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ORIGINAL STUDY

Effect of risedronate on bone metabolism after total hip arthroplasty : A prospective randomised study

Plamen KINOV, Peter TIVCHEV, Paulette DOUKOVA, Andreas LEITHNER

From the Medical University of Sofia, Sofia, Bulgaria

Aseptic loosening due to bone remodeling and osteolysis is the main reason for revision hip arthroplasty. At present, there is no established prophylaxis for this complication. On the other hand, it has been demonstrated that bisphosphonates prevent bone loss around total hip arthroplasties (THA). The aim of this study was to assess the efficacy of oral bisphosphonate risedronate for the prevention of deleterious changes in bone metabolism after hip replacement.

Twenty-four patients who underwent THA were randomised to two treatment arms : 35 mg risedronate once weekly for 6 months (12 patients) and no treatment for controls (12 patients). Markers of bone turnover bone specific alkaline phosphatase, serum osteocalcin and urinary deoxypiridinoline were evaluated at baseline, third and sixth postoperative month. Dual energy X-ray absorptiometry of the nonsurgical hip was performed preoperatively and at 6 months postoperatively.

There were no significant differences in clinical or radiographic findings between the two groups at either 3 or 6 months. In the two groups, all biochemical marker responses at the third postoperative month were suppressed compared with baseline. Values of bone resorption marker urinary deoxypiridinoline increased significantly at six months in the control group. For the 10 risedronate patients with bone densitometry bone mineral density reached 1.01% increase at 6 months.

Administration of oral risedronate led to a significant reduction in bone metabolism at 6 months after hip replacement. This therapeutic strategy may improve the results and longevity of total hip arthroplasty. The beneficial effect of risedronate should be confirmed in further studies including larger number of patients and longer follow-up. The action of risedronate could prevent aseptic loosening of hip arthroplasty by preserving periprosthetic bone stock.

Keywords : risedronate ; bisphosphonates ; bone metabolism ; hip arthroplasty ; aseptic loosening.

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■ Plamen Kinov, M.D., Orthopaedic Surgeon.

■ Peter Tivchev, M.D., Ph.D., Professor and Chairman.

Department of Orthopaedics and Traumatology, University Hospital Queen Giovanna, Medical University of Sofia, Sofia, Bulgaria.

■ Paulette Doukova, M.D., Associate Professor of Laboratory Medicine and Chairwoman.

Laboratory for Investigation of Markers for Bone Metabolism, Department of Laboratory Diagnostics, Medical University of Sofia, Sofia, Bulgaria.

■ Andreas Leithner, M.D. †, Associate Professor.

Department of Orthopaedic Surgery, Medical University of Graz, Auenbruggerplatz 5, A-8036 Graz, Austria.

Correspondence : Plamen Kinov, Department of Orthopaedics and Traumatology, University Hospital Queen Giovanna, ul. Belo more 8, 1527 Sofia, Bulgaria.
E-mail : plamenkinov@yahoo.com.

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INTRODUCTION

Aseptic loosening is the main long-term concern of total hip arthroplasty (THA). In young patients, this complication has been reported with failure rates reaching up to 40% (*1, 3, 14, 25*). This necessitates measures for improvement of long term survival of hip arthroplasty.

The clinical success of total hip arthroplasty is associated with the quality and quantity of the available bone. Periprosthetic bone loss and aseptic loosening are considered to occur mainly because of stress-shielding and osteolysis (*2*). Local operative trauma to the bone and soft tissues, in combination with immobilisation, has an additional impact on bone loss (*10*).

Recently, bisphosphonates have been investigated for their ability to prevent bony erosions in rheumatoid arthritis, postmenopausal osteoporosis and peri-prosthetic bone resorption (*6, 7, 13, 30*). Risedronate is a potent pyridinyl bisphosphonate which has been shown to decrease bone turnover and increase bone density in multiple myeloma (*22*), and Paget's disease of bone (*12, 16*), and to reduce the incidence of fractures, including hip fractures, in women with postmenopausal osteoporosis (*7, 15, 20*). This third generation bisphosphonate with its once-a-week dosing might be considered for numerous clinical indications, including prevention of aseptic loosening of THA. To date, no data from therapy of THA with risedronate have been reported in the available literature.

The aim of the present study was to determine the effects of oral bisphosphonate risedronate on behaviour of biochemical markers of bone turnover and changes in bone mineral density (BMD) after primary THA.

MATERIAL AND METHODS

Patients

Twenty-four consecutive patients (9 male, 15 female) scheduled for primary hip replacement were included in the study between November 2003 and June 2004. In 14 cases a cemented prosthesis was implanted and in 10 cases a hybrid prosthesis (cemented stem, cementless press-fit cup) was used. Low molecular weight heparin was used for thromboembolic prophylaxis for 45 days. All patients received prophylactic systemic 3rd generation cephalosporin intraoperatively and for three to five days postoperatively. Clinical characteristics of the 24 patients are shown in table I. The inclusion criteria were absence of total hip arthroplasty or previous hip surgery, and of significant osteoarthritis of the nonsurgical hip. Patients also had to be able to comply with a standardised postoperative mobilisation and physiotherapy regime, consisting of two months of 20% weight bearing on two crutches starting on the second or third postoperative day, followed by gradual full weight bearing. All patients were selected regardless of gender. Subjects over 75 years of age and in poor health (ASA class IV) were excluded from the study. Other exclusion criteria were recent therapy with drugs known to affect bone turnover, evidence of metabolic bone disease or psychiatric disease that could affect participation or interfere with the interpretation of data. Patients were advised of the nature of the study and written informed consent was obtained. The protocol was approved by the respective institutional review board.

Study design

This was a prospective, open, case-controlled study. Patients were randomly assigned to receive either 35 mg risedronate (12 patients) once weekly from the 20-th postoperative day for a period of 6 months or not to receive the medication (12 patients). Risedronate was administered as a cellulose film-coated tablet prepared by Procter & Gamble Pharmaceuticals (Weiterstadt, Germany). Patients were instructed to take their medication with 240 mL water 30-60 min before breakfast and to avoid lying down for 1 h after taking the tablet.

Prior to hip replacement surgery serum and urine samples were collected. Subsequent samples were obtained at the third and sixth postoperative month.

Bone mineral density of the nonsurgical hip was measured preoperatively and at six months postoperatively by dual energy X-ray absorptiometry (DXA) on a Lunar DPXMD (GE Lunar Corporation, Madison, WI). Data about patients' medical history, dietary calcium, and vitamin D intake was recorded.

Markers of bone metabolism

Preoperative serum and urine samples were collected in a fasting state between 9 and 11 a.m., prior to surgery. Postoperative serum and urine samples were collected in a nonfasting state between 9 and 11 a.m., except for three patients who had samples collected in the early

Table I. — Baseline data of the 24 patients included in the study

	Risedronate group (N = 12)	Control group (N = 12)
Number of hips (N)	12	12
Mean age (yr)*	58.3 ± 8.4	56 ± 11.3
Gender (M/F)	4/8	5/7
Mean body-mass index*	27 ± 5.4	27.7 ± 3.6
Years since menopause (females)*	5.5 ± 6.9	7.7 ± 6.6
Involved hip (Left/Right)	8/4	5/7
Mean HHS (points)	54.0 ± 18.1	45.3 ± 12.9
Diagnosis		
Osteoarthritis	8	7
Osteonecrosis	3	3
Hip fracture	1	2
BMD, nonsurgical hip (g/cm^2)*	0.979 ± 0.15	0.963 ± 0.18

* Data represented as mean ± SD.

afternoon. Serum samples were stored at -80°C, and urine samples were stored at -20°C. All pre- and postoperative samples for serum markers of bone formation and urinary markers for bone resorption were analysed by a single laboratory technician. Assays were performed at a Laboratory for Investigation of Markers for Bone Metabolism.

The markers of bone formation included bone-specific alkaline phosphatase levels (BSAP, U/L) and osteocalcin (OC, ng/mL). Levels of BSAP were determined by enzyme-linked immunosorbent assay (Alkphase-B, Metra Biosystems, Mountain View, CA, intra-assay CV 3.2-5.8%). Levels of OC were determined by enzyme-link immunosorbent assay (Novocalcin, Metra Biosystems, intra-assay CV 4.8-10.0%). The assessments of bone resorption included urinary deoxypiridinoline (DPD). Measurements of urinary deoxypiridinoline (nmol bone collagen equivalents [BCE]/mmol creatinine) were performed by enzyme-linked immunosorbent assay (Pyrylinks-D, Metra Biosystems, intra-assay CV 4.3-8.4%).

Radiological evaluation was performed on standard anteroposterior radiographs taken postoperatively and at third and sixth postoperative month at the same timepoints as the markers of bone metabolism. Implant stability was assessed as described earlier (*4, 9, 14*). At six-month visit in 10 risedronate patients BMD measurement was repeated.

Clinical assessments were made using Harris hip score (HHS) at preoperative baseline and at third and sixth postoperative month (*8*). Adverse events were recorded at all postbaseline visits, and their severity and relationship to treatment were evaluated by the investigators.

Statistical analysis

Descriptive statistics are presented as mean ± SD. Within-treatment groups, preoperative and third and sixth-month postoperative values of markers of bone turnover and the baseline and six-month BMD values were compared using the Wilcoxon signed-rank test. Between-group comparisons were carried out using Mann-Whitney U-test. Spearman's correlation coefficient was used to asses the relationship between variables.

All statistical analyses were performed at the 0.05 significance level (two-sided).

RESULTS

At six months, clinical result was excellent or good in all cases (mean Harris hip score 93.3 ± 5.9 points). There were no significant differences in clinical result or radiographic findings between the two groups at either 3 or 6 months and all implants were stable.

Baseline levels of bone turnover markers in the control group were higher compared with risedronate patients (table II) ; however, this difference was not statistically significant. Postoperatively, all biochemical marker responses at the third

Table II. — Mean values of markers for bone turnover in the two groups

	Baseline values (N = 12)	Three-month values (N = 12)	Six-month values
Risedronate (N12)			
BSAP (U/L)	20.99 ± 7.6	16.80 ± 7.1*	19.93 ± 6.6*
OC (ng/mL)	8.13 ± 6.7	7.31 ± 8.1	4.48 ± 3.1
Urine DPD (nmol/L)	9.58 ± 3.1	7.71 ± 5.3	4.62 ± 1.9*†
Controls (N12)			
BSAP (U/L)	23.92 ± 9.7	22.8 ± 3.1	26.9 ± 5.9
OC (ng/mL)	9.85 ± 7.7	5.57 ± 5.9	3.71 ± 3.7†
Urine DPD (nmol/L)	10.99 ± 5.3	7.74 ± 4.3	9.48 ± 5.2

* $p < 0.05$ in comparison between groups, Mann-Whitney.
† $p < 0.05$ in comparison with baseline level, Wilcoxon.

postoperative month were suppressed compared with baseline (table II, fig 1). In the risedronate group, the response of the bone-specific alkaline phosphatase was biphasic, with an initial fall from preoperative baseline at the third month ($p > 0.05$), followed by an increase at 6 months ($p > 0.05$) (fig 1a). Serum OC in this group continued to fall nonsignificantly ($p > 0.05$) to 55.1% below the baseline by the sixth month. Risedronate treatment decreased significantly ($p = 0.011$, Wilcoxon) by 51.8% the levels of marker of bone resorption urinary DPD at the sixth postoperative month (table II, fig 1c). In the control group, there was a decrease in bone formation marker BSAP by 4.6% at three months ($p > 0.05$) and an increase at six months compared with baseline ($p > 0.05$) (fig 1a). The average serum OC value of patients with no treatment was decreased (43.5%) nonsignificantly ($p > 0.05$) at three months and decreased significantly (62.3%) from 9.85 to 3.71 ng/mL at six months ($p = 0.06$, Wilcoxon, fig 1b). In the control group, values of bone resorption marker urinary DPD decreased nonsignificantly at three months postoperatively and increased at six months to 86.3% of baseline levels.

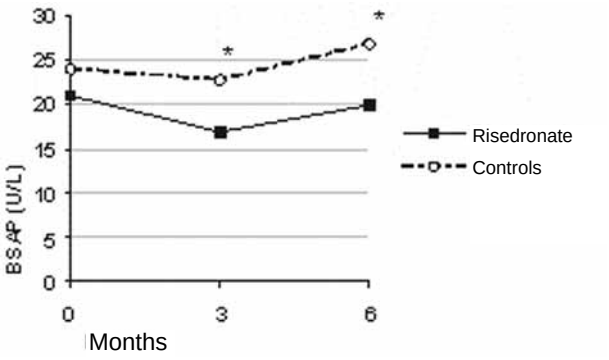
Risedronate therapy resulted in greater suppression of BSAP at the third ($p = 0.003$, Mann-Whitney) and sixth month ($p = 0.035$, Mann-Whitney) compared with controls. There was a trend towards higher OC in the risedronate group but this was not significant ($p > 0.05$, Mann-Whitney). After an initial fall below baseline at three months in both groups, the bone resorption marker urinary DPD continued to fall in the risedronate group. In the control group, significantly greater increase in urinary DPD compared to that in the risedronate group was measured ($p = 0.021$, Mann-Whitney) at six months. The changes in markers of bone formation (serum osteocalcin and BSAP) were not associated with changes in marker of bone resorption (urinary DPD). The effects of risedronate on changes in bone turnover markers were independent of gender or type of fixation of the prosthesis. The levels of BSAP preoperatively and at three months correlated significantly with the time since menopause in the 15 females in the series (Spearman rho = 0.591, $p = 0.02$ and Spearman rho = 0.627, $p = 0.022$, respectively).

Ten patients from the risedronate group had repeated measurement of BMD at the sixth postoperative month. The mean change in BMD of the nonsurgical hip was 1.01% (0.99 g/cm^2 ± 0.014) ($p > 0.05$). BMD measurements were not correlated with changes in markers of bone turnover. The effect of risedronate on change in BMD was independent of gender or type of implant fixation or the time since menopause in the females in the series.

Adverse events

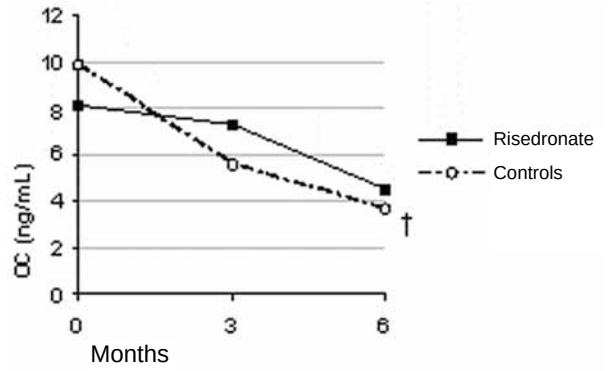
Risedronate was generally well tolerated. There was one incidence of diarrhea leading to withdrawal after the third month.

a. BSAP



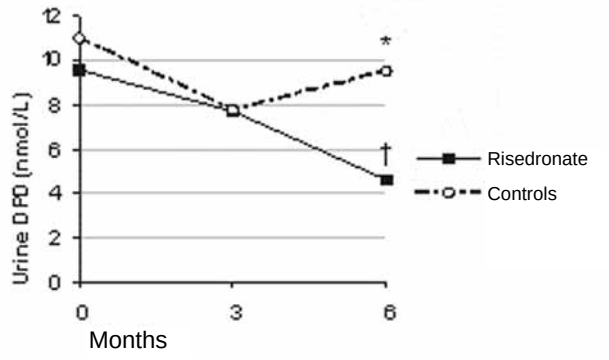
* p < 0.05, Mann-Whitney.

b. OC



† p = 0.006, Wilcoxon.

c. Urinary DPD



* p = 0.021, Mann-Whitney, † p = 0.011, Wilcoxon.

Fig. 1. — Diagram showing the mean changes in markers for bone turnover in patients receiving risedronate or controls. a) Bone-specific alkaline phosphatase (BSAP), b) Osteocalcin (OC) and c) Urinary deoxypiridinoline (DPD).

DISCUSSION

Administration of risedronate, a potent inhibitor of bone resorption, was associated with a decrease in markers of bone turnover and preservation of total hip BMD in the nonsurgical hip. After THA, the decrease in OC in the risedronate group was lower than that found in the control group. Risedronate therapy resulted in significant decrease in DPD levels at six months compared to controls. At six months postoperatively, a statistically significant decrease in values of urinary DPD in controls compared to risedronate patients occurred.

The results of this study are similar to the reported effects of other bisphosphonates on bone metabolism after THA. In two relatively small studies, Wilkinson *et al* discovered that pamidronate suppresses markers of bone turnover after THA (*28, 29*). Several other studies reported similar results of increase in periprosthetic BMD after alendronate administration (*10, 19*). On the other hand, an *in vitro* study and several studies on experimental animals showed that administration of alendronate inhibited wear debris mediated periprosthetic osteolysis (*11, 17, 24, 26*). Although the results of our study are, in general, consistent with these recent reports, a direct comparison with other studies is difficult.

After surgery, a similar trend in values of bone formation marker BSAP was observed in both groups. The statistically significant decrease in BSAP value in the risedronate group suggests that lower baseline levels as well as the shorter time since menopause in the females in this group may play a role. Influence of risedronate on osteoblast function is less probable. Third-generation bisphosphonates have been reported to have less effect on osteoblasts and bone formation than earlier-generation do (*21, 23*). *In vivo* studies have verified that nitrogen-containing bisphosphonates such as risedronate selectively inhibit the cholesterol pathway and subsequently disrupt the osteoclast cytoskeleton with associated osteoclast inactivation (*5, 21*). However, a recent study has found an inhibitory effect of nitrogen-containing bisphosphonate on the terminal differentiation of osteoblasts for bone remodeling consequently leading to a delay in bone

healing (*18*). Further research is needed to assess the effects of risedronate therapy on osteoblast function.

Our findings are consistent with the hypothesis that bone metabolism is altered by bone injury, perhaps as a stress response to trauma (*10*). All the risedronate patients exhibited decrease in markers of bone turnover. Decrease in bone resorption was connected with an increase in bone formation, producing a temporary gain in calcium balance. Lowered bone turnover lengthens the time span when bone is again destroyed, permitting more complete mineralisation. This is supported by measurement of BMD on the nonsurgical hip, which remained stable at 6 months. Significantly lower values of bone resorption marker in the risedronate group compared to controls show that risedronate may prevent bone loss after hip replacement.

It is possible that the metabolic response observed in this study was caused not by bone injury but by anaesthesia or antibiotic prophylaxis. The fall in bone markers at 3 months also may reflect suppression of osteoblast activity by a toxic effect of the polymethylmethacrylate bone cement used for fixation of the prosthesis. Another possible reason might be suppression of bone turnover by the low molecular weight thromboembolic prophylaxis that was given to all patients for 45 days after surgery. However, if this were due to these factors alone, we would expect a similar trend in both groups. The increase in bone turnover at 6 months in controls argues against this explanation.

The weakness of the present study is its small sample size. In addition, the study group involved patients with various diagnoses. Although the behaviour of the markers is similar in these patients, a more uniform surgical group may be preferable. There are also several strengths of this study. Its longitudinal design avoids the bias of cross-sectional studies of biochemical markers by allowing each subject to serve as his or her own control. Second, the study group included patients across a wide range of ages (37-72 years), and demonstrated that risedronate decreases markers of bone formation after hip replacement surgery throughout the surgical population. Finally, exclusion of patients over 75 years of age avoids some of the bias of increased bone resorption with advanced age.

Previously, efforts to retard fracture-associated bone loss have emphasised decreasing the time that the patient is immobilised following the injury (*27*). Some authors have used different materials in attempts to improve rates of periprosthetic bone loss by improving stress distribution around the implant (*2*). Data from our study suggest that patients receiving hip replacement surgery may potentially benefit from antiresorptive therapy in the postoperative period. By directly influencing bone metabolism, antiresorptive agent risedronate may prevent a deleterious shift in the balance of bone formation and bone resorption after the arthroplasty.

CONCLUSION

In this study, treatment with risedronate was well tolerated, reduced bone turnover and preserved BMD at the femoral neck. Risedronate 35 mg once weekly was effective as a mean of preserving periprosthetic bone after hip arthroplasty. However, longer-term studies would be necessary to detect its effects on the incidence of periprosthetic osteolysis and aseptic loosening of hip prosthesis.

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REFERENCES

1. **Ballard WT, Callaghan JJ, Sullivan PM, Johnston RC.** The results of improved cementing techniques for total hip arthroplasty in patients less than fifty years old. A ten-year follow-up study. *J Bone Joint Surg* 1994 ; 76-A : 959-964.
2. **Bobyn JD, Mortimer ES, Glassman AH, Engh CA, Miller JE, Brooks CE.** Producing and avoiding stress shielding : Laboratory and clinical observation of noncemented total hip arthroplasty. *Clin Orthop* 1992 ; 274 : 79-96.
3. **Emery DF, Clarke HJ, Grover ML.** Stanmore total hip replacement in younger patients : review of a group of patients under 50 years of age at operation. *J Bone Joint Surg* 1997 ; 79-B : 240-246.
4. **Engh CA, Bobyn JD, Glassman AH.** Porous-coated hip replacement. The factors governing bone ingrowth, stress

shielding, and clinical results. *J Bone Joint Surg* 1987 ; 69-B : 45-55.

5. **Fisher JE, Rodan GA, Reszka AA.** In vivo effects of bisphosphonates on the osteoclast mevalonate pathway. *Endocrinology* 2000 ; 141 : 4793-4796.
6. **Goldring SR, Gravallese EM.** Bisphosphonates : environmental protection for the joint ? *Arthritis Rheum* 2004 ; 50 : 2044-2047.
7. **Harris ST, Watts NB, Genant HK *et al.*** Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis. *JAMA*1999 ; 282 : 1344-1352.
8. **Harris WH.** Traumatic arthritis of the hip after dislocation and acetabular fractures : treatment by mold arthroplasty. An end-result study using a new method of result evaluation. *J Bone Joint Surg* 1969 ; 51-A : 737-755.
9. **Harris WH, McGann WA.** Loosening of the femoral component after use of the medullary-plug cementing technique. *J Bone Joint Surg* 1986 ; 68-A : 1064-1065.
10. **Hennigs T, Arabmotlagh M, Schwarz A, Zichner L.** Dose-dependent prevention of early periprosthetic bone loss by alendronate. *Z Orthop Ihre Grenzgeb* 2002 ; 140 : 42-47.
11. **Horowitz SM, Algan SA, Purdon MA.** Pharmacologic inhibition of particulate-induced bone resorption. *J Biomed Mater Res* 1996 ; 31 : 91-96.
12. **Hosking DJ, Eusebio RA, Chines AA.** Paget's disease of bone : Reduction of disease activity with oral risedronate. *Bone* 1998 ; 22 : 51-55.
13. **Iwamoto J, Takeda T, Ichimura S, Matsu K, Uzawa M.** Effects of cyclical etidronate with alfacalcidol on lumbar bone mineral density, bone resorption, and back pain in postmenopausal women with osteoporosis. *J Orthop Sci* 2003 ; 8 : 532-537.
14. **Kinov P, Tivchev P.** The problem of aseptic loosening of hip arthroplasty. *J Orthop Trauma* (*Bulgaria*) 2002 ; 38 : 117-130.
15. **McClung MR, Geusens P, Miller PD *et al.*** Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med* 2001 ; 344 : 333-340.
16. **Miller PD, Brown JP, Siris ES, Hoseyni MS, Axelrod DW, Bekker PJ.** A comparative trial of risedronate versus etidronate in the treatment of patients with Paget's disease of bone. *Am J Med* 1999 ; 106 : 513-520.
17. **Millett PJ, Allen MJ, Bostrom MP.** Effects of alendronate on particle-induced osteolysis in a rat model. *J Bone Joint Surg* 2002 ; 84-A : 236-249.
18. **Nagashima M, Sakai A, Uchida S, Tanaka S, Tanaka M, Nakamura T.** Bisphosphonate (YM529) delays the repair of cortical bone defect after drill-hole injury by reducing terminal differentiation of osteoblasts in the mouse femur. *Bone* 2005 ; 36 : 502-511.
19. **Nehme A, Maalouf G, Tricoire JL, Giordano G, Chiron P, Puget J.** Effect of alendronate on periprosthetic bone loss after cemented primary total hip arthroplasty : a prospective randomized study. *Rev Chir Orthop* 2003 ; 89 : 593-598.
20. **Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML *et al.*** Randomized trial of the effect of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int* 2000 ; 11 : 83-91.
21. **Rodan GA, Reszka AA.** Osteoporosis and bisphosphonates. *J Bone Joint Surg* 2003 ; 85-A Suppl 3 : 8-12.
22. **Roux C, Ravaud P, Cohen-Solal M *et al.*** Biologic, histologic, and densitometric effects of oral risedronate on bone in patients with multiple myeloma. *Bone* 1994 ; 15 : 41-49.
23. **Russell RG, Rogers MJ, Frith JC *et al.*** The pharmacology of bisphosphonates and new insights into their mechanisms of action. *J Bone Miner Res* 1999 ; 14 Suppl 2 : 53-65.
24. **Shanbhag AS, Hasselman CT, Rubash HE.** Inhibition of wear debris mediated osteolysis in a canine total hip arthroplasty model. *Clin Orthop* 1997 ; 344 : 33-43.
25. **Sporer SM, Callaghan JJ, Olejniczak JP, Goetz DD, Johnston RC.** Hybrid total hip arthroplasty in patients under the age of fifty : a five- to ten-year follow-up. *J Arthroplasty* 1998 ; 13 : 485-491.
26. **Thadani PJ, Waxman B, Sladek E, Barmada R, Gonzalez MH.** Inhibition of particulate debris-induced osteolysis by alendronate in a rat model. *Orthopedics* 2002 ; 25 : 59-63.
27. **Van der Wiel HE, Lips P, Nauta J, Patka P, Haarman HJ, Teule GJ.** Loss of bone in the proximal part of the femur following unstable fractures of the leg. *J Bone Joint Surg* 1994 ; 76-A : 230-236.
28. **Wilkinson JM, Eagleton AC, Stockley I, Peel NF, Hamer AJ, Eastell R.** Effect of pamidronate on bone turnover and implant migration after total hip arthroplasty : a randomized trial. *J Orthop Res* 2005 ; 23 : 1-8.
29. **Wilkinson JM, Jackson B, Eastell R.** Effect of pamidronate on excretion of pyridinium crosslinks of collagen after total hip arthroplasty. *Calcif Tissue Int* 2003 ; 73 : 326-331.
30. **Yamaguchi K, Masuhara K, Yamasaki S, Fuji T.** Efficacy of different dosing schedules of etidronate for stress shielding after cementless total hip arthroplasty. *J Orthop Sci* 2005 ; 10 : 32-36.