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Original Article

Bone turnover markers in the early stage of rapidly progressive osteoarthritis of the hip

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Abstract

Objective: Previous reports have demonstrated that patients with end-stage rapidly progressive osteoarthritis of the hip (RPOH) show significantly higher serum levels of bone turnover markers than those with osteoarthritis (OA). However, the characteristics of bone turnover markers in the early stage of RPOH remain unclear. This study aimed to elucidate the association of bone turnover markers with disease progression in the early stage of RPOH.

Methods: This study included 29 postmenopausal female patients with joint space narrowing >2 mm demonstrated on a series of radiographs and computed tomography within 1 year following the onset of hip pain. The study also included 9 postmenopausal female patients with hip OA secondary to developmental dysplasia showing femoral head destruction. Cortical thickness index (CTI) associated with bone mineral density of the hip was analyzed. Serum concentrations of tartrate-resistant acid phosphatase-5b (TRACP-5b) and bone alkaline phosphatase (BAP) were evaluated.

Results: RPOH was classified into two types on the basis of the absence (type 1, n=13) or presence (type 2, n=16) of subsequent destruction of the femoral head within 1 year following disease onset. TRACP-5b and BAP significantly increased in RPOH type 2 compared with type 1 and OA. Receiver operating characteristic curve analyses indicated that TRACP-5b and BAP could differentiate RPOH type 2 from type 1 within 1 year following the onset. CTI showed no difference among the RPOH types 1 and 2 and OA.

Conclusion: High serum levels of bone turnover markers may be associated with destruction of the femoral head in the early stage of RPOH.

Keywords: Alkaline phosphatase, biomarkers, hip joint, osteoarthritis, tartrate-resistant acid phosphatase

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Introduction

Rapidly progressive osteoarthritis of the hip (RPOH), also known as rapidly destructive arthritis/osteoarthritis/coxopathy, commonly occurs in elderly women and results in severe disability of the hip joint (1). RPOH has been defined as chondrolysis >2 mm in 1 year with no evidence of other forms of rapidly progressive arthropathy, including osteonecrosis, neuropathy, infection, or inflammatory disease (2). Potential causes of RPOH that have been suggested include increasing posterior pelvic tilt as a mechanical factor (3) and high serum levels of matrix metalloproteinase (MMP)-3 as a biological factor (4).

The mechanism of RPOH progress during its early phase from onset remains unclear. Although the current diagnostic criterion (chondrolysis >2 mm per year) requires the patient to be followed up for over 12 months, rapid progression of this disease makes it difficult to obtain sequential radiographs in its early stage (5). In some patients with RPOH, however, destruction of the femoral head and/or acetabulum is found within the first 6-24 months after the disease onset, following rapid joint space narrowing (5, 6). Our recent study has shown that RPOH progression within 1 year following disease onset can be classified into 2 distinct types on the basis of the absence and presence of destruction of the femoral head (7). We have also demonstrated, using the hematological and radiological data within 1 year following the disease onset, that the destruction of the femoral head in the early stage of RPOH is associated with higher serum levels of MMP-3 and an increase in the posterior pelvic tilt (7).

Although the mechanism leading to rapid bone destruction in RPOH remains uncertain, histological and *in vitro* studies have shown the presence of mature and activated osteoclasts in the synovium of RPOH with femo-

ral head destruction in contrast to their absence in the osteoarthritis (OA) synovium (8). Previous findings reveal that serum levels of bone turnover markers are significantly higher in patients with RPOH than those with OA (9, 10). Blood samples were obtained from patients who were scheduled to undergo total hip arthroplasty for end-stage RPOH with femoral head collapse in these studies (9, 10); however, no information is currently available on bone turnover markers in the early stage of RPOH, especially within 12 months of disease onset. Delayed treatment for patients with RPOH having severe bone destruction may cause considerable difficulties in arthroplasty owing to bone stock deficiency and intraoperative blood loss (6, 7). This leads to the requirement of early diagnosis before the initiation of significant bone destruction in patients with RPOH. This study aimed to characterize bone turnover markers that are associated with the destruction of the femoral head within 1 year from the onset of RPOH.

Methods

This retrospective study was conducted at a single institution. This study was approved by the Ethics Committee of Kobe City Medical Center General Hospital (Approval Date: February 24, 2018; Approval Number: k190516) with no requirement of informed consent because of the retrospective nature of the study. The inclusion criteria for this study were 1) postmenopausal female patients who met the diagnostic criteria of RPOH (joint space narrowing >2 mm in 1 year), 2) availability of clinical data at the onset of hip pain; availability of age and body mass index (BMI) at onset, 3) availability of sequential radiographs and computed tomography (CT) taken at the onset of hip pain and every 3-4 months thereafter during the 12 months following onset, and 4) availability of blood examination results of tartrate-resistant acid phosphatase-5b (TRACP-5b) and bone alkaline phosphatase (BAP). Blood samples were collected in the morning before breakfast at the first visit to our hospital. While TRACP-5b levels were measured using an enzyme immunoassay, BAP levels were measured using a chemiluminescent enzyme immunoassay. The exclusion criteria were 1) male patients because RPOH occurs commonly in elderly women, and the reference intervals (RIs) of the bone turnover markers are different for men and women and 2) premenopausal and postmenopausal patients who received anti-osteoporosis treatment. From a series of patients with hip pain from 2015 through 2018, we found 29 women who met the inclusion criteria. Each patient suffered from unilateral RPOH without evidence of other diseases. In addition, we found 9 postmenopausal female patients, with unilateral OA secondary to the developmental dysplasia of the hip (DDH), showing partial femoral head destruction with insufficient coverage of the femoral head by the acetabulum, at the first visit to our hospital.

On the first radiograph at the onset of hip pain, the femoral diaphyseal diameter and the intramedullary canal diameter were measured 10 cm below the midpoint of the lesser trochanter. The ratio of the former diameter minus the latter diameter to the former diameter provided the cortical thickness index (CTI) (11). CTI has been demonstrated to significantly correlate with bone mineral density (BMD) of the proximal femur (12, 13). CT was employed to assess the hip joint destruction. Magnetic resonance imaging was used to rule out other diagnoses.

Statistical analysis

The data were expressed as the mean±standard error (SE). The data were compared between three groups using one-way analysis of variance accompanied by post hoc Bonferroni correction for multiple comparisons. Receiver operating characteristic (ROC) curves were plotted, and the cut-off values for high specificity or high sensitivity were identified for TRACP-5b and BAP. The area under the curve (AUC) was also calculated from the ROC curves for the bone turnover markers. Statistical analyses were conducted in IBM Statistical Package for Social Sciences for Windows, version 25 (IBM SPSS Corp.; Armonk, NY, USA). The level of significance was set at $p<0.05$.

Main Points

- Rapidly progressive osteoarthritis of the hip (RPOH) is classified into 2 types on the basis of the absence or presence of subsequent femoral head destruction during the first 12 months after onset.
- RPOH with femoral head destruction within 12 months after the onset is associated with increased serum levels of tartrate-resistant acid phosphatase 5b (TRACP-5b) and bone alkaline phosphatase (BAP).
- TRACP-5b and BAP may differentiate the 2 types in early stage of RPOH.

Results

Classification of disease progression in the early stage of RPOH on the basis of destruction of the femoral head

We have already shown that RPOH can be classified into types 1 and 2 on the basis of the absence or presence of destruction of the femoral head, respectively, within 1 year following the onset of hip pain (7). Accordingly, 13 of 29 patients with RPOH were classified into type 1, showing only joint space narrowing without destruction of the femoral head within 1 year following onset (Figure 1). Subsequent to rapid chondrolysis, the CT showed destruction of the femoral head within 1 year following the disease onset in 16 patients who were classified into RPOH type 2 (Figure 1). There were 9 patients with OA secondary to DDH, demonstrating femoral head destruction at the first visit to our hospital (Figure 1). No differences in age at onset, BMI, CTI, or duration between blood test and the disease onset were found among the RPOH types 1 and 2 and OA (Table 1).

Comparison of bone turnover markers between RPOH types and OA

We compared TRACP-5b (RI: 120-420 mU/dL) and BAP (RI: 3.8-22.6 μg/L) within 1 year fol-

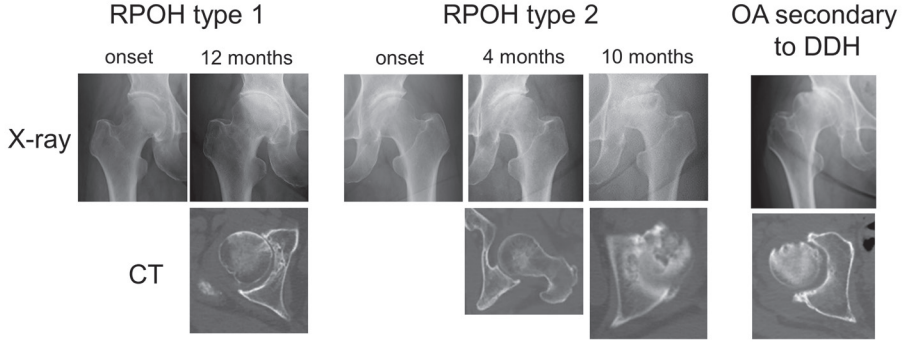

Figure 1. Disease progression of rapidly progressive osteoarthritis of the hip (RPOH) during 12 months after the onset of hip pain and osteoarthritis (OA) secondary to the developmental dysplasia of the hip (DDH). RPOH type 1: Right hip joint showing chondrolysis >2 mm/year in a series of radiographs without femoral head destruction or computed tomography (CT) at 12 months after the onset. RPOH type 2: Left hip joint demonstrating partial destruction of the anterior portion in the femoral head on CT at 10 months after onset following chondrolysis. OA: Right hip OA with DDH showing partial destruction of the anterior portion of the femoral head on CT at the first visit.

Table 1. Comparisons of demographic and radiographic data among patients with rapidly progressive osteoarthritis of the hip (RPOH) and osteoarthritis (OA) secondary to developmental dysplasia of the hip (DDH).

	RPOH		OA secondary to DDH	p values by ANOVA	p values by Bonferroni test		
	type 1 (n=13)	type 2 (n=16)	(n=9)		types 1-2	type 1-DDH	type 2-DDH
Age (years)	75.9±2.1	72.6±2.3	68.6±2.9	0.153	0.918	0.165	0.791
Body mass index (kg/m^2)	23.1±1.0	23.8±1.2	21.6±1.2	0.439	1.000	1.000	0.610
Cortical thickness index	0.526±0.019	0.541±0.012	0.541±0.022	0.779	1.000	1.000	1.000
Duration between the onset of hip pain and blood test (months)	4.77±0.79	5.13±0.77	4.89±0.79	0.944	1.000	1.000	1.000

Values are expressed as mean±SE. ANOVA: one-way analysis of variance.

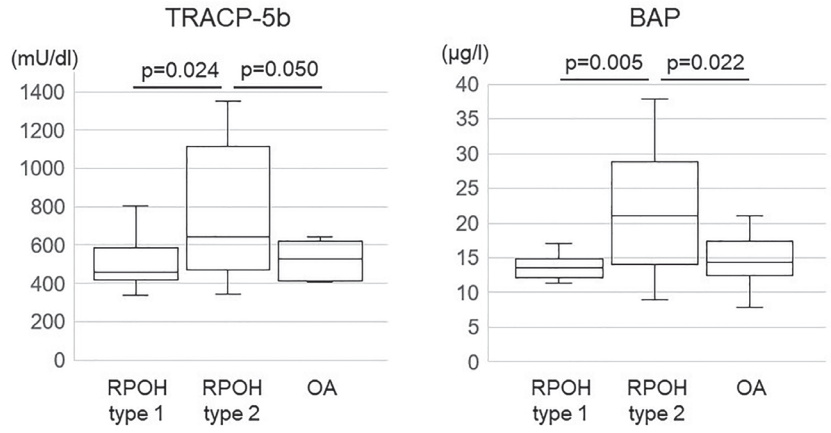

Figure 2. Comparison of bone turnover markers among rapidly progressive osteoarthritis of the hip (RPOH) types 1 and 2 and OA secondary to the developmental dysplasia of the hip (DDH). Box plots show serum levels of tartrate-resistant acid phosphatase-5b (TRACP-5b) and bone alkaline phosphatase (BAP) for RPOH types 1 (n=13) and 2 (n=16), and OA (n=9). The top and bottom of the box represent the interquartile range, the line within the box represents the median, and the whiskers indicate the range. p values are determined by a post hoc Bonferroni correction for multiple comparisons.

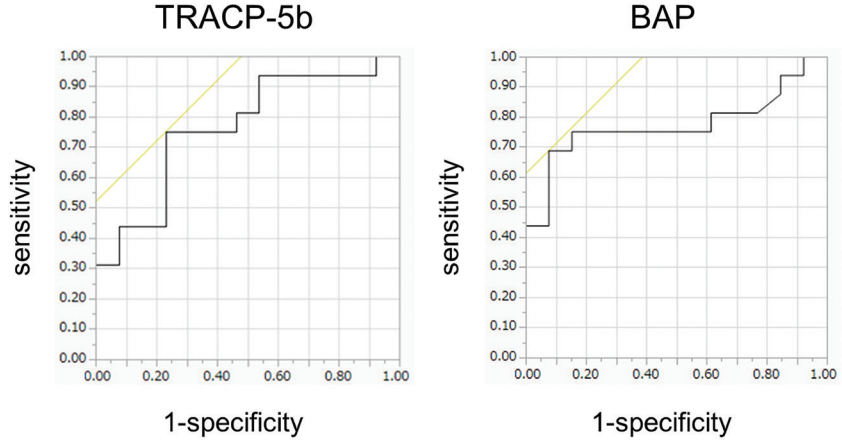

Figure 3. Receiver operating characteristic (ROC) curve analysis of tartrate-resistant acid phosphatase-5b (TRACP-5b) and bone alkaline phosphatase (BAP) for differentiation of rapidly progressive osteoarthritis of the hip type 2 (n=16) from type 1 (n=13) shown by ROC curve. The area under the curve values are TRACP-5b, 0.764 and BAP, 0.772.

lowing disease onset among RPOH types 1 and 2 and OA (Figure 2). A significant increase was found in TRACP-5b and BAP levels in RPOH type 2 compared with RPOH type 1 and OA. ROC curve analyses using the data of bone turnover markers indicated that TRACP-5b and BAP could differentiate RPOH type 2 from type 1 within 1 year following disease onset (Figure 3). The AUC for TRACP-5b was 0.764 (p=0.016, 95% confidence interval [CI]: 0.588-0.941). With regard to the cut-off value based on the ROC curve, TRACP-5b demonstrated 76.9% specificity and 75.0% sensitivity with a cut-off at 500 mU/dL. AUC for BAP was 0.772 (p=0.013, 95% CI: 0.590-0.953), and BAP showed 92.3% specificity and 68.8% sensitivity with the cut-off at 18.0 μg/L.

Discussion

As first reported in English literature in 1970 (14), there is a consensus that the first manifestation of RPOH is rapid chondrolysis with progressive joint space narrowing. Because of the lack of consecutive radiographs in the early phase of RPOH (5, 15), the disease progression in the early stage has been unclear. Using radiographs and CT taken at regular intervals within 12 months after the disease onset, we have found that RPOH may be distinguished into 2 different types on the basis of the radiological findings with and without destruction of the femoral head in the early stage, in accordance with our previous report (7). In addition, no study has stratified this disease by bone turnover markers in its early phase. This study has provided the first evidence of the association of femoral head destruction in RPOH with high serum levels of TRACP-5b and BAP using hematological and radiological data within 1 year following disease onset.

Bone turnover markers have been employed to find the pathological conditions with osteoclast activation, such as metastasis of malignant tumors (16). Compared with the OA synovial fluid, TRACP-5b levels have been shown to increase in the synovial fluid from patients with RPOH (9). Previous histological examinations have demonstrated the presence of mature and activated osteoclasts in the synovium (8) and the femoral head (10) of RPOH. Recently, increased serum levels of TRACP-5b have been reported in patients with RPOH compared with those with OA or femoral neck fracture. In

addition, the increased preoperative levels of TRACP-5b decreased at 3 weeks after total hip arthroplasty in patients with RPOH (10). There is no difference in BMD of the proximal femur between patients with RPOH and OA (10, 17), and no difference in generalized BMD is observed between them (18). Taken together, accelerated turnover of bone metabolism may occur in hip joints with RPOH, which could cause an increase in TRACP-5b levels. From the study results, the progression of femoral head destruction in RPOH type 2 is likely to be associated with increased levels of TRACP-5b and BAP within 1 year following disease onset. No significant difference was found in CTI among RPOH types 1 and 2 and OA, indicating that osteoporosis could play a minor role in femoral head destruction in RPOH type 2.

One of the major concerns regarding RPOH is that delayed diagnosis may result in severe joint destruction during the short period after disease onset, leading to considerable difficulties in total hip arthroplasty (6, 7). In diseases with osteoclast activation, bone turnover markers are helpful in monitoring the disease. Serum TRACP-5b and BAP levels can serve as useful tools for screening of bone metastasis from lung cancer (16). In addition, serum levels of these two markers are different between established RPOH and OA (10). Similarly, this study suggests that TRACP-5b and BAP may contribute to differentiation between the presence and absence of destruction of the femoral head during the early stage of RPOH within 1 year after disease onset. On the contrary, the synovial fluid obtained from the affected hip joint at surgery has shown no difference in BAP levels between patients with established RPOH (mean age: 70 years) and OA (mean age: 56 years) (9). Different background characteristics, including age and gender between the examined groups, may be related to the discrepancy in BAP levels. Additional studies may be required to elucidate bone turnover marker levels before the initiation of bone destruction in RPOH. If serum bone turnover markers can predict RPOH type 2 in the initial stage before the manifestation of femoral head destruction, early intervention may be possible to prevent bone destruction in RPOH type 2.

Mature and activated osteoclasts are observed in the synovium of patients with RPOH with femoral head destruction over a short period of time, compatible with RPOH type 2 in this study in contrast to their absence in the synovium of patients with OA (8). Synovial cells isolated from patients with RPOH with femoral head destruction show high mRNA expression of receptor activator of nuclear factor κB ligand (RANKL). However, no difference is found in its expression between the cells from patients with RPOH and patients with OA (8), suggesting another mechanism underlying the increased number of osteoclasts in RPOH. Osteoclast formation and activity are stimulated by proinflammatory cytokines including tumor necrosis factor α (TNFα), interleukin (IL)-1, and IL-6 (19, 20), which are found in the hips with RPOH (21, 22). Osteoclast differentiation can be driven by a combination of TNFα and IL-1 in a RANKL-independent manner (23). Osteoclast-like cells with bone-resorptive activity are also induced by a combination of TNFα and IL-6 (24). IL-8, whose levels are increased in the synovial fluid from hips of patients with RPOH (22), can stimulate osteoclast formation and activity in a RANKL-independent manner (25). Clarification of these cytokine pathways leading to osteoclast activation may help develop preventive treatment for bone destruction in RPOH.

This study has several limitations. First, this study was retrospective with some selection bias. Second, a relatively small number of female patients were included in this study without male patients or healthy subjects. In the literature review, previous studies on RPOH markers have included patients ranging from 12 to 28 cases (4, 9, 10, 22). Furthermore, the recruitment of a larger cohort of patients with RPOH with a complete set of data for 1 year following disease onset could be difficult. Third, this study has a cross-sectional design, and the serum markers were determined only once at the first visit to our hospital. Temporal changes of the markers, in association with progression of RPOH from onset, remain undetermined. Last, this study assessed CTI only with no data on BMD of the hip joint.

Overall, the process of RPOH progression within 1 year following onset could be distinguished into 2 types on the basis of the absence (type 1) and presence (type 2) of femoral head destruction in association with TRACP-5b and BAP. The bone turnover markers may differentiate these 2 types in the early stage of RPOH.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Kobe City Medical Center General Hospital (Approval Date: February 24, 2018; Approval Number: k190516).

Informed Consent: Informed consent was not obtained due to the nature of this study.

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Conflict of Interest: T.Y. was supported by grants from the Japan Hip Joint Foundation, during the conduct of the study. The other authors have no conflict of interest to declare.

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References

1. Bock GW, Garcia A, Weisman MH, Major PA, Lyttle D, Haghighi P, et al. Rapidly destructive hip disease: Clinical and imaging abnormalities. Radiology 1993; 186: 461-6. [Crossref]
2. Lequesne M. [Rapid destructive coxarthritis] (In French). Rheumatologie 1970; 2: 51-63.
3. Watanabe W, Sato K, Itoi E, Yang K, Watanabe H. Posterior pelvic tilt in patients with decreased lumbar lordosis decreases acetabular femoral head covering. Orthopedics 2002; 25: 321-4. [Crossref]
4. Masuhara K, Nakai T, Yamaguchi K, Yamasaki S, Sasaguri Y. Significant increases in serum and plasma concentrations of matrix metalloproteinases 3 and 9 in patients with rapidly destructive osteoarthritis of the hip. Arthritis Rheum 2002; 46: 2625-31. [Crossref]
5. Sugano N, Ohzono K, Nishii T, Sakai T, Haraguchi K, Yoshikawa H, et al. Early MRI findings of rapidly destructive coxopathy. Magn Reson Imaging 2001; 19: 47-50. [Crossref]
6. Zazgyva A, Gurzu S, Gergely I, Jung I, Roman CO, Pop TS. Clinico-radiological diagnosis and grading of rapidly progressive osteoarthritis of the hip. Medicine (Baltimore) 2017; 96: e6395. [Crossref]
7. Yasuda T, Matsunaga K, Hashimura T, Tsukamoto Y, Sueyoshi T, Ota S, et al. Characterization of rapidly progressive osteoarthritis of the hip in its early stage. Eur J Rheumatol 2020; 7: 130-4. [Crossref]
8. Ogawa K, Mawatari M, Komine M, Shigematsu M, Kitajima M, Kukita A, et al. Mature and activated osteoclasts exist in the synovium of rapidly destructive coxarthrosis. J Bone Miner Metab 2007; 25: 354-60. [Crossref]
9. Yamaguchi R, Yamamoto T, Motomura G, Ikemura S, Iwasaki K, Zhao G, et al. Bone and cartilage metabolism markers in synovial fluid of the hip joint with secondary osteoarthritis. Rheumatology (Oxford) 2014; 53: 2191-5. [Crossref]
10. Abe H, Sakai T, Ogawa T, Takao M, Nishii T, Nakamura N, et al. Characteristics of bone turnover markers in rapidly destructive coxopathy. J Bone Miner Metab 2017; 35: 412-8. [Crossref]
11. Yeung Y, Chiu KY, Yau WP, Tang WM, Cheung WY, Ng TP. Assessment of the proximal femoral mor-

phology using plain radiograph-can it predict the bone quality? J Arthroplasty 2006; 21: 508-13. [Crossref]
12. Baumgärtner R, Heeren N, Quast D, Babst R, Brunner A. Is the cortical thickness index a valid parameter to assess bone mineral density in geriatric patients with hip fractures? Arch Orthop Trauma Surg 2015; 135: 805-10. [Crossref]
13. Nguyen BN, Hoshino H, Togawa D, Matsuyama Y. Cortical thickness index of the proximal femur: A radiographic parameter for preliminary assessment of bone mineral density and osteoporosis status in the age 50 years and over population. Clin Orthop Surg 2018; 10: 149-56. [Crossref]
14. Postel M, Kerboull M. Total prosthetic replacement in rapidly destructive arthrosis of the hip joint. Clin Orthop Relat Res 1970; 72: 138-44. [Crossref]
15. Pivec R, Johnson AJ, Harwin SF, Mont MA. Differentiation, diagnosis, and treatment of osteoarthritis, osteonecrosis, and rapidly progressive osteoarthritis. Orthopedics 2013; 36: 118-25. [Crossref]
16. Tang C, Liu Y, Qin H, Li X, Guo W, Li J, et al. Clinical significance of serum BAP, TRACP 5b and ICTP as bone metabolic markers for bone metastasis screening in lung cancer patients. Clin Chim Acta 2013; 426: 102-7. [Crossref]
17. Richette P, Vicaut E, de Vernejoul MC, Orcel P, Bardin T. Bone mineral density in patients with rapidly destructive or common hip osteoarthritis. Clin Exp Rheumatol 2009; 27: 337-9.
18. Okano K, Aoyagi K, Enomoto H, Osaki M, Chiba K, Yamaguchi K. Bone mineral density in patients with destructive arthrosis of the hip joint. J Bone Miner Metab 2014; 32: 312-6. [Crossref]
19. Dewhirst FE, Stashenko PP, Mole JE, Tsurumachi T. Purification and partial sequence of human osteoclast-activating factor: Identity with interleukin 1 beta. J Immunol 1985; 135: 2562-8.
20. Nakashima T, Kobayashi Y, Yamasaki S, Kawakami A, Eguchi K, Sasaki H, et al. Protein expression and functional difference of membrane-bound and soluble receptor activator of NF-kappaB ligand: Modulation of the expression by osteotropic factors and cytokines. Biochem Biophys Res Commun 2000; 275: 768-75. [Crossref]
21. Tamai M, Sagawa K, Kawabata R, Inoue A, Itoh K. Production of IL-6 by T cells from the femoral head of patients with rapidly destructive coxopathy (RDC). Clin Exp Immunol 1996; 103: 506-13. [Crossref]
22. Abe H, Sakai T, Ando W, Takao M, Nishii T, Nakamura N, et al. Synovial joint fluid cytokine levels in hip disease. Rheumatology (Oxford) 2014; 53: 165-72. [Crossref]
23. Kim N, Kadono Y, Takami M, Lee J, Lee SH, Okada F, et al. Osteoclast differentiation independent of the TRANCE-RANK-TRAF6 axis. J Exp Med 2005; 202: 589-95. [Crossref]
24. Yokota K, Sato K, Miyazaki T, Kitaura H, Kayama H, Miyoshi F, et al. Combination of tumor necrosis factor α and interleukin-6 induces mouse osteoclast-like cells with bone resorption activity both in vitro and in vivo. Arthritis Rheumatol 2014; 66: 121-9. [Crossref]
25. Bendre MS, Montague DC, Peery T, Akel NS, Gaddy D, Suva LJ. Interleukin-8 stimulation of osteoclastogenesis and bone resorption is a mechanism for the increased osteolysis of metastatic bone disease. Bone 2003; 33: 28-37. [Crossref]