandra Czekajło[4], Bogna Drozdzowska[5], Dariusz Kajdaniuk[3], Beata Kos-Kudła[3], Władysław Grzeszczak[6]

[1]*Metabolic Bone Diseases Unit, Department and Clinic of Internal Diseases, Diabetology and Nephrology, Medical University of Silesia, Katowice, Poland*
[2]*Department and Clinic of Paediatrics, Medical University of Silesia, Katowice, Poland*
[3]*Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland*
[4]*Department of Nephrology, Racibórz, Poland*
[5]*Department of Pathomorphology, Medical University of Silesia, Katowice, Poland*
[6]*Department and Clinic of Internal Diseases, Diabetology and Nephrology, Medical University of Silesia, Katowice, Poland*

Abstract

Introduction: The aim of this study was to establish adiponectin and resistin serum levels and their relationship with skeletal status in women from the RAC-OST-POL study.

Material and methods: 40 women with the lowest and 40 women with the highest value of bone mineral density (BMD) measured at the femoral neck (FN) were selected from a total of 625 women after dividing them into six age categories. Mean age in the whole group of 80 women was 66.1 ± 8.0 years. 22 women had osteoporotic fractures. Adiponectin and resistin were measured, and skeletal assessment included measurements of BMD of FN and total hip (TH) using Lunar DPX (USA) and quantitative ultrasound (QUS) of hand phalanges by means of DBM Sonic 1200 (IGEA, Italy).

Results: Mean age did not differ between the subgroups, whereas height, weight, BMI and BMD were significantly higher in women with high BMD values. In women with high and low BMD, adiponectin concentration [μg/mL] was 24.81 ± 12.7 and 31.04 ± 12.64 respectively, and differed significantly ($p < 0.05$). Respective values for resistin concentration [ng/mL] were 3.29 ± 1.37 and 3.62 ± 1.45, and did not differ. Adiponectin negatively correlated with weight ($r = –0.34$, $p < 0.01$), BMI ($r = –0.37$, $p < 0.01$), FN BMD ($r = –0.26$, $p < 0.05$), TH BMD ($r = –0.33$, $p < 0.01$), and did not correlate with QUS result. Stepwise multiple regression analysis showed that TH BMD was negatively influenced by age and adiponectin and positively by weight, and that FN BMD was dependent on age and weight only.

Conclusions: Our results suggest that adiponectin may be an independent factor influencing skeletal status in women aged over 55 years. **(Endokrynol Pol 2012; 63 (6): 427–431)**

Key words: *adiponectin, bone mineral density, resistin*

Streszczenie

Wstęp: Celem pracy było zbadanie stężeń adiponektyny i rezystyny w surowicy krwi kobiet uczestniczących w badaniu RAC-OST-POL oraz analiza wpływu tych substancji na stan szkieletu badanych.

Materiał i metody: Spośród 625 uczestniczek badania RAC-OST-POL podzielonych na 6 kategorii wiekowych, wybrano 40 kobiet z najniższymi i 40 kobiet z najwyższymi wartościami gęstości mineralnej kości (BMD) szyjki kości udowej (FN).
Średni wiek w całej grupie 80 kobiet wynosił 66,1 ± 8,0 lat. 22 kobiety przebyły uprzednio złamanie osteoporotyczne. Stężenia adiponektyny i rezystywny zostały oznaczone w surowicy, a ocena stanu szkieletu obejmowała zbadanie BMD szyjki kości udowej i całego bliższego końca kości udowej (TH) densytometrem Lunar DPX (USA) oraz ilościowe badanie ultradźwiękowe (QUS) paliczków ręki przy pomocy urządzenia DBM Sonic 1200 (IGEA, Włochy).

Wyniki: Średni wiek nie różnił się pomiędzy podgrupami, natomiast wzrost, masa ciała, BMI oraz BMD były znamiennie wyższe w podgrupie kobiet z wysokimi wartościami BMD. Stężenia adiponektyny [μg/mL] w podgrupach kobiet z wysoką i niską wartością BMD wynosiły odpowiednio 24,81 ± 12,7 and 31,04 ± 12,64 i różniły się znamiennie ($p < 0,05$). Analogiczne wartości dla rezystyny [ng/mL] wynosiły 3,29 ± 1,37 oraz 3,62 ± 1,45 i nie różniły się pomiędzy podgrupami. Stężenie adiponektyny korelowało negatywnie z masą ciała ($r = –0,34$, $p < 0,01$), BMI ($r = –0,37$, $p < 0,01$), FN BMD ($r = –0,26$, $p < 0,05$), TH BMD ($r = –0,33$, $p < 0,01$), nie korelowało natomiast z wynikami QUS. W analizie wielorakiej regresji krokowej wykazano istotny statystycznie wpływ wieku i stężenia adiponektyny (negatywny) oraz masy ciała (pozytywny) na wartość TH BMD, podczas gdy FN BMD było zależne znamiennie jedynie od wieku i masy ciała.

Wniosek: Podsumowując, wyniki prezentowanego badania sugerują, że adiponektyna może być niezależnym czynnikiem determinującym stan szkieletu w grupie kobiet powyżej 55. roku życia. **(Endokrynol Pol 2012; 63 (6): 427–431)**

Słowa kluczowe: *adiponektyna, gęstość mineralna kości, rezystyna*

Wojciech Pluskiewicz M.D. Ph.D., Department and Clinic of Internal Diseases, Diabetology and Nephrology — Metabolic Bone Diseases Unit in Zabrze, Medical University of Silesia in Katowice, 3 Maja St. 13/15, 41–800 Zabrze, Poland, tel./fax: +48 32 370 43 89, e-mail: osteolesna@poczta.onet.pl

Introduction

Osteoporosis is one of the commonest chronic diseases in elderly women. The most important consequence of osteoporosis is non-traumatic fracture, typically occurring at the forearm, spine, hip, arm and sometimes at other skeletal sites. Fracture risk depends on several factors including skeletal status and falls. One of many various factors influencing bone metabolism (e.g. endocrine system, diet, physical activity) is the amount of fat mass. Usually, obesity is considered to be protective against osteoporosis [1], and low body weight is considered to be a risk factor for osteoporosis and fracture [2, 3]. Fracture risk is inversely related to body mass index (BMI) and BMI plays an important role in the FRAX algorithm for establishing the fracture probability. Although much data indicates that adipose tissue protects against osteoporosis, some recent studies have suggested that an increasing amount of fat may upgrade the fracture risk [4] and negatively affect bone status [5]. There are several mechanisms potentially linking fat and bone metabolism and skeletal status. Mechanical load connected with fat mass increases bone mass, but adipose tissue is also considered as an endocrine organ. Adipocytes produce not only oestrogen in postmenopausal women. Several adipokines like leptin, adiponectin, resistin, and visfatin are produced in fat tissue [6, 7]. Adiponectin, exclusively expressed by adipocytes, circulates in much higher concentrations than other adipocyte products [8], and is inversely related to visceral fat mass and BMI [9]. As recently shown in a review by Biver at al. [8], consistent and inverse correlations between circulating adiponectin levels and bone mineral density (BMD) at lumbar spine, total hip and total body in postmenopausal women have been found. Negative correlations between adiponectin and BMD remained significant even after adjusting for fat mass, BMI and body weight.

The aim of the present study was to establish adiponectin and resistin serum levels in women from the RAC-OST-POL study and to analyse their relationships with densitometric and quantitative ultrasound (QUS) measurements.

Material and methods

Material

Women assessed in this study were recruited from the RAC-OST-POL study, which has been described previously [10]. Women enrolled into the RAC-OST-POL project were randomly chosen from the general population aged 55 years or older in the district of Raciborz in southern Poland. The total number of women in the district was 57,357, and the total population of qualifiable women (i.e. those aged 55 years or over) inhabiting the region at the time of enrollment into the study was 17,500. 10% of that number (1,750 subjects) were randomly selected and invited by regular e-mail to participate in the study. A group of 625 women responded positively to the invitation and declared their intention to take part in the study, which was performed in May 2010. In order to perform the currently presented analysis, the whole RAC-OST-POL study group (n = = 625) was divided into six age categories (55–59, 60–64, 65–69, 70–74, 75–79 and 80+). From each subgroup, the subjects with the lowest (n = 40) and highest (n = 40) values of femoral neck BMD were selected for analysis. Such selection allowed us to maintain the representativeness in the whole age range, as age is an important factor influencing bone status. The clinical characteristics of patients in the studied group (the whole group and subgroups with high and low BMD) are set out in Table I.

Questionnaire

Each woman completed a questionnaire providing data on clinical risk factors for osteoporosis (prior fracture, family history of hip fracture, prolonged diseases, chronic medication, smoking, alcohol intake, falls). Only those fractures which had happened due to low-energy trauma resulting from a fall from a standing position or an even lower height and which had occurred after the age of 40 were considered as osteoporotic fractures for further analyses. Only falls in the previous 12 months were considered. The questionnaire was validated and qualified as an important source of input data. In women with high BMD, nine fractures were noted and in women with low BMD, 13 fractures were recorded. Forearm fractures were the most frequent.

Fracture probability

Ten-year hip and any fracture probability was established using a FRAX on-line calculator for the Polish population.

Bone densitometry

Skeletal status was assessed by bone densitometry on a Lunar DPX (GE, USA) and non-dominant femoral neck (FN) and total hip (TH) were evaluated. Densitometric variables were presented as BMD [g/cm^2], T-score (the number of standard deviations [SD] from young adults) and Z-score (the number of SD from age-matched subjects). All the measurements were performed by one operator. The coefficient of variation (CV%) was 1.6% for FN and 0.82% for TH. CV% was calculated on the basis of 50 measurements (two for each of 25 patients with reposition).

Table I. *Clinical characteristics of studied women (mean, SD)*
Tabela I. *Charakterystyka kliniczna kobiet uczestniczących w badaniu (wartości średnie, SD)*

Parameter	All women (n = 80)	Subgroup with high BMD (n = 40)	Subgroup with low BMD (n = 40)
Age (years)	66.1 ± 8.0	65.7 ± 8.1	66.4 ± 8.0
Height [cm]	155.8 ± 6.3	*157.6 ± 5.3	153.9 ± 5.4
Weight [kg]	76.9 ± 18.4	**88.0 ± 14.3	65.8 ± 15.1
Body mass index [kg/m^2]	31.6 ± 7.2	**35.4 ± 5.5	27.9 ± 6.7
Menarche (year)	13.8 ± 1.7	14.1 ± 1.6	13.6 ± 1.71
Menopause (year)	48.4 ± 4.8	***49.6 ± 5.0	47.1 ± 4.3

*significantly higher than in subgroup with low BMD, $p < 0.01$
**significantly higher than in subgroup with low BMD, $p < 0.0001$
***significantly higher than in subgroup with low BMD, $p < 0.05$

QUS bone measurements

A DBM Sonic 1200 (IGEA, Italy) device was used in the study. Amplitude-dependent sound speed (Ad-SoS [m/s]) levels were measured at distal metaphyses of the proximal phalanges II –V of a hand, and the mean value of four fingers was then taken into further analysis. T-score and Z-score values were also calculated. CV% was 0.64% based on serial measurements in 15 subjects.

Laboratory assays

Serum levels of adiponectin were determined by the radioimmunoassay (RIA) method and serum concentrations of resistin were assessed by enzyme-linked immunosorbent assay (ELISA) using commercial assays (Linco Research, St. Louis, MO, USA). The measures were made at the immunology laboratory of the Endocrinology Department. The intra- and inter-assay CV were less than 10% across the range of measured results.

The Ethics Committee at the Medical University of Silesia in Katowice, Poland, approved the study protocol. Each woman gave an informed written consent prior to participation.

Statistics

All calculations were done using the Microsoft Office Excel application and the Statistica program (StatSoft, Inc. 2008, Tulsa, OK, USA. STATISTICA, version 8.0, www.statsoft.com) run on a PC computer. Descriptive statistics for quantitative values were presented as mean values and SDs. The distribution of analysed data was checked by the Shapiro-Wilk test. Among statistical evaluations, the t-test for independent samples or the Mann-Whitney U-test was performed for the comparison of parameters between subgroups (in case of normal and abnormal distribution, respectively).

Stepwise multiple regression analysis was performed; FN BMD and TH BMD were regressed on age, weight, height and adiponectin. Correlation analysis was done by Pearson's or Spearman's correlation, whichever appropriate. All p values < 0.05 were considered statistically significant.

Results

Adiponectin serum concentration [μg/mL] was 24.81 ± 12.7 and 31.04 ± 12.64 in subgroups with high and low BMD respectively, and differed significantly ($p < 0.05$). Respective values for resistin serum concentration [ng/mL] were 3.29 ± 1.37 and 3.62 ± 1.45, and did not differ. As one would expect, BMD, T-score, Z-score and fracture probability differed in subgroups with high and low BMD (Table II). Due to differences in mean age, we provided comparisons only for Z-scores for FN and TH BMD and Z-score for Ad-SoS. Adiponectin and resistin levels did not correlate significantly with fracture probability.

Resistin concentration did not correlate with BMD variables and body size. In the whole group, adiponectin concentration negatively correlated with weight ($r = –0.34$, $p < 0.01$), BMI ($r = –0.37$, $p < 0.01$), FN BMD ($r = –0.26$, $p < 0.05$) and TH BMD ($r = –0.33$, $p < 0.01$). Figure 1 shows a relationship between adiponectin concentration and FN or TH BMD. FN and TH BMD correlated with Ad-SoS with r values of 0.4 and 0.38 ($p < 0.001$), respectively. However, Ad-SoS did not correlate with adiponectin and resistin levels.

Stepwise multiple regression analysis showed that TH BMD was negatively influenced by age and adiponectin and positively by weight, and that FN BMD was dependent on age and weight only. The following equations were obtained:

FN BMD [g/cm^2] = 0.598 [g/cm^2] + 0.009 × weight [kg] – 0.006 × age [years], $R^2 = 0.4$, SEE = 0.191, $p < 0.00001$,

Table II. *Densitometric variables and fracture probability in subgroups*
Tabela II. *Wyniki badania densytometrycznego i prawdopodobieństwo złamań w badanych podgrupach*

Parameter	Subgroup 1 with low BMD (n = 40)	Subgroup 2 with high BMD (n = 40)
FN BMD [g/cm^2]	0.655 ± 0.053	1.124 ± 0.083
T-score	–2.72 ± 0.38	0.62 ± 0.59
Z-score	–1.2 ± 0.4	1.64 ± 0.51*
Total hip BMD [g/cm^2]	0.741 ± 0.097	1.211 ± 0.086
T-score	–2.13 ± 0.072	1.62 ± 0.086
Z-score	–0.83 ± 0.69	2.13 ± 0.72*
FRAX — any fracture	11.1 ± 7.2	3.25 ± 1.77*
FRAX — hip fracture	5.5 ± 6.0	0.22 ± 0.43*
Ad-SoS [m/s]	1,937 ± 43	1,970 ± 59
T-score	–3.7 ± 0.88	–3.04 ± 1.21
Z-score	0.31 ± 0.84	0.85 ± 1.1**

*significantly different than in subgroup 1, $p < 0.00001$
**significantly different than in subgroup 1, $p < 0.05$

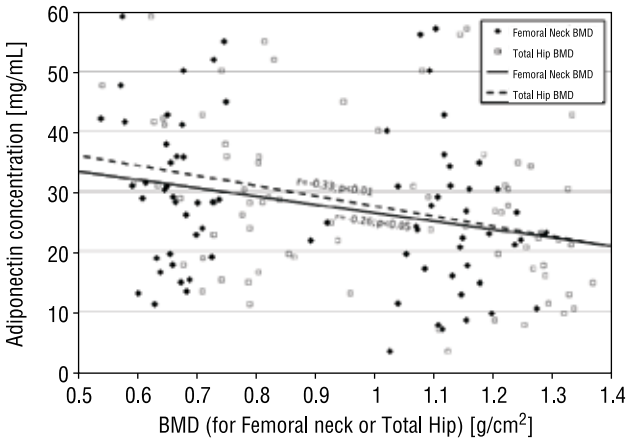

Figure 1. *Relationships between adiponectin concentration and BMD values measured at femoral neck or total hip region*

Rycina 1. *Zależność pomiędzy stężeniem adiponektyny a wartością BMD szyjki kości udowej i końca bliższego kości udowej*

TH BMD [g/cm^2] = 0.683 [g/cm^2] + 0.009 × weight [kg] –0.005 × age [years] –0.0025 × adiponectin [μg/mL], $R^2 = 0.47$, SEE = 0.184, $p < 0.00001$.

Adiponectin levels in fractured and non-fractured women were 28.2 ± 14.0 and 26.6 ± 9.8 respectively, and did not differ.

Discussion

In the current study, we have shown that adiponectin, but not resistin, influences bone status assessed by densitometric measurements of the proximal femur. We did not observe relationships between QUS parameter and adiponectin or resistin serum levels. To the best of our knowledge, ours is the first assessment of bone QUS in relation to adiponectin and resistin published in the medical literature. Our observations are consistent with data concerning the association of serum adiponectin with skeletal status evaluated by DXA given by some other authors [11–16]. In 36 postmenopausal women, adiponectin concentration correlated negatively with FN and TH BMD with r values of -0.45 and -0.46, respectively [11]. In 232 patients, TH BMD correlated negatively with r value of –0.26 [12] and other investigators [13] noted comparable results with regard to FN BMD (r = –0.24). Also, other authors have observed inverse relationships between BMD and serum level of adiponectin in women [14–16]. Generally, coefficients of correlation obtained in the current study were comparable with the results of other authors. The important results were shown by regression analysis; adiponectin remained a factor influencing bone variables only for TH BMD. Total hip consists of both cortical (mainly) and trabecular bone, and femoral neck and proximal diaphyses of hand phalanges contain almost only cortical bone. Also correlation analysis showed a slightly stronger relationship of adiponectin concentration with TH BMD than with FN BMD. We presume that adiponectin affects mainly trabecular bone, but further investigations are necessary. On the other hand, Koroglu et al. did not find a correlation between adiponectin levels and BMD values measured at spine and hip in a group of diabetic postmenopausal women [17].

One may expect that a negative relationship between adiponectin level and bone densitometry values should be followed by significant differences between osteoporotic and non-osteoporotic patients. In our

study, we noted the expected significant difference in serum adiponectin between women with low and high BMD at the proximal femur. Other authors have failed to prove such differences [18–20]. Recently, important observations of BMD loss rates among 3,075 men and women aged 70–79 from the Health Ageing and Body Composition Study were published [21]. Among women, the annualised rate of hip areal BMD (aBMD) loss in the highest tertile of adiponectin was –0.67% (95% CI –0.77, –0.58) compared to –0.43% (95% CI –0.51, –0.35) in the lowest tertile (p trend = 0.019) after adjusting for age, race, BMI, diabetes, baseline hip aBMD and weight change. In men, hip aBMD loss was greatest in the high adiponectin group (tertile 3), although this association was not significant (p trend = 0.148). The authors concluded that serum adiponectin was associated with increased hip aBMD loss in women only, which provides supporting evidence that adiponectin may have an important role in bone health.

Some studies have assessed the association between adiponectin and the incidence of fractures [22–24]. In a 15-year follow-up of 507 men, no association between adiponectin and fractures was observed [22]. In another study, the adiponectin level was independently associated with vertebral fractures in men, but in postmenopausal women an analogous association for vertebral and nonvertebral fractures did not occur [23]. In a prospective observation lasting 6.5 years of a cohort of 3,075 men and women aged 70–79 years, adiponectin was identified as a novel risk factor for fracture [24]. In the current study, we did not show a different level of adiponectin in regard to fracture status.

One should always take into consideration that both skeletal status and fat tissue hormones production are influenced by many cofactors, such as comorbidity [25]. As a result, the direct relation between fat and bone tissue assessed by selective diagnostic tools may be quite often confounded in a specific group of patients.

Our study has several limitations: our group was relatively small (due to limited access to biochemical tests, we were not able to carry out our current study in the whole RAC-OST-POL study group but only in selected subjects); we did not observe them prospectively; and we chose only some women from a random, population-based cohort. In addition, the number of fractures was small, and bone densitometry was limited to the proximal femur. It would be good to include quantitative ultrasound measurements of skeletal sites rich in trabecular bone such as the calcaneus.

Our results suggest that adiponectin may be an independent factor influencing skeletal status in women aged over 55 years.

References

1. Reid IR. Relationships among bone mass, its components, and bone. Bone 2002; 31: 547–555.
2. De Laet C, Kanis JA, Oden A et al. Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporos Int 2005; 16: 1330–1338.
3. 3. Bolanowski M, Jawiarczyk A, Jędrzejuk D, Milewicz A. Forearm SXA densitometry in 1,122 Polish women — a cohort study. Endokrynol Pol 2011; 62: 8–13.
4. Premaor MO, Pilbrow L, Tonkin C et al. Obesity and fractures in postmenopausal women. J Bone Miner Res 2010; 25: 292–297.
5. von Mühlen D, Safii S, Jassal SK et sl. Associations between the metabolic syndrome and bone health in older men and women: the Rancho Bernardo Study. Osteoporos Int 2007; 18: 1337–344.
6. Reid I, Richards J. Adipokine effects on bone. Clin Rev Bone Miner Metab 2009; 7: 240–248.
7. Schäffler A, Müller-Ladner U, Schölmerich J et al. Role of adipose tissue as an inflammatory organ in human diseases. Endocr Rev 2006; 27: 449–467.
8. Biver E, Salliot C, Combescure C et al. Influence of adipokines and ghrelin on bone mineral density and fracture risk: a systematic review and meta-analysis. J Clin Endocrinol Metab 2011; 96: 2703–2713.
9. Arita Y, Kihara S, Ouchi N. et al. Paradoxical decrease of an adipose-specific protein, adiponection in obesity. Biochem Biophys Res Commun 1999; 257: 79–83.
10. Pluskiewicz W, Adamczyk P, Czekajło A et al. Epidemiological data on osteoporosis in women from the RAC-OST-POL Study. J Clin Densitom 2012; 15: 308–314.
11. Zoico E, Zamboni M, Di Francesco V et al. Relation between adiponectin and bone mineral density in elderly post-menopausal women: role of body composition, leptin, insulin resistance, and dehydroepiandrosterone sulfate. J Endocrinol Invest 2008; 31: 297–302.
12. Peng XD, Xie H, Zhao Q et al. Relationships between serum adiponectin, leptin, resistin, visfatin levels and bone mineral density, and bone biochemical markers in Chinese men. Clin Chim Acta 2008; 387: 31–35.
13. Basurto L, Galván R, Cordova N. et al. Adiponectin is associated with low bone mineral density in elderly men. Eur J Endocrinol 2009; 160: 289–293.
14. Napoli N, Pedone C, Pozzilli P et al. Adioponectin and bone mass density: the InCHIANTI study. Bone 2010; 47: 1001–1005.
15. King GA, Deemer SE, Thompson DL. Relationship between leptin, adiponectin, bone mineral density, and measures of adiposity among pre-menopausal Hispanic and Caucasian women. Endocr Res 2010; 35: 106–117.
16. Zhang H, Xie H, Zhao Q et al. Relationship between serum adiponectin, apelin, leptin, resistin, visfatin levels and bone mineral density, and bone biochemical markers in post-menopausal Chinese women. J Endocrinol Invest 2010; 33: 707–711.
17. Koroglu BK, Kiris F, Ersoy IH et al. Relation of leptin, adiponectin and insulin resistance to bone mineral density in type 2 diabetic postmenopausal women. Endokrynol Pol 2011; 62: 429–435.
18. Gonnelli S, Caffarelli C, Del Santo K et al. The relationship of ghrelin and adiponectin with bone mineral density and bone turnover markers in elderly men. Calcif Tissue Int 2008; 83: 55-60.
19. Ozkurt B, Ozkurt ZN, Altay M et al. The relationship between serum adiponectin level and anthropometry, bone mass, osteoporotic fracture risk in postmenopausal women. Eklem Hastalik Cerrahisi 2009; 20: 78–84.
20. Kontogianni MD, Dafni UG, Routsias JG et al. Blood leptin and adiponectin as possible mediators of the relation between fat mass and BMD in perimenopausal women. J Bone Miner Res 2004; 19: 546–551.
21. Barbour KE, Zmuda JM, Boudreau R et al. The Health ABC Study. The effects of adiponectin and leptin on changes in bone mineral density. Osteoporos Int 2012; 23: 1699–1710.
22. Michaëlsson K, Lind L, Frystyk J et al. Serum adiponectin in elderly men does not correlate with fracture risk. J Clin Endorinol Metab 2008; 93: 4041–4047.
23. Araneta MR, von Mühlen D, Barrett-Connor E. Sex differences in the association between adiponectin and BMD, bone loss, and fractures: the Rancho Bernardo study. J Bone Miner Res 2009; 24: 2016–2022.
24. Barbour KE, Zmuda JM, Boudreau R et al. Adipokines and the risk of fractures in older adults. J Bone Miner Res 2011; 26: 1568–1576.
25. Niemczyk S, Niemczyk L, Romejko-Ciepielewska K. Basic endocrinological disorders in chronic renal failure. Endokrynol Pol 2012; 63: 250–257.