Obesity potentially protects against systemic bone loss in patients with rheumatoid arthritis treated with tumour necrosis factor inhibitors

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Abstract

Objective

We aimed to investigate how systemic bone metabolism was affected after 1 year of treatment with tumour necrosis factor (TNF) inhibitors in rheumatoid arthritis (RA) patients.

Methods

A total of 29 seropositive RA patients not treated for osteoporosis were enrolled and TNF inhibitors were administered for a year. Bone mineral density (BMD) at the lumbar spine, femur neck, and total hip was measured at baseline and 12 months after anti-TNF treatment. Blood samples were collected at baseline and 6 and 12 months after anti-TNF treatment and osteoclasts were cultured on bone slices. Weight was the strongest factor influencing systemic bone loss. Patients were categorised into two groups: obese (body mass index (BMI) ≥25 kg/m^2) and non-obese (BMI <25 kg/m^2).

Results

All patients showed decreased BMD at all sites. The obese group showed relatively little change in BMD, although the non-obese group showed significant decreases in BMD at all sites after 1 year of treatment with TNF inhibitors. Resorption pits created by osteoclasts decreased at 6 months and increased at 12 months in the non-obese group, while the obese group presented with steadily decreasing sizes of resorption pits at all-time points. Levels of receptor activator of nuclear factor kappa B ligand were significantly decreased at 12 months compared to baseline in the obese group, while they were increased in the non-obese group.

Conclusion

One year of treatment with TNF inhibitors failed to halt systemic bone loss in RA patients, but obesity may have protective effects against bone loss.

Key words

bone loss, obesity, rheumatoid arthritis, tumour necrosis factor

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Introduction

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease (1, 2). It can damage bones and joints, leading to three types of skeletal deterioration: marginal bone erosion, peripheral bone loss, and systemic bone loss (1, 3-5). The latter two are manifested as juxta-articular osteopenia and generalised osteoporosis, respectively (3). Bone loss is a central feature and a well-known complication of RA. Juxta-articular osteopenia presents characteristically in the early phase of RA, and osteoporosis occurs in RA patients up to four times more frequently than in the general population (1, 3, 6). Osteoporosis is an important co-morbidity of RA because it increases the risk of fracture, which further results in severe pain, functional disability, additional comorbidity, and death (3, 7). The general factors associated with bone loss include advanced age, menopause, use of glucocorticoids, limited functional capacity, and low body mass index (BMI) (1, 3, 6, 8).

Tumour necrosis factor (TNF) is a central cytokine in the pathogenesis of RA. TNF induces osteoclast formation and plays an important role in bone resorption, affecting systemic bone loss (9). TNF inhibitors have been considered as a treatment option to improve bone loss in RA. There have been many studies on the relationship between TNF inhibitors and bone mineral density (BMD). Several studies revealed beneficial effects of TNF inhibitors on attenuating bone loss by showing improvements in BMD (10-13). However, there are studies with conflicting results, showing insignificant associations of TNF inhibitors with bone loss (7, 8).

The aim of this study was to examine systemic bone metabolism after 1 year of treatment with TNF inhibitors in patients with RA. We also investigated what affects systemic bone metabolism in RA patients when the disease activity is controlled by anti-TNF treatment.

Methods

Patients

The patients were screened and participated in this study at the rheumatology outpatient department of the tertiary medical centre between April 2014 and December 2017. A total of 29 seropositive RA patients (22 women, 7 men) were enrolled. The mean age of the patients was 50.4 years (range, 37–68 years). All patients fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA. They were active RA patients with a Disease Activity Score based on 28 joints (DAS28) >3.2 at inclusion despite the use of conventional disease-modifying anti-rheumatic drugs over 6 months; thus, TNF inhibitors, etanercept, adalimumab, and infliximab, were administered to 12, 10, and 7 patients, respectively. All TNF inhibitors were used according to the dosages approved for the treatment of RA and administered by Korean national health insurance. Exclusion criteria were patients on osteoporotic medication including bisphosphonates and selective oestrogen receptor modulators, and current treatment with calcineurin inhibitors, medroxyprogesterone, anticonvulsants, aromatase inhibitors and gonadotropin-releasing hormone agonists, and patients with history of malignancy were also excluded. Obesity was categorised as BMI ≥25 kg/m^2. This classification was designated for Asians by the Western Pacific Region of WHO, considering the regional and ethnical differences such as relative high abdominal fat at low BMI and low prevalence of people over 30 kg/m^2 of BMI among Asians (14-16). Clinical disease activity was determined using the DAS28 for RA patients at baseline and after 6 and 12 months of anti-TNF treatment. This study complied with the recommendations of the Declaration of Helsinki and was approved by the institutional review board of Inha University Hospital (IRB 14-016). Written informed consent was obtained from all patients.

Cell preparation and culture

Blood sampling along with RA disease activity was done at baseline and after 6 and 12 months of TNF inhibitor initiation. Osteoclast preparation and culture were performed as previously described (17). Peripheral blood was collected and peripheral blood mononuclear cells

(PBMCs) were isolated from the blood sample using Ficoll-Hypaque density gradient centrifugation. To culture osteoclast precursor cells, we suspended the isolated PBMCs in alpha-minimum essential medium containing 1% penicillin-streptomycin and 10% fetal bovine serum, and seeded them at a density of 1×10^6 cells per well in 96-well plates. We settled the cells in culture medium for 7 days, and exchanged this medium to differentiation medium supplemented with human receptor activator of nuclear factor kappa B ligand (RANKL) and macrophage colony-stimulating factor (both 50 ng/mL; Peptro Tech EC Ltd., London, UK) (18). To stain the cells cytochemically for tartrate-resistant acid phosphatase (TRAP), an acid phosphatase kit (386-A; Sigma-Aldrich, St. Louis, MO, USA) was used after fixation of the cells. TRAP positive giant cells were classified as osteoclasts if they had more than three nuclei (19). After counting all the osteoclasts in three wells, we calculated the average number of cells per well. For the resorption assay, PBMCs were seeded on bovine bone slices to be incubated in culture medium for 7 days and subsequently in differentiation medium for another 2 weeks. After removal of the cells, the remained pits in the bone slices were stained with 0.5% toluidine blue. Review of the bone slices was conducted by two researchers blinded to the sequence of culture, and morphometric quantification of the resorption areas was performed by a computer image analysis program. Normal bone structures, such as Haversian canals and canaliculi, were stained more lightly than bone resorption pits of osteoclasts. Thus, grey scale was used to determine a threshold to ensure the detection of only the areas with stronger staining than that found on normal bone surface. The threshold could be adjusted with respect to the intensity of bone staining for each sample. The programme summed the whole area of resorption pits for each bone slice detecting areas with darker staining. We calculated the ratios of total pit resorption area per bone slice at baseline and 6 and 12 months after TNF inhibitor initiation.

Serum samples were drawn from each patient before and after 6 and 12 months of TNF inhibitor initiation and were processed for routine laboratory tests, including those for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, and for markers for bone metabolism. Serum levels of RANKL, C-terminal telopeptide (CTX), bone-specific alkaline phosphatase (BSALP) and osteoprotegerin (OPG) were measured using commercially available, enzyme-linked immunosorbent assay kits (RANKL, Biomedica, Wien, AT: inter-assay coefficient of variation (CV) 3% to 5%; CTX, Nordic Bioscience Diagnostics A/S, Herlev, DK: inter-assay CV 2.5% to 10.9%; BSALP, Quidel, San Diego, CA, USA: inter-assay CV 5% to 8%; OPG, Biomedica, Wien, AT: inter-assay CV 3% to 5%).

BMD (g/m^2) was measured by dual energy X-ray absorptiometry (Luna Prodigy Advance, GE Healthcare, Diegem, BE). It was measured at baseline and 12 months after anti-TNF treatment.

Statistical analysis

Data are presented as mean ± standard

Table I. Characteristics of patients enrolled in the study at baseline.

Variable	All enrolled patients (n=29)	Obese group (BMI ≥25 kg/m^2) (n=9)	Non-obese group (BMI <25 kg/m^2) (n=20)
Age (years)	50.4 ± 8.2	50.5 ± 7.1	50.3 ± 8.7
Female (%)	79.3	55.6	90.0
Menopausal state (%)*	56.5	80.0	50.0
Smoking status (%)			
non-current smoker	96.6	88.9	100.0
current smoker	3.4	11.0	0.0
Disease duration (years)	6.5 ± 6.5	7.7 ± 7.2	6.1 ± 6.4
BMD at lumbar spine (g/cm^2)	1.144 ± 0.148	1.257 ± 0.140	1.087 ± 0.120**
at femur neck	0.890 ± 0.111	0.970 ± 0.136	0.852 ± 0.075**
at total hip	0.954 ± 0.144	1.084 ± 0.146	0.892 ± 0.096**
Glucocorticoids daily dose (prednisolone equivalent, mg/day)***	5.0 (3.8–6.3)	5.0 (2.5–5.0)	5.0 (5.0–7.5)
Duration of glucocorticoid use (years***	3.0 (0.9–8.0)	3.0 (0.6–7.5)	3.5 (1.0–9.5)
MTX use (%)	96.6	100.0	95.0
DAS28-ESR	6.59 ± 0.90	6.40 ± 0.99	6.68 ± 0.87
DAS28-CRP	6.21 ± 0.82	5.98 ± 1.00	6.31 ± 0.73

Values are expressed as mean ± SD, * denotes the values among female patients, **p-value <0.05 compared to the obese group, ***median (interquartile range).
TNF: tumour necrosis factor; BMI: body mass index; BMD: bone mineral density; MTX: methotrexate; DAS: disease activity score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

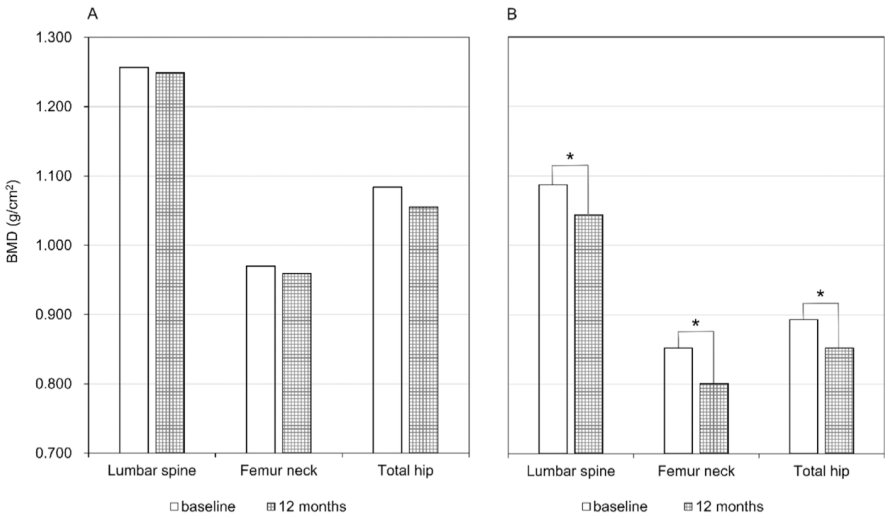

Fig. 1. BMDs with respect to obesity, (**A**) obese group, (**B**) non-obese group.
* p-value <0.05; BMD: bone mineral density; BMI: body mass index.

deviation, and if not distributed normally, as median (interquartile range). Comparisons between two independent groups were performed by the Mann-Whitney test. Comparisons of variables over time points within the same group were performed by the Wilcoxon signed rank test. Linear regression analysis was used to identify the factor that exerted the greatest influence on systemic bone loss. Results were analysed using SPSS v. 19.0 (SPSS Inc., Chicago, IL, USA). Two-sided *p*-values <0.05 were considered statistically significant.

Results

The characteristics of patients at baseline are shown in Table I. Linear regression analysis was performed and baseline weight was found to be the strongest factor influencing systemic bone loss, which was manifested as low BMD. Thus, we hypothesised that obesity may affect bone metabolism and divided RA patients into two groups: an obese group (BMI ≥25 kg/m^2, n=9) and a non-obese group (BMI <25 kg/m^2, n=20). There were no statistical differences in age, glucocorticoids dose, and duration of glucocorticoids use between the two groups. However, BMDs measured at baseline were significantly higher at all sites in the obese group than in the non-obese group (Table I).

All RA patients showed significantly lower BMD at the lumbar spine, femur neck, and total hip after 1 year of anti-TNF treatment. BMDs at the lumbar spine, femur neck, and total hip significantly decreased after 1 year of anti-TNF treatment in the non-obese group, while BMDs did not change at any site in the obese group (Fig. 1, Table II). There was a difference in the proportion of women and men between the obese group and the non-obese group. To exclude effects of the difference in the sex ratio, BMDs were analysed among only female patients. The results of BMDs at baseline and 12 months in the female obese group were as follows: lumbar spine (1.186±0.069, 1.156±0.022, *p*=1.000), femur neck (0.922±0.129, 0.905±0.124, *p*=0.715), and total hip (1.014±0.102, 0.979±0.084, *p*=0.465). And those of BMDs at baseline and 12 months in the female non-obese group were as follows: lumbar spine (1.081±0.119, 1.034±0.115, *p*=0.012), femur neck (0.863±0.075, 0.809±0.084, *p*=0.004), and total hip (0.907±0.095, 0.864±0.109, *p*=0.005). The same trend of change of BMD after treatment of TNF inhibitors were observed in both the separate analysis of female patients

Table II. Changes of BMD after anti-TNF treatment.

Variable	All patients (n=29)			
	Baseline (g/cm^2)	12 months (g/cm^2)	Absolute change from baseline (g/cm^2)	Relative change from baseline (%)
BMD at lumbar spine	1.144 ± 0.148	1.113 ± 0.164*	-0.031 ± 0.054	-2.8 ± 4.8
at femur neck	0.890 ± 0.111	0.851 ± 0.127*	-0.039 ± 0.051	-4.5 ± 5.9
at total hip	0.954 ± 0.144	0.917 ± 0.153*	-0.037 ± 0.042	-4.0 ± 4.6
Variable	Obese group (BMI ≥25 kg/m^2) (n=9)			
	Baseline (g/cm^2)	12 months (g/cm^2)	Absolute change from baseline (g/cm^2)	Relative change from baseline (%)
BMD at lumbar spine	1.257 ± 0.140	1.249 ± 0.165	-0.008 ± 0.062	-0.8 ± 4.8
at femur neck	0.970 ± 0.136	0.959 ± 0.144	-0.012 ± 0.056	-1.2 ± 5.5
at total hip	1.084 ± 0.146	1.055 ± 0.149	-0.029 ± 0.040	-2.7 ± 3.7
Variable	Non-obese group (BMI <25 kg/m^2) (n=20)			
	Baseline (g/cm^2)	12 months (g/cm^2)	Absolute change from baseline (g/cm^2)	Relative change from baseline (%)
BMD at lumbar spine	1.087 ± 0.120	1.044 ± 0.116*	-0.043 ± 0.048	-3.9 ± 4.6
at femur neck	0.852 ± 0.075	0.801 ± 0.082*	-0.051 ± 0.045	-6.0 ± 5.6
at total hip	0.892 ± 0.096	0.852 ± 0.107*	-0.041 ± 0.043	-4.7 ± 4.9

Values are expressed as mean ± SD, *p-value <0.05 compared to baseline.
TNF: tumour necrosis factor; BMD: bone mineral density; BMI: body mass index.

Table III. Changes in *ex vivo* cultures and bone turnover markers after anti-TNF treatment.

Variable	Obese group (BMI ≥25 kg/m^2) (n = 9)		
	Baseline	6 months	12 months
Number of osteoclasts (per well)	499.4 ± 233.5	392.1 ± 237.2	434.1 ± 188.3
Resorption pits (mm)	296.32 ± 59.09	150.46 ± 71.47*	120.96 ± 104.73
Resorption pits (%)	5.36 ± 9.49	2.18 ± 3.40*	0.62 ± 0.54
CTX (nM)	0.629 ± 0.585	0.829 ± 0.760	0.410 ± 0.156
BSALP (U/L)	25.38 ± 8.53	27.33 ± 9.09	27.74 ± 6.37
RANKL (pmol/L)	0.149 ± 0.109	0.141 ± 0.079	0.089 ± 0.043
OPG (pmol/L)	3.787 ± 1.122	3.615 ± 1.217	4.820 ± 1.375
Variable	Non-obese group (BMI <25 kg/m^2) (n = 20)		
	Baseline	6 months	12 months
Number of osteoclasts (per well)	533.7 ± 306.3	313.2 ± 135.4*	292.5 ± 210.0**
Resorption pits (mm)	185.65 ± 99.60	86.15 ± 69.57*	164.83 ± 115.62
Resorption pits (%)	1.21 ± 0.86	0.44 ± 0.36**	1.10 ± 0.85
CTX (nM)	0.587 ± 0.331	0.620 ± 0.281	0.489 ± 0.224
BSALP (U/L)	24.55 ± 9.74	25.94 ± 8.21	24.86 ± 7.41
RANKL (pmol/L)	0.128 ± 0.077	0.140 ± 0.055	0.169 ± 0.083
OPG (pmol/L)	4.357 ± 1.915	4.520 ± 1.880	3.460 ± 1.417

Values are expressed as mean ± SD, *p-value <0.05 compared to baseline, **p-value <0.001 compared to baseline.
TNF: tumour necrosis factor; BMI: body mass index; CTX: C-terminal telopeptide; BSALP: bone-specific alkaline phosphatase; RANKL: receptor activator of nuclear factor kappa B ligand; OPG osteoprotegerin.

Table IV. RA disease activity and inflammatory markers after anti-TNF treatment.

Variable	Obese group (BMI ≥25 kg/m^2) (n=9)		
	Baseline	6 months	12 months
ESR (mm/hr)	31.67 ± 18.12	20.89 ± 14.86*	17.22 ± 16.75**
CRP (mg/dL)	1.69 ± 1.28	0.45 ± 0.60**	0.35 ± 0.52**
DAS28-ESR	6.40 ± 0.99	4.48 ± 1.19*	3.21 ± 1.14*
DAS28-CRP	5.98 ± 1.00	3.98 ± 0.90**	3.15 ± 0.53*
Variable	Non-obese group (BMI <25 kg/m^2) (n=20)		
	Baseline	6 months	12 months
ESR (mm/hr)	35.40 ± 20.85	30.30 ± 33.42	21.90 ± 21.73**
CRP (mg/dL)	2.00 ± 1.95	1.09 ± 1.85	0.34 ± 0.34**
DAS28-ESR	6.68 ± 0.87	4.62 ± 1.55**	3.44 ± 0.96**
DAS28-CRP	6.31 ± 0.73	4.21 ± 1.24**	3.16 ± 0.63**

Values are expressed as mean ± SD, *p.value <0.05 compared to baseline, **p-value <0.001 compared to baseline.
RA: rheumatoid arthritis; TNF: tumour necrosis factor; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS: disease activity score.

and the combined analysis of male and female patients.

The obese group showed the steadily decreasing sizes of resorption pits produced by cultured osteoclasts, suggesting reduced osteoclast activity. The serum levels of RANKL also decreased at 12 months after 1 year of treatment with TNF inhibitors in the obese group. On the other hand, the non-obese group presented with the decreased numbers of osteoclasts and the sizes of resorption pits produced by cultured osteoclasts decreased at 6 months and then increased at 12 months, suggesting increasing osteoclast activity. The serum levels of RANKL increased from baseline to 12 months after 1 year of anti-TNF treatment (Table III).

RA disease activity was markedly improved in both groups. Inflammatory markers, including ESR and CRP, decreased at 12 months in both groups (Table IV).

Discussion

The present study demonstrated that BMD of lumbar spine, femur neck, and total hip decreased significantly in RA patients not treated for osteoporosis, despite the administration of TNF inhibitors over 1 year. When these patients were categorised with respect to BMI, BMDs in the obese group remained stable but those in the non-obese group decreased. Osteoclast activity decreased in the obese group, but increased in the non-obese group. Disease activity and inflammatory markers, including ESR and CRP, were reduced in both groups. Our study, supported by *ex vivo* cultures and bone turnover markers, is the first to demonstrate that systemic bone metabolism after 1 year of anti-TNF treatment in RA patients not treated for osteoporosis is strongly affected by obesity. One year of anti-TNF treatment failed to improve the BMD of RA patients not treated for osteoporosis in this study. A few recent studies showed that TNF inhibitors were not associated with change of BMD (7, 8). These retrospective studies revealed no added beneficial effect of TNF inhibitors to bisphosphonates on BMD and suggested that the action of TNF inhibitors was insignificant compared to that of bisphosphonates (8). This is in accordance with our study, since BMD decreased in our patients, who received TNF inhibitors without anti-osteoporosis medication. To eliminate effects of medication on bone metabolism, patients on bisphosphonates and selective oestrogen receptor modulators were excluded. In real practice, it is interesting to observe that patients on both bisphosphonates and TNF inhibitors did not show any change of BMD at any site. However, most studies on the relationship between TNF inhibitors and BMD have supported an inhibitory effect of TNF inhibitors on systemic bone loss (10, 11, 20-22). Because these studies included up to 23% of subjects treated with bisphosphonates, the effect of TNF inhibitors on BMD independent of the effect of bisphosphonates needs to be further investigated.

The most interesting finding of our study is that BMD did not change at any site and that osteoclast activity decreased in the obese group, pointing to improved bone metabolism. There have been very few studies to explore the association between body mass and systemic bone loss in RA patients (1, 4-6, 23). These studies showed that BMI was positively correlated with BMD and that BMI was a protective factor in osteoporosis. None of these studies provided a theoretical basis for explaining the relationship between BMI and BMD in RA. In contrast to sparse studies on systemic bone loss, there have been several studies on the relationship of body mass with marginal bone erosion in RA (24-30). They demonstrated that higher BMI was associated with less severe bone erosion. Considering that marginal bone erosion and systemic bone loss might have a common underlying mechanism, potential explanations for the protective effect of obesity on BMD may be found in studies on marginal bone erosion and BMI (1, 3, 4). The effects of greater body mass on bone remodeling through mechanical loading and the roles of anti- or pro-inflammatory mediators, including interleukin (IL)-1 receptor antagonist, oestrogen, and adiponectin, were suggested to have protective effects on BMD in obesity (24-28). Patients with higher serum levels of adiponectin showed higher rates of radiographic progression in RA (31). In this study a sex ratio was different depending on the obesity status. Accordingly, the change of BMD was analysed separately in female patients to determine whether there was the effect of the sex ratio on BMD evaluation. The number of male patients was too small to be included in this analysis. Furthermore, only two men were present in the non-obese group which showed the significant results. The BMD in the non-obese group was significantly reduced by 12 months compared to the baseline, but the BMD in the obese group did not change sig-

nificantly. These results were consistent with those of the combined analysis of male and female patients. It was unclear whether BMD evaluation was affected by the difference of a sex ratio between the obese and the non-obese group.

The osteoclast pathway is one of the factors behind developing bone loss in RA (1, 3, 32-34). Pro-inflammatory cytokines, such as TNF, IL-1, IL-6, and IL-17, activate osteoclastogenesis by exerting direct effects on osteoclasts, inducing RANKL, and increasing osteoclast-associated receptor expression. RANKL binds to RANK receptor on osteoclast precursors and mature osteoclasts, leading to osteoclast differentiation and activation. RANKL is the pivotal mediator in the osteoclast pathway (3, 32). The excessive production of RANKL is not controlled by its physiologic inhibitor and decoy receptor OPG. This imbalance in RANKL/OPG ratio seems to be directly related to bone resorption in RA. One thing to note in the present study is that bone loss was manifested through not only BMD, but also through several markers of osteoclastogenesis. In the obese group, sizes of osteoclast resorption pits declined steadily. However, in the non-obese group, osteoclast resorption pits decreased in sizes by 6 months but increased by 12 months. It could be suggested that the increase in the sizes of resorption pits manifesting osteoclast activity meant acceleration of bone loss and this was reflected in BMD. The augmented functional activity of osteoclasts rather than the increased osteoclastogenesis is known to be involved in systemic bone loss in RA (35, 36). Although not statistically significant, RANKL levels decreased in the obese group, but increased in the non-obese group in the present study. To the best of our knowledge, there has been no study to show differences in changes of RANKL levels depending on BMI, after anti-TNF treatment.

A finding of the present study to be mentioned finally is that disease activity and inflammatory markers improved regardless of BMI after anti-TNF treatment. Disease activity and inflammatory markers at baseline also showed no significant differences between the obese and non-obese groups in the present study. Obesity is generally regarded as a pro-inflammatory condition, due to increased production of pro-inflammatory molecules in the obese state (2). However, in studies on the association between marginal bone erosion and BMI, this association was independent of the degree of inflammation (27, 28). TNF inhibitors are involved in systemic bone loss in RA by their anti-inflammatory action and specific inhibition of TNF (8, 33, 37, 38). Therefore, bone metabolism in RA treated with TNF inhibitors might be dependent mainly on their specific inhibition of TNF rather than their anti-inflammatory effects.

Because of chronic inflammation associated with the disease itself and consequent decreased mobility, RA patients usually experience altered body composition, which includes obesity as well as rheumatoid cachexia. The prevalence of obesity in RA patients seems to be higher than in the general population (2). Although weight and height measurements can be easily performed in rheumatology clinics, this anthropometric information is mostly used to characterise demographic findings rather than to be studied in its own. Obesity in RA exerts contradictory effects on different aspects of the disease. One meta-analysis showed that increased BMI was associated with a higher risk of RA development (39). Many studies revealed that achieving low disease activity in RA was impeded by high BMI (40-43). However, obesity might protect against the marginal bone erosion and generalised osteoporosis experienced by RA patients.

This study has some limitations. First, the sample size was too small to derive statistical significance in all investigated parameters. Second, all the patients enrolled in this study were responders to TNF inhibitors. The patients unresponsive to TNF inhibitors were excluded from the study earlier than 6 months and their data were not included in analysis. Third, patients with higher BMI had greater BMD than those with lower BMI. It would have been preferable if BMDs could have been matched between the two groups, but this could also be the result of rapid bone loss in patients with lower BMI. Additionally, there were very few enrolled male patients. Further studies are required to clarify the relationship between body mass and BMD in male patients. However, we think our study is valuable because it is the first to investigate the relationship between BMI and bone loss using both BMD and osteoclast culture in RA patients.

Conclusion

TNF inhibitors did not halt systemic bone loss in RA patients not treated for osteoporosis, but obesity may have protective effects against systemic bone loss. It is advisable for physicians to consider BMI in choosing the optimal treatment for RA, including for osteoporosis and control of RA disease activity.

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