Delayed Administration of Risedronate Does Not Restore Bone Loss In Patients Following Total Hip Arthroplasty

A randomized, double blinded clinical study

David R. Lionberger, MD^{1§}, Joshua M. Liao², Mitchell D. Eggers, PhD³, Sahar Bawker, BS³

Abstract

Background: Periprosthetic bone loss after total hip arthroplasty (THA) increases the risk of serious post-operative complications. Previous studies have reported the beneficial effect of risedronate therapy to improve periprosthetic bone mineral density (BMD) around new implants. The current study is to evaluate the effect of risedronate treatment in enhancing mature well fixed THA implants one year or more after implantation.

Methods and Results: A total of 32 osteoarthritic patients received total hip replacement surgeries and were enrolled from the primary investigator's clinical practice between February and September 2007. All eligible patients who met the inclusion criteria underwent total hip arthroplasty for reasons other than low traumatic hip fracture due to osteoporosis with normal or osteopenic lumbar spine BMD scores. Subjects received oral risedronate or a placebo with daily calcium plus Vitamin D. DEXA BMD scanning and bone-specific biomarkers, NTx and ALK phosphatase were collected at 6 and 12 months post-surgery. The result showed that risedronate did not increase BMD values of operative femur nor levels in NTx or ALK phosphatase.

Conclusions: This study suggests that risedronate treatment is not effective in preventing periprosthetic bone loss nor enhancing existing density in well fixed osteointegrated following total hip arthroplasty.

Key words: risedronate, bisphosphonate therapy, total hip arthroplasty

Background

The most profound and dynamic changes in periprosthetic bone mineral density (BMD) have been observed in the first 6 to 12 months following total hip arthroplasty (THA). This early bone loss may have latent implications in implant loosening and mechanical failure as well as an increased risk of fracture due to general bone weakness. [1,2] Periprosthetic bone remodeling is a complex, multifunctional process caused by stress shielding and wear-induced osteolysis, among other factors. Stress shielding is

regional and reproducible around the proximal femur. The reduction in weight-bearing stress leads to a significantly higher incidence of bone resorption, most prominently in Gruen zone 7, both in the early and late stages of recovery following THA.

1 Southwest Orthopedic Group, L.L.P., 6560 Fannin, Suite 1016, Houston, TX 77030, USA

2 Baylor College of Medicine, One Baylor Plaza, MS BCM368, Houston, TX 77030, USA

3 Foundation for Southwest Orthopedic Research, 6560 Fannin, Suite 1020, Houston, TX 77030, USA

§ Corresponding author

[3,4] Femoral stems have been developed and engineered to reduce bone resorption in the proximal part and enhance the long-term survival of the implant through specific design modifications. [5,6,7] In spite of these changes, osteolysis resulting from byproducts of wear is not a regional or design-specific process and may present a continuing concern. [8,9,10,11,12] In a typical osteoarthritic patient undergoing THA, the greatest bone loss from implants of wear and stress shielding occurs during the first 3-6 months post-surgery. The altered load conduction in the femoral bone, however, continues to cause periprosthetic bone resorption in the proximal femur well beyond 6 months. The effects of implanted byproducts of wear due to incomplete implant osteointegration and fixation are key factors impacting further periprosthetic bone remodeling. [1,13]

Several therapeutic options such as calcium and vitamin D supplements, oestrogen receptor agonists, parathyroid hormone (PTH), and calcitonin have been suggested to reduce the severity and duration of periprosthetic bone resorption as well as early remodeling post-THA by enhancing bone mineral density (BMD) systemically and bone tissues around the prosthesis. [2] Recently, bisphosphonates have emerged as an alternative to anti-osteoporosis treatments by increasing BMD. [14,15,16] Bisphosphonates are widely used in the treatment of Paget's disease, hypercalcemia of malignancy, corticosteroid induced osteopenia, and post-menopausal osteoporosis. [17,18] They have also been indicated in the treatment of fibrous dysplasia, osteogenesis imperfecta, osteoarthritis, and rheumatoid arthritis. Bisphosphonate treatment has recently been incorporated in the management of periprosthetic bone remodeling. Several studies have investigated the benefits of bisphosphonate therapy in the first 6 to 12 months following surgery, while bone resorption is most dramatic. However, clinical evidence suggests that the short-term gains of bisphosphonate therapy may not be sustained in the long term or reversed once they have occurred. [17,19,20,21]

Although the benefits of risedronate administration on enhancing periprosthetic BMD have been observed in the first year post-THA, currently, there is no evidence to show that the risedronate therapy may reverse the delayed periprosthetic bone loss occurring after the initial post-operative year. We hypothesized that oral risedronate may augment or prevent bone loss in well osteointegrated patients following THA, just as it has been demonstrated in recent post-

operative THA patients. [2,5,17] To test our hypothesis, we designed a randomized, double-blinded clinical trial to observe the effects of risedronate therapy on periprosthetic BMD in the period of 1 to 10 years after surgery. We also monitored the systemic effects of risedronate treatment such as gastrointestinal intolerance, myalgias, or joint pain, in order to observe any adverse effects in this cohort of patients potentially resulting from long-term bisphosphonate administration. The primary endpoint of this pilot study was to evaluate the effects of risedronate prospectively on a group of patients one year or more after THA compared to a control cohort receiving no study medication. Secondary endpoints would include adverse events or medication intolerance.

Patients and Methods

A total of 32 osteoarthritic patients received total hip replacement surgeries were enrolled from the primary investigator's clinical practice between February and September 2007. All eligible patients who met the inclusion criteria underwent total hip arthroplasty for reasons other than low traumatic hip fracture due to osteoporosis with normal or osteopenic lumbar spine BMD scores. Recruited subjects were of the ages 30 – 80 (Mean age: 71.24, Range: 37, 10 Female, 22 Male) and able to understand and tolerate instructions for taking risedronate (Actonel, Proctor & Gamble Pharmaceuticals, Cincinnati, Ohio). Average BMI was 32 with gender distribution of 22 males and 10 females. No difference was found in demographics between groups with regards to age, BMI, or sex. Exclusion criteria included a history of prosthetic hip infection, retained hardware in the hip region, previous fracture induced-femur deformity, cancer, thyroid disease, debilitating psychiatric disease, alcohol dependence or substance abuse, coagulation disorders, or hepatic disorders. Subjects who had recently taken parathyroid hormone, bisphosphonates, estrogen receptor modulators, fluorides, calcitonin, calcitrol, corticosteroids, or any other osteoactive drugs were also excluded from this study. While tight entry level BMD's may identify at-risk or causal factors for higher incidence of post traumatic fractures, we felt a better representation of a real world variance of fracture incidence would be provided by not restricting patients to have either low or normal BMD. As such, all levels of risk factors would be provide more merit for the efficacy of proactive intervention of bisphosphonates similar to

what the original bisphosphonate literatures depicted. [7,16,19] Therefore, no control over BMD was used to represent a more real world cross section of what a typical trauma practice would see in an emergency room where BMD's are simply unavailable. The study protocol received full approval from Institutional Review Board, Patient Advocacy Council, Inc.

To determine the appropriate sample size of the study, several assumptions were made for the t-test employed to determine significance of the endpoint outcome in addition to a power assessment based on previous density response rates over the study period of one year. A-prior statistics were determined to compute the sample size from published literature. Based on a meta-analysis of bisphosphonate use following total joint arthroplasty that included 5 trials with a total 224 subjects, the baseline BMD standard deviation to mean ratio was chosen to be 14%. [17] The meaningful average BMD difference between the cohorts was selected to be at least 15%.

All enrolled subjects underwent the cementless THA fiber-coated metal taper femoral stem (Zimmer Company, Warsaw, Indiana). Enrolled patients were randomly assigned to either the study group or the control group. Patients and the primary investigator remained blinded throughout the trial. During the 52-week treatment period, subjects in the study group received a weekly dose of 35mg risedronate sodium (Actonel, Procter & Gamble Pharmaceuticals, Cincinnati, Ohio) and a twice-daily dose of 500mg calcium with 200 IU of vitamin D (Caltrate, a total of daily dose of 1000mg calcium with 400 IU of vitamin D). The rationale for the selective dosage of 35 mg weekly of risedronate originates from several previous studies. [22,23,24] Patients in the control group were placed on the placebo regimen with a twice-daily 500mg calcium plus 200 IU of vitamin D. The primary investigator gave each patient specific oral and written instruction for taking risedronate and Caltrate to ensure that the calcium did not interfere with the risedronate. Patients returned to the primary investigator's clinic at 6 and 12 months for evaluation. Measurements of BMD of the operative hip and spine, creatinine, NTx, and bone-specific alkaline phosphatase were performed at each follow-up visit in the same manner and location as the initial visit. If a dose failure of greater than 10% of the year's allotment of medication was witnessed, the patient was withdrawn from the study.

At the initial study visit, the baseline BMD mea-

surement of the operative femur and spine were taken by using a dual energy x-ray absorptiometry (DEXA) BMD scanning system (GE Lunar Prodigy Bone Densitometer with enCORE software). In order to measure BMD, two X-ray beams that have differing energy levels, are aimed at the subject's bones. BMD is then determined by subtracting the soft tissue absorption and measuring the absorption of each beam by bone. Creatinine, collagen-type I N-telopeptides (NTx), and bone-specific alkaline phosphatase levels were assayed from blood serum and second morning void urine specimens were collected at the initial visit. [25,26] These critical biochemical markers were used to show homogeneity between cohorts. All bio-fluid samples were collected and performed at the Department of Laboratory Medicine at the Methodist Hospital, Houston, Texas.

Patient demographics, specifically age and months between their surgery and enrollment in the study, were evaluated using Welch's t-test to ensure homogeneity between the study and control groups. Mean periprosthetic BMD in the study and control groups were evaluated using Welch's t-test in each of the seven Gruen zones. The percentage profiles of initial BMD were determined in each zone by dividing the average measured BMD at 6 or 12 months when compared to the average initial BMD value. In order to assess the systemic effects of risedronate therapy, BMD, and t-scores of the lumbar spine and biochemical markers of bone metabolism at 6 and 12 months, specifically levels of collagen-type I N-telopeptides (NTx) and bone-specific alkaline phosphatase, were assessed by using Welch's t-test analysis.

Results

Initially, 66 patients were considered for the study and randomized, but only 32 subjects were eligible for the completion of the study. This was due to the exceedingly tight exclusion criteria of dose administration, bone scan, and follow-up visits to maintain consistency of endpoint sampling. Patients were monitored through a weekly diary that was overseen by the investigative team. If a 10% total deviation was found, the patient was excluded from the study. This guaranteed tight control on timeline changes that may have existed in the study while ensuring that the patients did not result in becoming a placebo rather than the study group. Patient demographics and biochemical assays were used to establish homogeneity between the two groups. The average age

of patients upon enrollment in study was 69 years in the control group and 71 years in the study group ($p = 0.221$). While age stratification was not controlled on entry, it was evaluated post-hoc. Risedronate carries no recommendation of onset institution of therapy guidelines for THR and therefore an unrestricted window of enrollment was intentionally allowed. Primary hip replacements took place between 1 and 10 years prior to enrollment in the study, with an average time-period from surgery to enrollment of 62.7 months in the control group and 76.2 months in the study group ($p = 0.625$). Finally, initial creatinine, NTx, and bone-specific alkaline phosphatase levels indicated no significant differences between the two groups ($p = 0.288, 0.720, 0.254$, respectively). Homogeneity in biochemical function was essential to ensure that no other osteoactive condition such as osteoporosis affected the outcome of the study.

No significant difference in periprosthetic BMD was observed between the control and study cohorts for any of the seven regions of interest (Table 1 and Figure 1). In zones 2, 3, and 5, both risedronate and

the control agents yielded slightly higher, though not statistically significant at six months. In zone 4, the study and control groups yielded similar results. Finally, in zones 1, 6, and 7, the group taking Caltrate alone appeared to yield slightly better BMD, yet statistically insignificant when compared to the risedronate group (Table 1 and Figure 1). All the p -values detected are greater than 0.05. In Figures 2 and 3, the change in percent profiles of BMD over time for each Gruen zone is seen for the control and study groups. Neither group revealed a distinct, consistent pattern.

Mean BMD measurements in the lumbar spines (L-1 to L-4) also show no significant difference between the control and study cohorts (Table 2), indicating that risedronate did not produce a significant systemic effect on BMD value in our enrolled groups. BMD of the spine was maintained in both the control and study group with no significant difference between the cohorts in any lumbar region (Table 2). Statistical analysis did not show any significant difference between the two groups at 6 months

Table 1. Summary Statistics for Periprosthetic Bone Mineral Density in Gruen Zones 1 - 7

		Initial			6 Months			12 Months		
		Control	Study	t-test	Control	Study	t-test	Control	Study	t-test
Zone 1	Average	0.914839	0.958017		0.987171	0.969830		0.942382	0.966046	
	Stdev	0.205018	0.324272	0.650	0.268978	0.328247	0.871	0.203439	0.337999	0.808
	% Initial BMD	100%	100%		107.91%	101.23%		103.01%	100.84%	
Zone 2	Average	1.992605	1.965311		1.994915	1.985935		2.007402	1.982757	
	Stdev	0.369568	0.316124	0.827	0.391753	0.310239	0.945	0.385522	0.310908	0.847
	% Initial BMD	100%	100%		100.12%	101.05%		100.74%	100.89%	
Zone 3	Average	2.264854	2.108745		2.256865	2.152704		2.287772	2.134658	
	Stdev	0.253643	0.299067	0.121	0.263905	0.335177	0.333	0.274879	0.283805	0.134
	% Initial BMD	100%	100%		99.65%	102.08%		101.01%	101.23%	
Zone 4	Average	2.058250	1.985164		2.018321	1.948280		2.023194	1.948122	
	Stdev	0.411474	0.458377	0.639	0.348387	0.359368	0.582	0.335253	0.314298	0.524
	% Initial BMD	100%	100%		98.06%	98.14%		98.30%	98.13%	
Zone 5	Average	2.262189	2.146768		2.231091	2.190629		2.246679	2.185048	
	Stdev	0.245129	0.192242	0.160	0.221163	0.211757	0.605	0.257030	1.063623	0.474
	% Initial BMD	100%	100%		98.63%	102.04%		99.31%	101.78%	
Zone 6	Average	1.851831	1.781677		1.842337	1.768810		1.872155	1.754615	
	Stdev	0.397378	0.292214	0.585	0.409617	0.334000	0.590	0.423214	0.309608	0.392
	% Initial BMD	100%	100%		99.49%	99.28%		101.10%	98.48%	
Zone 7	Average	1.312915	1.174041		1.276148	1.134982		1.312177	1.088361	
	Stdev	0.454741	0.346348	0.352	0.432930	0.309008	0.313	0.463216	0.293162	0.129
	% Initial BMD	100%	100%		97.20%	96.67%		99.94%	92.70%	

Table 1. Measurements of perioperative Bone Mineral Density (BMD) show no significant difference between the control ($n = 19$) and study groups ($n = 13$) in any of Gruen Zones 1 through 7. Table 1a, baseline; Table 1b, six month time point; Table 1c, twelve month time point. Values are measured as gram per cm^2 (Mean $\pm$ SD).

Figure 1. The percentage profiles of measured BMD in each Gruen zone in the control (n=19) and study group (n=13) at 6 months and 12 months are assessed and no statistical significance was found between any time point. Blue lines, control group; orange lines, study group.

or 12 months post-surgery ($p > 0.05$).

Biochemical markers indicating bone resorption and turn-over from blood and urine samples were also evaluated to assess the systemic effect of risedronate and control therapy. The results showed that there are no significant differences in levels of collagen-type I N-telopeptides (NTx) or bone-specific alkaline phosphatase between the control and study groups at any point in the study ($p=0.09$; Figures 2 and 3). The detailed numbers of values of NTs and bone-specific alkaline phosphatase tested from subjects, as well as p-values are present in Table 2.

Table 2. Summary Statistics for Spine Bone Mineral Density in Lumbar Regions 1 - 4																
		Baseline BMD					6 month BMD					1 year BMD				
		L1	L2	L3	L4	L1-L4	L1	L2	L3	L4	L1-L4	L1	L2	L3	L4	L1-L4
Control	Mean	1.223	1.406	1.454	1.404	1.381	1.245	1.410	1.470	1.441	1.400	1.235	1.426	1.505	1.453	1.412
	St. Dev	0.215	0.259	0.260	0.248	0.214	0.208	0.258	0.282	0.241	0.217	0.239	0.288	0.279	0.231	0.232
	n=	10					10					10				
Study	Mean	1.105	1.239	1.327	1.303	1.249	1.094	1.239	1.321	1.287	1.238	1.110	1.237	1.314	1.313	1.253
	St. Dev	0.104	0.198	0.209	0.252	0.173	0.128	0.204	0.209	0.278	0.185	0.142	0.216	0.234	0.283	0.206
	n=	12					12					12				
t test		0.140	0.113	0.228	0.353	0.134	0.065	0.108	0.185	0.178	0.080	0.168	0.106	0.104	0.216	0.108

Table 2. Assessments of Bone Mineral Density (BMD) of the lumbar spines show no systemic difference between groups treated with the control agent and with risedronate. Table 2a, baseline; Table 2b, six month time point; Table 2c, twelve month time point. Values are measured as gram per cm² (Mean $\pm$ SD).

Discussion

This study investigated the potential benefits of bisphosphonate therapy for delayed periprosthetic bone remodeling and hypothesized that risedronate treatment would significantly reduce long-term bone loss in patients following THA. Previous studies have reported that bisphosphonate therapy reduced the dramatic loss in bone mineral density in the six months immediately following surgery, as well as potentially reducing the risk of post-operative fractures and implant loosening in the short-term. [3] The long-term sustainability of these benefits, however, has not been explored since wear-induced osteolysis appears to be related to a group of key factors not necessarily related to osteoporosis. These factors include the mevalonate pathway induced by osteoclastic stimulation; the differentiation of macrophages into osteoclastic bone reabsorbing cells with the involvement of macrophage colony stimulating factor (M-CSF), tumor necrosis factor- α , interleukin-1 β , prostaglandin E₂ (PGE₂), synovial parathyroid hormone (PTH) and nuclear factor- κ B ligand (RANKL). [8,11,12,27] Any of these alone may be responsible for the destructive pathway inducing osteolysis around an implant and leading to loosening and other post-surgical complications. [9,10,17,28]

Risedronate, a synthetic analogue of pyrophosphate, is one of the clinically available bisphosphonates binding to hydroxyapatite crystals in the mineralized bone matrix to prevent the degradation of pyrophosphatase through its influence on the mevalonate pathway. It has been tested in the treatment of Paget's disease, heterotopic ossification, hypercalcaemia, and postmenopausal osteoporosis. [24] In a long term multi-center study, risedronate significantly reduced the risk of hip fracture among elderly female subjects. This was additionally shown to increase the BMD level as early as 6 months despite the extent

of osteoporosis. [29] Several previous studies on bisphosphonate application for preventing bone loss reported that the administration of medication began immediately after surgery. Bhandari's group reported that cementless THAs can achieve greater gains from early bisphosphonate therapy than cemented THAs. [17] The outcome differences in cemented and uncemented THA have been well documented in another study less than one year after implantation with improvement in BMD suggesting again the anabolic effects on density are time limited. [30] With various numbers of enrolled subjects and different hip implants, other groups have definitely shown that an early treatment of bisphosphonate works well in preventing bone loss. [23,24,30,31,32,33] Those studies strongly suggest that oral bisphosphonate treatment may be one of the effective therapeutic options to improve bone strength in patients at an early administration following THA. They cannot however conclude effectiveness in the late administration following THA. [32,33]

In our study, patients represent a wide window of latent post-operative time frames consistent with a typical total joint practice where patients may develop loss at varying times after the initial implantation stabilization period of one year. Though late intervention may first seem unimportant, our results show that while other investigators show improvement earlier, late treatment will not be effective in preventing bone loss. Although the study was not powered to determine when the window opportunity ceases; it is clear that treatment after a year has elapsed will not help. As such, this study cannot make any conclusions other than late treatment will not reverse years of encapsulated established osteolysis after THR.

This compares to other work showing that the most dramatic changes in periprosthetic BMD are observed within the first 6 months. It may be reasonable to conclude that any of the years following the

initial 6-12 months of implantation will present similar patterns of bone loss in the femur as in the vertebral region. [1,17,29,30,31,34] Our results show that the risedronate treatment did not significantly improve the value of BMD in Gruen zones around the hip stem. Once the most dramatic changes in bone density subside and optimal window of therapeutic opportunity have passed, bisphosphonates have no effects. This may be due to the absence of the systemic rather than a regional mechanical or metabolic process. Given this scenario, bisphosphonates do not appear to reverse or suppress the local regional osteoporotic condition of a resorbing implant even though they work effectively in the global diseases state of an osteoporotic patient.

This study has several study limitations in this prospective pilot trial. The study is a small sample with tightly controlled medication and lab value time lines. The strict control of medication compliance in patients excluded virtually half of the enrolled patients. However, this tight control group validates strict adherence to dosimetry as well as the importance of early intervention. There is no stratification for new THR (< 5 years) versus older aging THA with more mechanical wear debris potentially creating osteolysis. We investigated implant age related to response to treatment in the study cohort and found no trends. While not powered to detect this, more research in this group should reveal a more distinct time for optimal to suboptimal treatment efficacy.

It has been accepted that stress shielding, byproducts of wear, and proximal periprosthetic bone loss lead to complications such as fracture or implant failure and reduce the quality of bone around the stem essential in revision surgeries. Furthermore, we performed a bioassay of two critical serum biomedical markers of bone resorption, N-telopeptides of Type I collagen (NTx) and bone-specific alkaline phos-

phatase. The results indicate that risedronate therapy does not have an impact on these two bone remodeling-related molecules in our investigative setting (Table 3; Figures 2-3). This supports the premise that there was no significant change in the metabolic osteoporotic systemic state. More prosthetic resorptive loss is not enough to trigger therapeutic effects from bisphosphonates. The p value of 0.09 for alkaline phosphatase may suggest more patients could eventually power a significant change in bone resorption response. However, this effect was very weak and not seen in the other marker or BMD which may not represent an adequate dose response to justify an extension study.

Conclusion

Our data demonstrates that risedronate treatment instituted in a latent setting of a fully ingrown THA provides no significant beneficial effects on periprosthetic or systemic BMD values when administered after the first postoperative year. While we cannot make conclusions on timing of earlier interventions, it suggests there may be a window of opportunity where intervention may retard loss. However, once the osteo-resorption is underway, treatments with bisphosphonates will not arrest or suspend the catabolic process. The lack of evidence supporting a long-term implemented therapy of combined risedronate with calcium suggests that novel therapeutic strategies should be developed to preserve periprosthetic BMD sustainably following total hip arthroplasty. This study shows that bisphosphonate treatment to enhance bone density is not effective in reversing osteolysis once bone loss is radiographically detected one year or more after implantation has occurred.

Table 3. Summary Statistics for Biochemical Bone Markers

		NTx (Resorption Marker)			Bone-specific Alk. Phosphatase		
		Baseline	6 mo	1yr	Baseline	6 mo	1 yr
Control (Caltrate)	Average	35.5556	25.7778	33.4444	12.1375	12.0000	11.8667
	StDev	31.7809	14.8894	25.1700	5.3452	6.3257	5.5066
	n=	9	9	9	8	9	9
Study (Actonel + Caltrate)	Average	35.7273	30.0000	25.7500	13.8000	10.5182	10.9417
	StDev	17.5162	16.4384	10.3408	3.2241	3.9217	3.0276
	n=	11	10	12	9	11	12
	p-value		0.8760526	0.4136380		0.2435755	0.0903372

Table 3. Analysis of bone-specific biochemical markers (NTx and alkaline phosphatase) showed no significant difference between the control (n=19) and risedronate treated groups (n=13). Values are measured as nmol BCE/mmol creatinine in NTx analysis and µg/L in alkaline phosphatase, respectively (Mean ± SD).

Figure 2: BMD Change vs Time in each Gruen Zone in Caltrate Cohort

Figure 2. Measurement of a bone-specific biochemical marker, NTx showed no significant difference between the control (blue color, n=19) and resdronate (orange color, n=13) treated groups. Values are expressed as Mean $\pm$ SD.

Figure 3: BMD Change vs Time for each Gruen Zone in Actonel + Caltrate Cohort

Figure 3. Analysis of a bone-specific alkaline phosphatase in specimen collected from groups of the control (blue color, n=19) and resdronate (orange color, n=13) treatment. No significance was found between groups at the time points examined. Data shown as Mean $\pm$ SD.

Competing interests

All research herein was conducted in accordance with ethical standards in compliance with privacy guidelines and in accordance with The Methodist Hospital Research Institute and Patient Advocacy Council, Inc. IRB. This study was funded in part by Proctor & Gamble Pharmaceuticals. None of the authors have any other financial or non-financial competing interests to disclose.

Authors' contributions

DRL, MDE designed the study and performed the clinical evaluation, JML collected the data. DRL, JML, MDE analyzed the data. DRL, MDE prepared and organized the manuscript. DRL, MDE ensured the accuracy of the data and analysis. All authors have read and approved the final manuscript.

Acknowledgements

The authors wish to thank Jennifer Hallett and Lauren Gaubert for their contributions to this study.

References

- Aldinger PR, Sabo D, Pritsch M, Thomsen M, Mau H, Ewerbeck V, Breusch SJ. Pattern of periprosthetic bone remodeling around stable uncemented tapered hip stems: a prospective 84-month follow-up study and a median 156-month cross-sectional study with DXA. *Calcif Tissue Int.* 2003;73:115-21
- Tsiridis E, Gamie Z, Conaghan PG, Giannoudis PV. Biological Options to enhance periprosthetic bone mass. *Injury* 2007;38:704-13
- Silverman SL, Watts NB, Deimas PD, Lange JL, Lindsay R.. Effectiveness of bisphosphonates on nonvertebral and hip fractures in the first year of therapy: The risedronate and alendronate (REAL) cohort study. *Osteoporosis Int.* 2007;18:25-34
- Venesmaa PK, Kröger HPJ, Miettinen HJ, Suomalainen OT, Alhava EM. Periprosthetic bone loss after cemented total hip arthroplasty, a prospective 5-year dual energy radiographic absorptiometry study of 15 patients. *Acta Orthop. Scand.* 2003;74:31-6
- Peter B, Ramaniraka N, Rakotomanana LR, Zambelli PY, Pioletti DP. Peri-implant bone remodeling after total hip replacement combined with systemic alendronate treatment: a finite element analysis. *Comput Methods Biomech Biomed Engin.* 2004;7:73-78
- Scott DF, Jaffe WL. Host-bone response to porous-coated cobalt-chrome and hydroxyapatite-coated titanium femoral components in hip arthroplasty, Dual-energy x-ray absorptiometry analysis of paired bilateral cases at 5 to 7 years. *J Arthroplasty.* 1996;11:429-37.
- Spittlehouse AJ, Smith TW, Eastell R. Bone loss around 2 different types of hip prostheses. *J Arthroplasty.* 1998;13:422-7
- Granchi D, Pellacani A, Spina M, Serum levels of osteoprotegerin and receptor activator of nuclear factor- κ B ligand as markers of periprosthetic osteolysis. *J Bone Joint Surg.* 2006;88-A:1501
- Lohmann CH, Dean DD, Bonewald LF, Schwartz Z, Boyan BD. Nitric oxide and prostaglandin E2 production in response to ultra-high molecular weight polyethylene particles depends on osteoblast maturation state. *J Bone Joint Surg.* 2002;84-A:411-9
- Maciel FMB, Sarrazin P, Morisset S, Lora M, Patry C, Dumais R, de Brum-Fernandes AJ. Induction of cyclooxygenase-2 by parathyroid hormone in human osteoblasts in culture. *J Rheumatology.* 1997;24:2429-35.
- Sabokbar A, Fujikawa Y, Neale S, Murray DW, Athanasou NA. Human arthroplasty derived macrophages differentiate into osteoclastic bone resorbing cells. *Ann Rheum Dis.* 1997;56:414-20
- Vermes C, Chandrasekaran R, Jacobs JJ, Galante JO, Roebuck KA, Glant TT. The effects of particulate wear debris, cytokines, and growth factors on the functions of MG-63 osteoblasts. *J Bone Joint Surg.* 2001;83-A:201-11
- Aspenberg P, Van der Vis H. Migration, particles, and fluid pressure: a discussion of causes of prosthetic loosening. *Clin Orthop Relat Res.* 1998;352:75-80
- Fokter SK, Komadina R, Repše-Fokter A. Effect of etidronate in preventing periprosthetic bone loss following cemented hip arthroplasty: a randomized, double blind, controlled trial. *Wien Klin Wochenschr.* 2006;118:23-8
- Fokter SK, Komadina R, Repše-Fokter A, Yerby SA, Kocijancic A, Marc J. Etidronate does not suppress periprosthetic bone loss following cemented hip arthroplasty. *Int Orthop.* 2005;29:362-7
- Knoch F, Jaquiere C, Kowalsky M, Schaeren S, Alabre C, Martin I, Rubash HE, Shanbhag AS. Effects of bisphosphonates on proliferation and osteoblast differentiation of human bone marrow stromal cells. *Biomaterials.* 2005;26:6941-9
- Bhandari M, Bajammal S, Guyatt GH, Griffith L, Busse JW, Schünemann H, Einhorn TA. Effect of bisphosphonates on periprosthetic bone mineral density after total joint arthroplasty. *J Bone Joint Surg.* 2005;87:293-301
- Im GI, Qureshi SA, Kenney J, Rubash HE, Shanbhag AS. Osteoblast proliferation and maturation by bisphosphonates. *Biomaterials.* 2004;25:4105-15
- Digas G, Kärrholm J. Five-year DEXA study of 88 hips with cemented femoral stem. *Int Orthop.* 2009;33:1495-500
- Soininvarra TA, Jurvelin JS, Miettinen JH, Suomalainen OT, Alhava EM, Kröger PJ. Effect of alendronate on periprosthetic bone loss after total knee arthroplasty: a one-year, randomized, controlled trial of 19 patients. *Calcif Tissue Int.* 2002;71:472-7
- Venesmaa PK, Kröger HPJ, Miettinen HJA, Jurvelin JS, Suomalainen OT, Alhava EM. Monitoring of periprosthetic BMD after uncemented total hip arthroplasty with dual-energy x-ray absorptiometry - a 3-year follow-up study. *J Bone Mineral Res.* 2001;16:1056-61
- Ringe JD, Farahmand P, Faber H, Dorst A. Sustained efficacy of risedronate in men with primary and secondary osteoporosis: results of a 2-year study. *Rheumatol Int.* 2009; 29:311-5
- Pazianas M, Epstein S, Zaidi M. Evaluating the antifracture efficacy of bisphosphonates. *Rev Recent Clin Trials.* 2009; 4:122-30
- Bell NH, Johnson RH. Bisphosphonates in the treatment of osteoporosis. *Endocrine.* 1997;6:203-206
- Clemens JD, Herrick MV, Singer FR, Eyre DR. Evidence that serum NTx (collagen-type I N-telopeptides) can act as an immunochemical marker of bone resorption. *Clin Chem.* 1997;43:2058-63
- 2Ross PD, Kress BC, Parson RE, Wasnich RD, Armour KA, Mizrahi IA. Serum bone alkaline phosphatase and calcaneus bone density predict fractures: a prospective study. *Osteoporos Int.* 2000;11:76-82
- Jevon M, Hirayama T, Brown MA, Wass JA, Sabokbar A, Ostelere S, Athanasou NA. Osteoclast formation from circulating precursors in osteoporosis. *Scand J Rheumatol.* 2003;32:95-100
- Steinberg JJ, Sledge CB. Chondrocyte mediated cartilage degradation: regulation by prostaglandin E2, cyclic AMP and interferon α . *J Rheumatology Suppl.* 1991;18:63-5
- McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, Adami S, Fogelman I, Diamond T, Eastell R, Meunier PJ, Reginster JY; Hip Intervention Program Study Group. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med.* 2001;344:333-40
- Theis JC, Beadel G. Changes in proximal femoral bone mineral density around a hydroxyapatite-coated hip joint arthroplasty. *J Orthop Surg.* 2003;11:48-52
- Venesmaa PK, Kroger HPJ, Miettinen HJA, Jurvelin JS, Suomalainen OT, Alhav EM. Alendronate reduces periprosthetic bone loss after uncemented primary total hip arthroplasty: a prospective randomized study. *J Bone Mineral Res.* 2001;16:2126-31
- Yamasaki S, Masuhara K, Yamaguchi K, Nakai T, Fuji T, Seino Y. Risedronate reduces postoperative bone resorption after cementless total hip arthroplasty. *Osteoporos Int.* 2007;18:1009-15
- Arabmotlagh M, Rittmeister M, Hennigs T. Alendronate prevents femoral periprosthetic bone loss following total hip arthroplasty: prospective randomized double-blind study. *J Orthop Res.* 2006;24:1336-41
- Yamaguchi K, Mashuhara K, Yamasaki S, Fuji T, Seino Y. Effects of discontinuation as well as intervention of cyclic therapy with etidronate on bone remodeling after cementless total hip arthroplasty. *Bone.* 2004;35:217-23