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Association between omentin-1, bone metabolism markers, and cytokines of the RANKL/RANK/OPG system in girls with anorexia nervosa

Ocena związku między omentyną-1 a markerami metabolizmu kostnego i cytokinami systemu RANKL/RANK/OPG u dziewcząt z jadłowstrętem psychicznym

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Abstract

Introduction: Omentin-1, secreted by visceral adipose tissue, has been indicated in the regulation of bone metabolism in girls with anorexia nervosa (AN). The aim of the study was to evaluate the relationship between omentin-1 and bone metabolism in girls with AN as well as the potential involvement of OPG and RANKL in this relationship.

Material and methods: Serum omentin-1, OC, CTx, OPG, and sRANKL were determined by ELISA in 49 girls with AN and in 30 healthy controls, aged 13 to 17 years.

Results: Girls with AN exhibited significant reduction in body weight, BMI, and Cole index as well as a significant increase in serum omentin-1 levels, compared to healthy participants. These changes were associated with a significant decrease in serum OC and CTx levels and a significant increase in OPG and sRANKL while the OC/CTx and OPG/sRANKL ratios were significantly decreased. BMI and the Cole index correlated negatively and significantly with omentin-1 levels, positively with CTx levels and the OC/CTx ratio in the control group (C), girls with AN, and all study participants (C + AN). Girls with AN showed a significant negative correlation between BMI, the Cole index, and OPG levels. The combined group (C + AN) showed a significant positive correlation between BMI, the Cole index, and the OPG/sRANKL ratio. Omentin-1 levels correlated negatively and significantly with OC and CTx levels as well as with the OC/CTx and OPG/sRANKL ratios in the C, AN, and C + AN groups.

Conclusions: The relationship between omentin-1, bone markers, and the OC/CTx and OPG/sRANKL ratios observed in girls with AN indicates the involvement of this adipokine in the regulation of dynamic balance between bone formation and resorption processes. Omentin-1 might exert a negative effect on bone remodelling in girls with AN by inhibiting both bone formation and resorption. The OPG/sRANKL system plays an important role in the latter. **(Endokrynol Pol 2015; 66 (6): 514–520)**

Key words: *anorexia nervosa; girls; omentin-1; bone metabolism; OPG; sRANKL*

Streszczenie

Wstęp: Sugeruje się, że omentyna-1 produkt wisceralnej tkanki tłuszczowej, może współuczestniczyć w regulacji metabolizmu kostnego u dziewcząt z jadłowstrętem psychicznym (AN). Celem pracy była ocena związku między omentyną-1 a metabolizmem kostnym u dziewcząt z AN z uwzględnieniem ewentualnego udziału OPG i RANKL w mechanizmie powiązań między nimi.

Materiał i metody: U 49 dziewcząt z AN i 30 zdrowych w wieku 13–17 lat oceniono stężenia omentyny-1, OC, CTx, OPG i sRANKL w surowicy metodą ELISA.

Wyniki: U dziewcząt z AN wykazano istotne zmniejszenie masy ciała, wskaźnik masy ciała (BMI), wskaźnika Cole'a oraz znamienny wzrost stężenia omentyny-1 w surowicy w porównaniu z grupą dziewcząt zdrowych. Zmianom tym towarzyszyła znamienna supresja stężeń OC, CTx oraz wzrost stężeń OPG i sRANKL w surowicy przy istotnie obniżonych wartościach wskaźników OC/CTx i OPG/sRANKL. Wartości wskaźników BMI i Cole'a korelowały istotnie ujemnie ze stężeniami omentyny-1 oraz dodatnio ze stężeniami CTx i wartościami wskaźnika OC/CTx w grupie kontrolnej (C), u dziewcząt z AN i u wszystkich dziewcząt łącznie (grupa C + AN). Znamienną ujemną korelację między wartościami wskaźników BMI i Cole'a a stężeniami OPG stwierdzono w grupie dziewcząt z AN. U dziewcząt grupy C + AN wykazano natomiast istotną dodatnią korelację między wartościami wskaźników BMI i Cole'a a wskaźnikiem OPG/sRANKL. Stężenia omentyny-1 korelowały istotnie ujemnie ze stężeniami OC, CTx i wartościami wskaźników OC/CTx i OPG/sRANKL w grupach: C, AN oraz C + AN.

Wnioski: Wykazana zależność między omentyną-1 a markerami kostnymi oraz wskaźnikami OC/CTx i OPG/sRANKL u dziewcząt z AN wskazuje na udział tej adipokiny w regulacji dynamicznej równowagi między procesami kościotworzenia i resorpcji kości. Omentyna-1 działa niekorzystnie na remodeling kostny u dziewcząt z AN wpływając zarówno na tworzenie tkanki kostnej, jak i jej resorpcję. W tym ostatnim mechanizmie istotną rolę odgrywa układ OPG/sRANKL. **(Endokrynol Pol 2015; 66 (6): 514–520)**

Słowa kluczowe: *jadłowstręt psychiczny; dziewczęta; omentyna-1; metabolizm kostny; OPG; sRANKL*

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Introduction

Adipose tissue plays an important role in the regulation of bone metabolism [1–4]. It has been shown that adipose tissue-derived adipokines including leptin, adiponectin, resistin, visfatin, or apelin are capable of modulating bone metabolism both *in vitro* and *in vivo* [1, 4]. Recent studies indicate that a novel visceral adipose tissue-derived adipokine, omentin-1 [5], might also participate in the regulation of bone metabolism. *In vitro* studies revealed that omentin-1 inhibited osteoblast differentiation [6]. In co-culture systems, it reduced osteoclast formation, probably via its effect on osteoprotegerin (OPG) and receptor activator of nuclear factor κB ligand (RANKL) production in osteoblasts [7, 8]. Dysregulation of this cytokine system is thought to underlie bone loss due to different somatic disorders [9, 10].

There are very few human studies confirming the effect of omentin-1 on bone tissue. Omentin-1 level appears to be significantly higher in pre- compared to postmenopausal women. It was also shown that total body mass, lean mass, and omentin-1 were independent predictors of bone mineral density (BMD) at the spine, total hip, and femoral neck [11]. In premenopausal women, a negative and significant correlation was found between omentin-1 and bone formation and resorption markers. However, omentin-1 was not a BMD predictor in postmenopausal women [11]. Tohidi et al. [12] reported that, in postmenopausal women, omentin-1 levels were significantly correlated with BMD at the lumbar spine but did not correlate with femoral neck BMD.

Since Wang et al. [11] found that body weight, BMI, and lean mass might modulate the effect of omentin-1 on bone metabolism in premenopausal women, a few researchers [13–20] have undertaken investigations into the relationship between omentin-1 and the determinants of the nutritional status and/or bone metabolism and BMD in individuals with eating disorders. Obese individuals exhibited a decrease in omentin-1 level compared to those with normal weight [13–16, 18–20], while in AN patients an increase in serum omentin-1 level was shown [17, 20]. Changes in omentin-1 level were negatively and significantly correlated with body weight and BMI both in obese [13–16, 20] and in AN patients [17, 20]. In girls with AN, the relationship between omentin-1, bone metabolism, and BMD at lumbar spine and total hip was only studied by Guo et al. [17]. They found significant negative correlations between this adipokine and BMD as well as bone formation and resorption markers. They also revealed that omentin-1, BMI, and lean mass were independent predictors of BMD. Guo et al. [17] concluded that omentin-1 might exert a negative effect on bone mass by inhibiting bone formation in girls with AN. To our knowledge, neither the relationship between serum omentin-1 and OPG and/or RANKL levels nor the relationship between omentin-1 and OC/CTx and/or OPG/sRANKL ratios have been assessed in girls with AN. The OC/CTx or CTx/OC ratios have been widely used as indices of bone remodelling balance [21,22]. The relative OPG/RANKL balance is important in maintaining an appropriate balance of bone remodelling [9, 10, 23–29]. Munoz-Calvo et al. [23] and our previous studies in girls with AN [26] demonstrated that the OPG/RANKL ratio may prove to be a more relevant marker in predicting bone loss compared to absolute levels of these factors. Thus we investigated the relationship between omentin-1 and bone remodelling as assessed by serum osteocalcin (OC, a marker of bone formation), C-terminal telopeptide of type I collagen α 1 chain (CTx, a marker of bone resorption), and the OC/CTx ratio, as well as potential participation of OPG, its soluble ligand sRANKL, and the OPG/sRANKL ratio in this relationship.

Material and methods

The study group consisted of 49 girls aged 13 to 17 years, hospitalised at the Paediatric Department in Zabrze, who, following examinations by paediatricians and a psychiatrist, were diagnosed with AN based on the American Psychiatric Association's classification and diagnostic tool, i.e. the DSM-IV of 1994. Girls with AN underwent all tests during the first three days of hospital stay, that is prior to the launch of therapy. All other somatic or mental disorders that might lead to cachexia were ruled out. The mean age of the AN patients was 15.43 ± 0.87 years (Table I). All had secondary amenorrhea. The duration of the disease was 3–60 months. The control group consisted of 30 healthy, regularly menstruating girls (mean age 15.39 ± 0.92 years) with no endocrine or other disorders that could affect bone tissue metabolism; they were all schoolgirls from the city of Zabrze, who volunteered to participate in the study.

The height and body weight of all participants were measured, and their body mass index (BMI) calculated. The mean body weight of girls with AN was 38.67 ± 2.01 kg, and mean BMI was 15.91 ± 2.17 kg/m^2. The Cole index was also calculated, which reflects the nutritional status of an individual and encompasses the following categories: wasting — < 75%; undernourished — 75–85%; mildly undernourished – 85-90%; adequately nourished — 90–100%; overnourished — > 110% [acc. to 30]. The mean value of the Cole index in AN patients was 76.30 ± 0.19%. The mean body weight of the control participants was 58.21 ± 4.79 kg, BMI 20.63 ± 2.19 kg/m^2, and Cole index 102.10 ± 0.18% (Table I).

Table I. *Mean values of age, body weight, height, body mass index (BMI), the Cole index, mean serum levels of omentin-1, osteocalcin (OC), C-terminal telopeptide of type I collagen α 1 chain (CTx), osteoprotegerin (OPG), soluble receptor activator of nuclear factor-κB ligand (sRANKL), and mean values of the OC/CTx and OPG/sRANKL ratios in girls with anorexia nervosa and in the control group*

Tabela I. *Średni wiek, masa ciała, wzrost, wskaźnik masy ciała (BMI), wskaźnik Cole'a, średnie stężenia omentyny-1, osteokalcyny (OC), C-terminalnego usieciowanego telopeptydu łańcucha α 1 kolagenu typu I (CTx), osteoprotegeryny (OPG), rozpuszczalnego ligandu receptora aktywatora czynnika jądrowego-κB (sRANKL) oraz wartości wskaźników OC/CTx i OPG/sRANKL w grupie kontrolnej i u dziewcząt z jadłowstrętem psychicznym*

Variables	Groups	
	Control group (n = 30)	Anorexia nervosa (n = 49)
Age (years)	15.39 ± 0.92	15.43 ± 0.87
Height [m]	1.63 ± 0.05	1.61 ± 0.06
Body mass [kg]	58.21 ± 4.79	38.67 ± 2.01*
BMI [kg/m^2]	20.63 ± 2.19	15.91 ± 2.17*
Cole index (%)	102.10 ± 0.18	76.30 ± 0.19*
Omentin-1 [ng/mL]	139.45 ± 15.41	184.23 ± 25.20*
OC [μmol/L]	4.32 ± 3.05	2.12 ± 3.19*
CTx [nmol/L]	5.91 ± 3.51	3.55 ± 2.50*
OC/CTx ratio [μmol/L/nmol/L]	0.93 ± 0.10	0.65 ± 0.08*
OPG [pmol/L]	3.39 ± 1.29	4.69 ± 1.61*
sRANKL [pmol/L]	0.26 ± 0.08	0.31 ± 0.09*
OPG/sRANKL ratio	12.36 ± 1.12	8.88 ± 1.05*

*p ≤ 0.05 *vs.* control group

On the day of the examination the girls did not report any complaints; none of them suffered from an acute infection during the preceding month. Blood samples for the determination of omentin-1, OC, CTx, OPG, and sRANKL were collected between 08.00 and 09.00 hours after a 12-hour fast. Centrifuged serum was frozen and stored at –75°C until assay. Determinations of omentin-1, OC, CTx, OPG, and sRANKL levels were performed using High-Sensitivity Human ELISA kits: omentin-1 (BioVendor – Laboratorni Medicina a.s., Czech Republic), OC (DSL Inc., USA), CTx (Nornic Bioscience Diagnostics A/S, Denmark), OPG, and sRANKL (Biomedica, Austria). The respective sensitivity, intra- and interassay errors were: 0.5 ng/mL, 3.7 and 4.6% for omentin-1; 0.05 μmol/L, 5.8 and 7.3% for OC; 0.08 nmol/L, 5.2 and 6.7% for CTx; 0.14 pmol/L, 7 and 7.5% for OPG; 0.04 pmol/L, 5 and 7% for sRANKL.

The database was prepared using Excel 2000 (Microsoft Corporation). Statistical analysis was carried out with Statistica 10 for Windows (StatSoft Inc., USA). The Student *t*-test was used to determine the significance of intergroup differences (normal distribution of variables). In the case of non-normal distribution, the significance was tested using the Mann-Whitney U test. The relationships between the BMI and Cole indexes, omentin-1, OC, CTx, OPG, sRANKL levels, and the OC/CTx and OPG/sRANKL ratios in control participants (C), girls with AN, and the combination group of C + AN were analysed using Spearman's correlation. The level of significance was set at $p \leq 0.05$.

The study was approved by the Bioethics Committee of the Silesian Medical University in Katowice (KNW/0022/KB1/105/09). Informed consent to participate in the study was obtained from the patients, their parents, or guardians.

Results

The mean age of AN girls was comparable to that of the control participants (Table 1). The mean body weight, BMI, and Cole index were significantly lower in girls with AN compared to healthy controls. The mean serum omentin-1, on the other hand, was significantly higher in the AN group. The changes in the mean level of omentin-1 were associated with considerable suppression of the mean serum levels of OC and CTx and elevation of the mean OPG and sRANKL levels compared to healthy participants, while the OC/CTx and OPG/sRANKL ratios were significantly decreased (Table I).

In the control participants, girls with AN, and the total study population (C + AN), BMI and the Cole index were negatively and significantly correlated with omentin-1 levels, while their correlation with CTx and the OC/CTx ratio was positive. Girls with AN had a significant negative correlation between BMI, the Cole index, and OPG. The control and AN groups (C + AN) exhibited a significant positive correlation between BMI and the OPG/sRANKL ratio (Table II).

A significant negative correlation was revealed between omentin-1 and OC, CTx levels as well as between omentin-1 and the OC/CTx and OPG/sRANKL ratios in the total study population and also in the individual groups (AN, C) (Table III).

Discussion

Recent *in vitro* and *in vivo* studies indicate that omentin-1, secreted predominantly by visceral adipose tissue, is an important modulator of bone metabolism [6–8, 11, 12, 17, 31].

Table II. *Correlation between body mass index (BMI), the Cole index and omentin-1, osteocalcin (OC), C-terminal telopeptide of type I collagen α 1 chain (CTx), osteoprotegerin (OPG), soluble receptor activator of nuclear factor-κB ligand (sRANKL) and the OC/CTx and OPG/sRANKL ratios in the control group (C), in girls with anorexia nervosa (AN), and in all girls (C + AN)*

Tabela II. *Korelacja między wskaźnikiem masy ciała (BMI), wskaźnikiem Cole'a a omentyną-1, osteokalcyną (OC), C-terminalnym usieciowanym telopeptydem łańcucha α 1 kolagenu typu I (CTx), osteoprotegeryną (OPG), rozpuszczalnym ligandem receptora aktywatora czynnika jądrowego-κB (sRANKL) i wartościami wskaźników OC/CTx i OPG/sRANKL w grupie kontrolnej (C), u dziewcząt z jadłowstrętem psychicznym (AN) i u wszystkich dziewcząt łącznie (C+AN)*

Variables		Values of correlation coefficients		
		C (n = 30)	AN (n = 49)	C + AN (n = 79)
BMI [kg/m^2]	Omentin-1 [ng/mL]	–0.352*	–0.524*	–0.422*
	OC [μmol/L]	NS	NS	NS
	CTx [nmol/L]	0.492*	0.303*	0.334*
	OC/CTx ratio [μmol/L/nmol/L]	0.400*	0.649*	0.423*
	OPG [pmol/L]	NS	–0.759*	NS
	sRANKL [pmol/L]	NS	NS	NS
	OPG/sRANKL ratio	NS	NS	0.268*
Cole index (%)	Omentin-1 [ng/mL]	–0.524*	–0.615*	–0.503*
	OC [μmol/L]	NS	NS	NS
	CTx [nmol/L]	0.520*	0.330*	0.332*
	OC/CTx ratio [μmol/L/nmol/L]	0.455*	0.651*	0.520*
	OPG [pmol/L]	NS	–0.308*	NS
	sRANKL [pmol/L]	NS	NS	NS
	OPG/sRANKL ratio	NS	NS	0.254*

*p ≤ 0.05 — statistically significant values of correlation coefficients

Omentin-1 stimulates proliferation and inhibits differentiation of mouse osteoblasts *in vitro* [6]. It also induces human osteoblast proliferation — most probably through the PI3K/Akt signal pathway [31]. In the co-culture system of osteoblasts and osteoclasts precursors, omentin-1 also reduced osteoclasts formation by stimulating OPG and inhibiting RANKL production in osteoblasts [7, 8]. Xie et al. [7] showed that omentin-1 reduces serum RANKL, tartrate-resistant acid phosphatase (TRAP) and OC levels, which increase dramatically in OPG knockout (OPG–/–) mice. Adenovirus-mediated overexpression of omentin-1 partially restored BMD and bone strength in ovariectomised mice. This was associated with decreased levels of serum OC and TRAP and lower serum RANKL/OPG ratio [8].

The data above seem to suggest that omentin-1 might play a role in the regulation of bone remodelling — also in humans. Its effect might be modulated by cytokines of the RANKL/RANK/OPG system. However, the relationship between omentin-1 and bone markers, and especially between omentin-1 and OPG, RANKL and the OPG/RANKL ratio in humans, has been studied only by a few researchers. Tohidi et al. [12] reported that circulating omentin-1 level had an inverse correlation with BMD at the lumbar spine in Iranian postmenopausal women. Wang et al. [11] study in pre- and postmenopausal women demonstrated that the effects of omentin-1 on bone metabolism depend on the menopausal status. They showed that omentin-1 was significantly negatively correlated with bone-specific alkaline phosphatase (BAP) and NTx, and was an independent negative predictor of BMD at lumbar spine, total hip, and femoral neck only in premenopausal Chinese women. Body weight, BMI, and lean mass were also independent BMD predic-

Table III. *Correlation between omentin-1 and osteocalcin (OC), C-terminal telopeptide of type I collagen α 1 chain (CTx), osteoprotegerin (OPG), soluble receptor activator of nuclear factor-κB ligand (sRANKL) and the OC/CTx and OPG/sRANKL ratios in the control group (C), girls with anorexia nervosa (AN), and all girls studied (C + AN)*

Tabela III. *Korelacja między omentyną-1 a osteokalcyną (OC), C-terminalnym usieciowanym telopeptydem łańcucha α 1 kolagenu typu I (CTx), osteoprotegeryną (OPG), rozpuszczalnym ligandem receptora aktywatora czynnika jądrowego-κB (sRANKL) i wartościami wskaźnika OPG/sRANKL w grupie kontrolnej (C), u dziewcząt z jadłowstrętem psychicznym (AN) i u wszystkich dziewcząt łącznie (C + AN)*

Variables	Bone markers		OC/CTx ratio [μmol/L/nmol/L]	Cytokines of RANKL/RANK/OPG system		OPG/sRANKL ratio	Groups
	OC [μmol/L]	CTx [nmol/L]		OPG [pmol/L]	sRANKL [pmol/L]		
Omentin-1 [ng/mL]	–0.410*	–0.366*	–0.350*	NS	NS	–0.360*	C (n = 30)
	–0.391*	–0.354*	–0.277*	NS	NS	–0.481*	AN (n = 49)
	–0.521*	–0.487*	–0.230*	NS	NS	–0.387*	C + AN (n = 79)

*p ≤ 0.05 — statistically significant values of correlation coefficients

tors in these women. However, in postmenopausal women, years after menopause, BMI, lean mass, estradiol, and adiponectin (but not omentin-1) were independent predictors of BMD. Omentin-1 level is significantly lower in post- than in premenopausal women and its effect on bone metabolism might be smaller. Differences in oestrogen levels caused by the menopause status may also contribute to the influence of omentin-1 on BMD in Chinese women [11]. High BMI is known to be a protecting factor against excessive bone loss in aging, and higher BMI is associated with a slower rate of bone loss [32]. Omentin-1 level decrease in obese patients and increase after weight loss; these changes are positively correlated with adiponectin and negatively correlated with BMI and leptin [13–16, 18–20]. In patients with AN, an increase in serum omentin-1 levels was shown compared to healthy controls, correlating negatively with body weight and BMI [17, 20]. Guo et al. [17] studied girls with AN and found that omentin-1 was negatively and significantly correlated with total body, lumbar spine, and total hip BMD. They also showed that BMD at various skeletal regions correlated negatively and significantly with adiponectin and positively with leptin. Several independent variables were entered in the regression analysis models, including age, BMI, fat mass, lean mass, serum 25-hydroxyvitamin D (the best indicator of vitamin D), estradiol, omentin-1, adiponectin, and leptin levels. In models with total body, lumbar spine, and total hip BMD as the dependent variables, the significantly independent variables for the total study population and individual groups were omentin-1, lean mass, 25-hydroxyvitamin D, and BMI. Guo et al. [17] also found that omentin-1 was negatively and significantly correlated with BAP and NTx, both in the AN group and in the healthy group. This suggested that omentin-1 might play a role both in the AN group and in the healthy group. However, the omentin-1 level in girls with AN was higher than in girls with proper body weight, which indicated that omentin-1 might play a role in the decreased BMD in these patients.

Similar to our previous studies [20], a significant reduction in body weight, BMI, and Cole index observed in girls with AN was associated with an increase in serum omentin-1 compared to healthy participants. The present study also revealed significant suppression of OC and CTx levels and elevation of serum OPG and sRANKL along with a decrease in the OC/CTx and OPG/sRANKL ratios. In the total study population and individual groups, the BMI and Cole index were negatively and significantly correlated with omentin-1 levels, while their correlation with CTx and the OC/CTx ratio was positive. On the other hand, a negative significant correlation between BMI, Cole index, and OPG levels was found in girls with AN, while the total study population showed a positive significant correlation between BMI, Cole index, and OPG/sRANKL ratio. The highest correlation coefficients were generally found in the AN group. The obtained results indicate that undernourishment might be a cause of the abnormalities in serum levels of omentin-1 and bone status indicators observed in girls with AN.

Similarly to Guo et al. [17], we also found a negative significant correlation between omentin-1 levels and bone metabolism markers (OC and CTx) in the total study population and individual groups. Guo et al. [17] suggest that omentin-1 may have a negative effect on bone mass only by inhibiting bone formation. The hypothesis was put forward by Duan et al. [6] and Xie et al. [7, 8] based on results of experimental studies. Guo et al. [17] believe that omentin-1 might act via indirect suppression of osteoclastogenesis, through stimulating OPG secretion and inhibition of RANKL in osteoblasts. It might also exert a direct effect via inhibition of osteoblast differentiation. However, it should be emphasised that Guo et al. [17] did not evaluate OPG and sRANKL levels or the OPG/sRANKL ratio in girls with AN, which might allow better clarification of omentin-1 action on bone tissue. Our results in girls with AN indicate that omentin-1 might exert a negative effect on bone metabolism by inhibiting both bone formation and resorption. The negative effect of omentin-1 is more noticeable with respect to bone formation than bone resorption, as reflected by a significant decrease in the OC/CTx ratio in girls with AN, negatively and significantly correlated with omentin-1 level. On the other hand, our previous and present studies of girls with AN demonstrated an increase in OPG and sRANKL levels (more pronounced regarding sRANKL than OPG), which resulted in a significant decrease in the OPG/sRANKL ratio. Our previous investigations also revealed a negative correlation between CTx and sRANKL [26]. In the present study, omentin-1 levels correlated negatively and significantly not only with bone markers and the OC/CTx ratio but also with the OPG/sRANKL ratio in both the total study population and in individual groups.

The increase in OPG and sRANKL along with the decrease in OC and CTx is difficult to account for, especially if there are similar negative correlations between omentin-1 and both marker groups. It might be associated with changes in the levels of several osteotropic factors, mainly hormones and cytokines (especially melatonin, hormones of the calciotropic, somatotropic, pituitary-ovarian, -thyroid, -adrenal axes as well as changes in the production of some pro-inflammatory cytokines or adipose tissue hormones), which have

been observed in girls with AN in response to RANKL expression [25, 27–29, 33–37]. It has been established that RANKL expression in osteoblasts and osteogenic stromal stem cells is stimulated by growth hormone, parathormone, vitamin D, cortisol, prostaglandin E_2, interleukin (IL)-1, IL-6, IL-8, IL-11, IL-17, tumour necrosis factor α, and is inhibited by oestrogens, androgens, leptin, melatonin, IL-4, IL-10, IL-13, IL-18, interferon γ, and transforming growth factor β, thus modifying serum levels of bone resorption markers [9, 10]. Moreover, some of the above-mentioned factors might directly affect osteoclastogenesis, metabolic activity and/or osteoclast survival. On the other hand, changes in the levels of several osteotropic factors may modify the effect of omentin-1 on the dynamic balance between bone formation and resorption and/or the expression of OPG and/or RANKL. Previous investigations indicate that the mechanism might primarily be affected by several adipokines, including adiponectin and leptin as well as oestrogens and 25-hydroxyvitamin D [11, 13, 15, 17, 23, 29, 34]. The above-mentioned modulators, which not only affect bone resorption but also bone formation, might lead to desynchronisation of the relationship between bone markers and OPG, sRANKL, and the OPG/sRANKL ratio. Low values of OPG/sRANKL ratio in association with high OPG and sRANKL levels and desynchronisation of the relationship with bone markers (especially CTx) seem to suggest that girls with AN may suffer from an imbalance of bone remodelling events or mechanism compensating for bone remodelling enhancement. In our stepwise regression model including age, BMI, OPG, sRANKL, and the OPG/sRANKL ratio, only the latter was a significant independent predictor of serum OC and CTx values [26]. OC and CTx suppression coupled with OPG levels elevation might indicate a compensatory mechanism suppressing the osteoclastic activity in adolescents with AN to preserve bone density [38]. The above data seem to confirm the hypothesis that omentin-1 plays and important role in the regulation of bone metabolism in girls with AN, also via its effect on the balance of the OPG/sRANKL system.

Conclusions

The relationship between omentin-1, bone markers, and OC/CTx and OPG/sRANKL ratios observed in girls with AN indicates the involvement of this adipokine in the regulation of the dynamic balance between bone formation and resorption processes.

Omentin-1 negatively influences bone turnover in girls with anorexia nervosa, affecting both bone tissue formation and resorption. The OPG/sRANKL system plays an important role in the latter process.

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