The Lasting Effect of Discontinuing Zoledronic Acid On Periprosthetic Bone Mineral Density Five Years After Total Hip Arthroplasty

Allen Herng Shouh Hsu
Kaohsiung Chang Gung Memorial Hospital
Chun-Hsien Yen
Kaohsiung Chang Gung Memorial Hospital
Yu-Der Lu
Kaohsiung Chang Gung Memorial Hospital
Feng-Chih Kuo
Kaohsiung Chang Gung Memorial Hospital
Cheng-Ta Wu
Kaohsiung Chang Gung Memorial Hospital
Tsan-Wen Huang
Chiayi Chang Gung Memorial Hospital
Mel S. Lee (bone@doctor.com)
Kaohsiung Chang Gung Memorial Hospital

Research Article

Keywords: Bisphosphonate, Zoledronic acid, Total hip arthroplasty, Bone mineral density, Bone turnover marker

Posted Date: September 21st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-808228/v1

Abstract

Background: Previous study has shown that a short-term use of zoledronic acid (ZA) after cementless total hip arthroplasty (THA) significantly increases bone mineral density (BMD) over the proximal femur and inhibits bone turnover markers (BTMs) after two years. However, could the discontinuation of ZA have a lasting effect is of interest.

Method: This is an extension study of a two-year prospective randomized controlled trial on 54 cementless THA treated with either two doses of ZA or placebo. We compared BTMs [alkaline phosphatase (ALP); osteocalcin (OC); procollagen 1 intact N-terminal propeptide (P1NP)], serum calcium, renal function, radiological findings, and functional outcomes (Harris hip score and UCLA activity score) from baseline to 5 years post-THA in 49 patients, and periprosthetic BMD of the seven Gruen zones in 19 patients.

Result: All patients had well-functioning hip prostheses, normal renal function, and normal serum calcium levels at 5-year follow-up. At the fifth year, the BMD levels were not statistically different between the two groups, but the change in BMD from baseline (BMD change ratios) in ZA group were significantly increased in zone 2, 4, and 6 as compared with control group. Parallel to that, in ZA group, levels of ALP were significantly lower at the fifth year; OC were significantly lower at the second and the fifth year; P1NP were significantly lower from 6 weeks to 2 years as compared with those in control group.

Conclusion: This study demonstrates the lasting effect of a two-dose ZA given within one year after THA on bone metabolism and periprosthetic BMD at five years. The short-term dosing of ZA followed by a 4-year drug holiday had no adverse events and resulted in significant inhibition of periprosthetic bone loss and BTMs.

Trial Registration:

This extension study on a randomized, open label, single-center clinical trial was conducted under Institutional Review Board of Chang Gung Memorial Hospital Protocol Records 98-1150A3; 105-1296C1; 105-7004D, and was registered July 19th, 2016 on public registry ClinicalTrials.gov trial registration number NCT02838121.

Introduction

Periprosthetic bone loss after total hip arthroplasty (THA) is a perturbing phenomenon associated with stress shielding and bone remodeling [1, 2] leading to a higher risk of periprosthetic fracture, implant migration, and implant loosening [3, 4]. Several studies have suggested that the use of bisphosphonate after THA can preserve periprosthetic bone mass and improves long-term outcome. [5–9] However, specific treatment duration of bisphosphonate in THA patients and whether the effect can be lasting after drug discontinuation remain unknown. Adverse events such as osteonecrosis of the jaw (ONJ) and atypical bony fractures are also of concern in the long-term safety of bisphosphonate treatment.

In two randomized controlled studies using zoledronic acid (ZA) treatment after THA, periprosthetic bone mineral density (BMD) was effectively preserved after 2 years.[10, 11] ZA, a third-generation bisphosphonate, avidly binds to bone and rapidly inhibits HMB-CoA reductase pathway.[12] In a 3-year extension of the HORIZON (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly) pivotal fracture trial, patients who discontinued drug therapy for 3 years had minimal difference in bone density and bone turnover markers (BTMs) compared to those with continuous therapy.[13] These findings suggest that the residual effects of ZA after drug holiday may be associated with its high affinity and potency. In our previous study, 60 cementless THAs had been randomized to receive either 2 doses of ZA (administered one-day postoperatively and one-year postoperatively) or placebo.[11] Upon completion of the designed treatment, no anti-osteoporotic medication was administered in both groups for 4 years. It is of interest to know whether the inhibition of periprosthetic bone loss and BTMs after ZA discontinuation in THA patients would be lasting as observed in the HORIZON pivotal fracture trial. For this purpose, we conducted an extension study (five years post-THA) by reassessing the periprosthetic BMD, BTMs, renal function, radiological findings, and functional outcomes.

Materials And Methods

A 5-year extension study of a prospective, randomized clinical trial on periprosthetic bone preservation and BTMs suppression using ZA in cementless THA (ClinicalTrials.gov: NCT02838121) was conducted with Institutional Review Board approval (98-1150A3; 105-1296C1; 105-7004D). Our original randomized controlled trial study included 30 patients in ZA group who received intravenous 5mg ZA (Novartis Pharmaceuticals Corporation) at one day and at one year after THA, and a control group of 30 patients who received placebo of intravenous saline infusion. A cohort of 54 patients completed the two-year follow-up study. This extension study comprises of 49 patients in the original study who completed a five-year follow-up, without receiving further anti-osteoporotic medication. Data on 49 patients from the initial enrollment were reassessed including periprosthetic BMD via dual-energy X-ray absorptiometry (DEXA, Hologic Inc., Waltham, MA), BTMs [alkaline phosphatase (ALP); osteocalcin (OC); procollagen 1 intact N-terminal propeptide (P1NP)], serum biomarkers (serum creatinine and serum calcium), radiological examination (pelvis anteroposterior view and hip lateral view), and functional outcome [Harris hip score and University of California at Los Angeles (UCLA) activity score].

The periprosthetic BMD for 7 Gruen zones of the proximal femur were quantified as previously described. [11, 14] Time-dependent changes in BMD with reference to preoperative (baseline) BMD in each Gruen zone (BMD change ratios) were analyzed. Radiological assessments include implant position, presence of prosthesis-bone interface radiolucent lines, and presence of implant subsidence, loosening, or migration. [15, 16]

Statistical Analysis

Statistical analysis was performed using SPSS Statistics (version 19, IBM, Armonk, New York, USA). Group differences in all parameters at each time-point were analyzed by a repeated measure of generalized estimating equations. Significance was set at *p*-value less than 0.05.

Results

The period of patient enrollment was between January 2010 and August 2011 as previously described. At two years, 27 patients in each group had completed follow-up examinations. At the end of 5 years, 2 patients in ZA group and 3 patients in control group dropped out due to medical illnesses or unwilling to continue participation. A remaining recruitment of 25 patients (15 females/10 males; mean age 60.6 ± 11.9 years; mean BMI 26 ± 4) in ZA group and 24 patients (13 females/11 males; mean age 58.8 ± 13.3 years; mean BMI 25 ± 5) in control group underwent analysis of BTMs, serum biomarkers, radiological analysis, and functional outcome. At the fifth year, BMD was acquired in 9 patients (ZA group) and 10 patients (Control group). Patient enrollment is shown in Fig. 1.

Periprosthetic bone mineral density

Both groups had a similar baseline BMD prior to THA. The BMD values were significantly higher for ZA group in Gruen zones 1, 2, 6, 7 at 1 year; zones 1, 6, 7 at 2 years. BMD values in all Gruen zones of ZA group were higher than control group at five years, but no statistical significance was observed. (Table 1)

Table 1

Mean BMD (g/cm^2) for each group by Gruen zones

Gruen zones		**1**	**2**	**3**	**4**	**5**	**6**	**7**
Baseline	*n*							
ZA	27	0.63 (0.14)	1.25 (0.20)	1.51 (0.24)	1.62 (0.18)	1.56 (0.18)	1.24 (0.20)	0.96 (0.18)
Control	27	0.64 (0.15)	1.24 (0.22)	1.53 (0.21)	1.66 (0.20)	1.61 (0.22)	1.24 (0.21)	0.97 (0.24)
p-value		0.863	0.773	0.774	0.511	0.434	0.95	0.826
1 year								
ZA	27	0.65 (0.15)	1.37 (0.19)	1.50 (0.24)	1.67 (0.19)	1.66(0.15)	1.40 (0.21)	1.00 (0.26)
Control	27	0.56 (0.16)	1.25 (0.29)	1.51 (0.25)	1.60 (0.22)	1.56 (0.23)	1.20 (0.24)	0.78 (0.21)
p-value		0.04	0.035	0.913	0.194	0.072	0.016	0.017
2 years								
ZA	27	0.66 (0.14)	1.37 (0.19)	1.49 (0.24)	1.67 (0.18)	1.65 (0.19)	1.42 (0.21)	0.98 (0.27)
Control	27	0.55 (0.14)	1.35 (0.75)	1.52 (0.23)	1.59 (0.22)	1.62 (0.20)	1.22 (0.24)	0.78 (0.21)
p-value		0.007	0.912	0.69	0.192	0.552	0.002	0.004
5 years								
ZA	9	0.72 (0.98)	1.41 (0.13)	1.60 (0.14)	1.76 (0.19)	1.71 (0.16)	1.38 (0.21)	0.93 (0.27)
Control	10	0.62 (0.16)	1.22 (0.28)	1.52 (0.20)	1.66 (0.21)	1.71 (0.26)	1.24 (0.26)	0.81 (0.21)
p-value		0.1	0.56	0.26	0.26	0.95	0.19	0.26

n: number of patients; Data presented as Mean (Standard Deviation)

The BMD change ratios from baseline were significantly higher for ZA group in Gruen zones 1, 2, 4, 5, 6, 7 at 1 year (ZA = 27/C = 27); zones 1, 4, 6, 7 at 2 years (ZA = 27/C = 27); zones 2, 4, 6 at 5 years (ZA = 9/C = 10). In ZA group, BMD change ratios showed positive values (> 1) in all Gruen zones except for zone 7 (0.97) at the fifth year. (Table 2)

Table 2
Mean BMD change ratios by Gruen zone

Gruen zones		1	2	3	4	5	6	7
1 year	*n*							
ZA	27	1.05 (0.19)	1.10 (0.10)	1.00 (0.09)	1.03 (0.08)	1.07 (0.12)	1.13 (0.13)	1.07 (0.22)
Control	27	0.86 (0.24)	0.98 (0.25)	0.95 (0.22)	0.93(0.20)	0.95 (0.24)	0.97 (0.28)	0.84 (0.29)
p-value		0.002	0.027	0.753	0.002	0.031	0.013	0.003
2 years								
ZA	27	1.08 (0.21)	1.12 (0.11)	1.00 (0.11)	1.04 (0.09)	1.08 (0.15)	1.16 (0.13)	1.06 (0.22)
Control	27	0.89 (0.14)	1.10 (0.46)	1.00 (0.08)	0.96 (0.07)	1.02 (0.10)	1.00 (0.19)	0.83 (0.20)
p-value		0.001	0.815	0.984	0.001	0.134	0.001	0.001
5 years								
ZA	9	1.15 (0.35)	1.14 (0.16)	1.14 (0.39)	1.07 (0.11)	1.07 (0.11)	1.11 (0.19)	0.97 (0.34)
Control	10	1.01 (0.27)	0.95 (0.13)	0.98 (0.11)	0.98 (0.07)	1.04 (0.09)	0.96 (0.10)	0.86 (0.19)
p-value		0.307	0.005	0.211	0.043	0.506	0.031	0.406
Data presented as Mean (Standard Deviation)								

Radiologic evaluation

Standard pelvis anteroposterior view and lateral hip radiography were analyzed at all time intervals. All implants were well fixed with radiological evidence of prosthesis bony ingrowth. No progressive radiolucent lines, osteolysis, subsidence or migration of prostheses were observed in both groups. No patients developed periprosthetic fracture, infection, or other implant-related complications at 5 years.

Serum Biomarkers and BTMs

A decrease in serum ALP was observed in ZA group throughout different time-points since the first dosage, with significance at 12 weeks ($p = 0.004$) and five years ($p = 0.002$). OC levels were significantly higher at baseline in ZA group ($p = 0.044$). After ZA treatment, a suppressive trend throughout each time-point was observed. OC levels were significantly lower at two years ($p = 0.034$) and five years ($p = 0.007$) in ZA group as compared with control group. P1NP levels were also found to be significantly higher in ZA group at baseline ($p = 0.03$). Following the first dose of ZA, P1NP levels were decreased with significant differences at time-points from 6 weeks to 2 years as compared with control group. (Table 3) No differences were observed between the two groups in regards to renal function and serum calcium levels.

Table 3
Comparison of serum biomarkers and BTMs between ZA (n = 25) and control (n = 24)

	Baseline	6 weeks	12 weeks	6 months	1 year	2 years	5 years
Alkaline phosphatase (µg/L)							
ZA	79.8 (17.9)	78.3 (19.4)	66.6 (11.4)	69.1 (27)	69.4 (24.7)	66.6 (17.5)	64.3 (11.3)
Control	76 (18.3)	87.9 (21.9)	81.9 (22.4)	74.8 (20.6)	74.6 (18.4)	74.5 (15.6)	76.7 (14.7)
p-value			0.004				0.002
Osteocalcin (µg/mL)							
ZA	21.9 (8.6)	18.3 (8.2)	17.3 (10.6)	14.8 (5)	16.9 (7.1)	14.5 (7)	12.5 (6.8)
Control	17.1 (7.4)	19.9 (12.2)	20.1 (10.8)	17.1 (5.4)	21.3 (9.8)	19.4 (8.5)	19.1 (8.6)
p-value	0.044					0.034	0.007
P1NP [Procollagen 1 Intact N-Terminal] (ng/mL)							
ZA	55.2 (23.1)	55.5 (22)	37.5 (14.8)	30 (12.2)	35.2 (19.7)	27.7 (11.4)	NA†
Control	41.3 (20.2)	77.7(39.3)	70.2 (37.5)	58.9 (25.1)	51.6 (34)	45.4 (19.6)	NA†
p-value	0.030	0.020	0.000	0.000	0.047	0.001	-
Cr (mg/dL)							
ZA	0.77 (0.21)	0.74 (0.24)	0.8 (0.28)	0.84 (0.61)	0.77 (0.25)	0.78 (0.25)	0.82 (0.27)
Control	0.82 (0.2)	0.79 (0.22)	0.78 (0.18)	0.78 (0.19)	0.81 (0.2)	0.81 (0.21)	0.82 (0.21)
GFR (mL/min)							
ZA	59.7 (1.7)	60.5 (4.8)	62 (11.1)	79.1(27.7)	84.8 (28.6)	94.7 (22.6)	90.8 (25.8)
Control	59.8 (0.6)	59.8 (1.2)	63.6 (13.3)	73.7 (24.1)	81.4 (21.8)	87.7 (18.4)	85.9 (21)
Ca (mg/dL)							
ZA	9.51 (0.5)	9.27 (0.53)	9.52(0.45)	9.44 (0.46)	9.41 (0.48)	9.37 (0.37)	9.25 (0.4)
Control	9.6 (0.43)	9.16 (1.88)	9.53(0.37)	9.43 (0.51)	9.48 (0.36)	9.28 (0.3)	9.38 (0.42)

Data presented as Mean (Standard Deviation)

†NA: Not Available

Functional outcomes

Patients in both groups had comparable good to excellent functional outcomes at the final follow-up as compared to one-year post-THA. Harris Hip Score improved from 86 ± 7.1 to 87 ± 9.7 in ZA group and from 85 ± 7.3 to 89 ± 3.6 in control group. UCLA activity score improved from 5.7 ± 1.1 to 7.2 ± 0.8 in ZA group and from 5.5 ± 1.2 to 7.2 ± 0.7 in control group.

Discussion

Periprosthetic bone loss after cementless THA is a well-cited phenomenon and may contribute to the longevity of implant survivorship. Periprosthetic bone mass decrease after joint replacement is a continuous process and has been reported to last for over 10 years.[17] At the proximal femur, loss of bone stock has been reported to account for 16–30%.[18] This phenomenon increases the risk of early implant migration, aseptic loosening, periprosthetic fracture, and hence decreased implant survivorship. [4, 19]

BMD value is an important factor to the fixation and stability of the implanted prosthesis.[20] Early stem migration and rotation has been detected in osteoporotic bone compared to bones of normal BMD values in patients undergoing THA.[21] Patients with low preoperatively BMD values are at risk of major complications, including stem migration or even subsidence. [22] Currently, many studies support the role of bisphosphonate in the preservation of periprosthetic bone after THA.[23, 24] ZA, a third-generation bisphosphonate, has shown to be more potent than its second-generation predecessor in multiple in-vivo studies.[25–27] In our previous study, a short term use of ZA effectively increased periprosthetic BMD values.[11] In this five year extension study, ZA group retained higher BMD values across all seven Gruen zones. Although BMD levels at the fifth year were not statistically different between ZA group and control group, fifth year BMD change ratios in Gruen zones 2, 4, and 6 were significantly higher in ZA group as compared to the control group. Parallel to the above findings, the levels of BTMs (ALP, OC, and P1NP) were shown to be persistently suppressed in ZA group after ZA discontinuation for 4 years. In our previous study that included 54 patients, the baseline OC and P1NP levels were not different between groups. However, the 25-patient ZA group within the 49-patient extension study had significantly higher baseline levels of OC and P1NP ($p = 0.044$ and $p = 0.030$, respectively) as compared to the control group, suggesting a higher pre-trial bone turnover status. Nevertheless, ZA given one day after THA could potently inhibit P1NP and ALP levels in ZA group as early as 6 weeks, and booster dose of ZA at one year after THA further inhibited P1NP, ALP and OC levels at 2 years or 5 years. High bone turnover status with increased serum OC and P1NP is associated with low BMD in osteoporotic population. [28, 29] OC and P1NP are also useful BTMs for monitoring antiresorptive therapy and fracture risk assessment. [30–32] We found 2 doses of ZA given within one year after THA had lasting effects on the inhibition of P1NP/OC at 2 years and ALP/OC at 5 years. To the best of our knowledge, the interesting findings of the lasting effect of ZA on periprosthetic BMD and bone turnover after drug holiday for 4 years has not been reported. It may be related to ZA's high affinity to bone and high potency pharmacological nature such as seen in the extension study of HORIZON pivotal fracture trial.[33] Reports of other bisphosphonates (risedronate, alendronate, or pamidronate) have shown good periprosthetic bone preservation in early follow-up but not in mid-term [19, 23, 34, 35] as the increased periprosthetic BMD would eventually decrease after discontinuation of these aforementioned medications. Some authors have thus suggested that lifelong administration of bisphosphonate may be warranted, especially for patients with poor preoperative bone stock.[36, 37] Our results are in accordance with other studies on ZA drug holiday, as it demonstrates a prolonged effect after discontinuation.[38] Findings in this study show that a 4-year drug holiday of ZA can preserve periprosthetic BMD, inhibits BTMs, and exhibit no adverse reactions such as the rebounding phenomenon seen in RANKL antagonist withdrawal [39, 40], ONJ, or atypical bony fractures. However, no difference was found in regards to the functional outcomes and implant survival. All implants are well fixed without loosening, migration, or pedestal formation. No patients received revision surgery for periprosthetic joint infection or periprosthetic fracture. Nevertheless, we find the protective potential of a short-term administration of ZA lasting up to 5 years encouraging.

This study has limitations. Firstly, the sample size was small, with the initial study including 60 THA's randomized to ZA and placebo. At the fifth year, 49 recruits completed the clinical follow-up while only 19 cases had completed BMD study. Secondly, randomization of open label ZA or placebo was not blinded by a dummy for control subjects. Thirdly, while good patient compliance was achieved with no other anti-osteoporotic medication administered during the study period, calcium

and vitamin D supplements were not strictly controlled. Finally, this study reports the cross-sectional results at the fifth year in a cohort receiving 2 doses of ZA and subsequent drug holiday for 4 years. These results may not be translated onto other dosing regimen or projected for long-term outcomes. However, there are merits in this extension study in that data of the prospective randomized clinical trial is unbiased and unique, and all surgeries were performed by an experienced surgeon. The study was stringently performed and audited by the institutional research board.

In conclusion, this study demonstrates the lasting effect of a two-dose ZA given within one year after THA on bone metabolism and periprosthetic BMD at 5 years. The short-term dosing of ZA and drug holiday for 4 years has no adverse events and results in significant inhibition of periprosthetic bone loss and bone turnover markers.

Declarations

Ethics approval and consent to participate

All methods were carried out in accordance to the ethical principles for medical research involving human subjects under Declaration of Helsinki. Informed consent was obtained from all study participants on collection of medical history and examination data. This is an extension study on a randomized, open label, single-center clinical trial registered on public registry July 19th, 2016 on ClinicalTrials.gov (reference number NCT02838121) and was conducted under Institutional Review Board of Chang Gung Memorial Hospital Protocol Records 98-1150A3; 105-1296C1; 105-7004D.

Consent for publication

Not Applicable

Availability of data and materials

Dataset supporting the contents of this article is included within the manuscript in the form of text and tables. Participants did not consent to public release of personal medical data. However, data can be made available for researchers under confidential terms by the Department of Orthopaedic Surgery, Kaohsiung Chang Gung Memorial Hospital, Taiwan.

Competing interests

All authors declare to have no potential financial or non-financial competing interests in the subject matter of this manuscript. All authors certify to have no employment, consultancies, stock ownership, equity of interest affiliation with the pharmaceutical company which funded this clinical trial.

Funding

This study was funded by by Novartis and Lotus Pharmaceutical (XMRPG381086).

Authors' contributions

MSL and T-WH contributed to the conception and design of the study. AHSH and C-HY analyzed and interpreted the data and drafted the main manuscript text. Y-DL, F-CK, and C-TW revised it critically for important intellectual content. All authors reviewed, edited, and approved of the final manuscript.

Acknowledgements

We offer our gratitude towards Chao-Jan Wang, Hsin-Nung Shih, Chang, Kuo-Chin Huang, Kuo-Ti Peng for their authorship and contribution in the original research article.

Author Information

Mel S. Lee[1], Allen Herng Shouh Hsu[1], Chun-Hsien Yen[1], Yu-Der Lu[1], Feng-Chih Kuo[1], Cheng-Ta Wu[1], Tsan-Wen Huang[2]

[1]**Kaohsiung Chang Gung Memorial Hospital**, Taiwan

[2]**Chiayi Chang Gung Memorial Hospital**, Taiwan

References

1. Oh I, Harris WH: Proximal strain distribution in the loaded femur. An in vitro comparison of the distributions in the intact femur and after insertion of different hip-replacement femoral components. *The Journal of bone and joint surgery American volume* 1978, 60(1):75–85.
2. Alm JJ, Makinen TJ, Lankinen P, Moritz N, Vahlberg T, Aro HT: Female patients with low systemic BMD are prone to bone loss in Gruen zone 7 after cementless total hip arthroplasty. *Acta Orthop* 2009, 80(5):531–537.
3. Aro HT, Alm JJ, Moritz N, Makinen TJ, Lankinen P: Low BMD affects initial stability and delays stem osseointegration in cementless total hip arthroplasty in women: a 2-year RSA study of 39 patients. *Acta Orthop* 2012, 83(2):107–114.
4. Skoldenberg OG, Sjoo H, Kelly-Pettersson P, Boden H, Eisler T, Stark A, Muren O: Good stability but high periprosthetic bone mineral loss and late-occurring periprosthetic fractures with use of uncemented tapered femoral stems in patients with a femoral neck fracture. *Acta Orthop* 2014, 85(4):396–402.
5. Ott SM: What is the optimal duration of bisphosphonate therapy? *Cleveland Clinic journal of medicine* 2011, 78(9):619–630.
6. Bhandari M, Bajammal S, Guyatt GH, Griffith L, Busse JW, Schunemann H, Einhorn TA: Effect of bisphosphonates on periprosthetic bone mineral density after total joint arthroplasty. A meta-analysis. *The Journal of bone and joint surgery American volume* 2005, 87(2):293–301.
7. Lin T, Yan SG, Cai XZ, Ying ZM: Bisphosphonates for periprosthetic bone loss after joint arthroplasty: a meta-analysis of 14 randomized controlled trials. *Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 2012, 23(6):1823–1834.
8. Knusten AR, Ebramzadeh E, Longjohn DB, Sangiorgio SN: Systematic analysis of bisphosphonate intervention on periprosthetic BMD as a function of stem design. *The Journal of arthroplasty* 2014, 29(6):1292–1297.
9. Shi J, Liang G, Huang R, Liao L, Qin D: Effects of bisphosphonates in preventing periprosthetic bone loss following total hip arthroplasty: a systematic review and meta-analysis. *Journal of orthopaedic surgery and research* 2018, 13(1):225.
10. Scott DF, Woltz JN, Smith RR: Effect of zoledronic acid on reducing femoral bone mineral density loss following total hip arthroplasty: preliminary results of a prospective randomized trial. *The Journal of arthroplasty* 2013, 28(4):671–675.
11. Huang TW, Wang CJ, Shih HN, Chang Y, Huang KC, Peng KT, Lee MS: Bone turnover and periprosthetic bone loss after cementless total hip arthroplasty can be restored by zoledronic acid: a prospective, randomized, open-label, controlled trial. *BMC Musculoskelet Disord* 2017, 18(1):209.
12. Russell RG, Watts NB, Ebetino FH, Rogers MJ: Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 2008, 19(6):733–759.
13. Black DM, Reid IR, Boonen S, Bucci-Rechtweg C, Cauley JA, Cosman F, Cummings SR, Hue TF, Lippuner K, Lakatos P *et al*: The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research* 2012, 27(2):243–254.
14. Iolascon G, Di Pietro G, Capaldo A, Gioia C, Gatto S, Gimigliano F: Periprosthetic bone density as outcome of therapeutic response. *Clinical cases in mineral and bone metabolism: the official journal of the Italian Society of Osteoporosis, Mineral Metabolism, and Skeletal Diseases* 2010, 7(1):27–31.

15. Engh CA, Massin P, Suthers KE: Roentgenographic assessment of the biologic fixation of porous-surfaced femoral components. *Clinical orthopaedics and related research* 1990(257):107–128.
16. Johnston RC, Fitzgerald RHJ, Harris WH, Poss R, Müller ME, Sledge CB: Clinical and radiographic evaluation of total hip replacement. A standard system of terminology for reporting results. *JBJS* 1990, 72(2):161–168.
17. Boden HS, Skoldenberg OG, Salemyr MO, Lundberg HJ, Adolphson PY: Continuous bone loss around a tapered uncemented femoral stem: a long-term evaluation with DEXA. *Acta Orthop* 2006, 77(6):877–885.
18. Tapaninen TS, Venesmaa PK, Jurvelin JS, Miettinen HJ, Kroger HP: Alendronate reduces periprosthetic bone loss after uncemented primary total hip arthroplasty - a 5-year follow-up of 16 patients. *Scandinavian journal of surgery: SJS : official organ for the Finnish Surgical Society and the Scandinavian Surgical Society* 2010, 99(1):32–37.
19. Muren O, Akbarian E, Salemyr M, Boden H, Eisler T, Stark A, Skoldenberg O: No effect of risedronate on femoral periprosthetic bone loss following total hip arthroplasty. A 4-year follow-up of 61 patients in a double-blind, randomized placebo-controlled trial. *Acta Orthop* 2015, 86(5):569–574.
20. Nixon M, Taylor G, Sheldon P, Iqbal SJ, Harper W: Does bone quality predict loosening of cemented total hip replacements? *The Journal of bone and joint surgery British volume* 2007, 89(10):1303–1308.
21. Aro E, Moritz N, Mattila K, Aro HT: A long-lasting bisphosphonate partially protects periprosthetic bone, but does not enhance initial stability of uncemented femoral stems: A randomized placebo-controlled trial of women undergoing total hip arthroplasty. *Journal of biomechanics* 2018, 75:35–45.
22. van der Voort P, Pijls BG, Nieuwenhuijse MJ, Jasper J, Fiocco M, Plevier JW, Middeldorp S, Valstar ER, Nelissen RG: Early subsidence of shape-closed hip arthroplasty stems is associated with late revision. A systematic review and meta-analysis of 24 RSA studies and 56 survival studies. *Acta Orthop* 2015, 86(5):575–585.
23. Venesmaa PK, Kroger HP, Miettinen HJ, Jurvelin JS, Suomalainen OT, Alhav EM: Alendronate reduces periprosthetic bone loss after uncemented primary total hip arthroplasty: a prospective randomized study. *Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research* 2001, 16(11):2126–2131.
24. Arabmotlagh M, Pilz M, Warzecha J, Rauschmann M: Changes of femoral periprosthetic bone mineral density 6 years after treatment with alendronate following total hip arthroplasty. *Journal of orthopaedic research: official publication of the Orthopaedic Research Society* 2009, 27(2):183–188.
25. McClung M, Recker R, Miller P, Fiske D, Minkoff J, Kriegman A, Zhou W, Adera M, Davis J: Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. *Bone* 2007, 41(1):122–128.
26. Saag K, Lindsay R, Kriegman A, Beamer E, Zhou W: A single zoledronic acid infusion reduces bone resorption markers more rapidly than weekly oral alendronate in postmenopausal women with low bone mineral density. *Bone* 2007, 40(5):1238–1243.
27. Orwoll ES, Binkley NC, Lewiecki EM, Gruntmanis U, Fries MA, Dasic G: Efficacy and safety of monthly ibandronate in men with low bone density. *Bone* 2010, 46(4):970–976.
28. Biver E, Chopin F, Coiffier G, Brentano TF, Bouvard B, Garnero P, Cortet B: Bone turnover markers for osteoporotic status assessment? A systematic review of their diagnosis value at baseline in osteoporosis. *Joint Bone Spine* 2012, 79(1):20–25.
29. Schousboe JT, Bauer DC: Clinical use of bone turnover markers to monitor pharmacologic fracture prevention therapy. *Curr Osteoporos Rep* 2012, 10(1):56–63.
30. Koivula MK, Risteli L, Risteli J: Measurement of aminoterminal propeptide of type I procollagen (PINP) in serum. *Clin Biochem* 2012, 45(12):920–927.
31. Rogers A, Glover SJ, Eastell R: A randomised, double-blinded, placebo-controlled, trial to determine the individual response in bone turnover markers to lasofoxifene therapy. *Bone* 2009, 45(6):1044–1052.
32. Garnero P: Biomarkers for osteoporosis management: utility in diagnosis, fracture risk prediction and therapy monitoring. *Mol Diagn Ther* 2008, 12(3):157–170.

33. Black DM, Reid IR, Cauley JA, Cosman F, Leung PC, Lakatos P, Lippuner K, Cummings SR, Hue TF, Mukhopadhyay A *et al*: The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). *Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research* 2015, 30(5):934–944.
34. Wang CJ, Wang JW, Ko JY, Weng LH, Huang CC: Three-year changes in bone mineral density around the knee after a six-month course of oral alendronate following total knee arthroplasty. A prospective, randomized study. *The Journal of bone and joint surgery American volume* 2006, 88(2):267–272.
35. Shetty N, Hamer A, Stockley I, Eastell R, Willkinson J: Clinical and radiological outcome of total hip replacement five years after pamidronate therapy: a trial extension. *The Journal of bone and joint surgery British volume* 2006, 88(10):1309–1315.
36. Skoldenberg OG, Salemyr MO, Boden HS, Ahl TE, Adolphson PY: The effect of weekly risedronate on periprosthetic bone resorption following total hip arthroplasty: a randomized, double-blind, placebo-controlled trial. *The Journal of bone and joint surgery American volume* 2011, 93(20):1857–1864.
37. Thillemann TM, Pedersen AB, Mehnert F, Johnsen SP, Soballe K: Postoperative use of bisphosphonates and risk of revision after primary total hip arthroplasty: a nationwide population-based study. *Bone* 2010, 46(4):946–951.
38. Lee SH, Gong HS, Kim TH, Park SY, Shin JH, Cho SW, Byun DW: Position Statement: Drug Holiday in Osteoporosis Treatment with Bisphosphonates in South Korea. *J Bone Metab* 2015, 22(4):167–174.
39. Tsourdi E, Zillikens MC: Certainties and Uncertainties About Denosumab Discontinuation. *Calcif Tissue Int* 2018, 103(1):1–4.
40. Lamy O, Stoll D, Aubry-Rozier B, Rodriguez EG: Stopping Denosumab. *Curr Osteoporos Rep* 2019, 17(1):8–15.

Figures

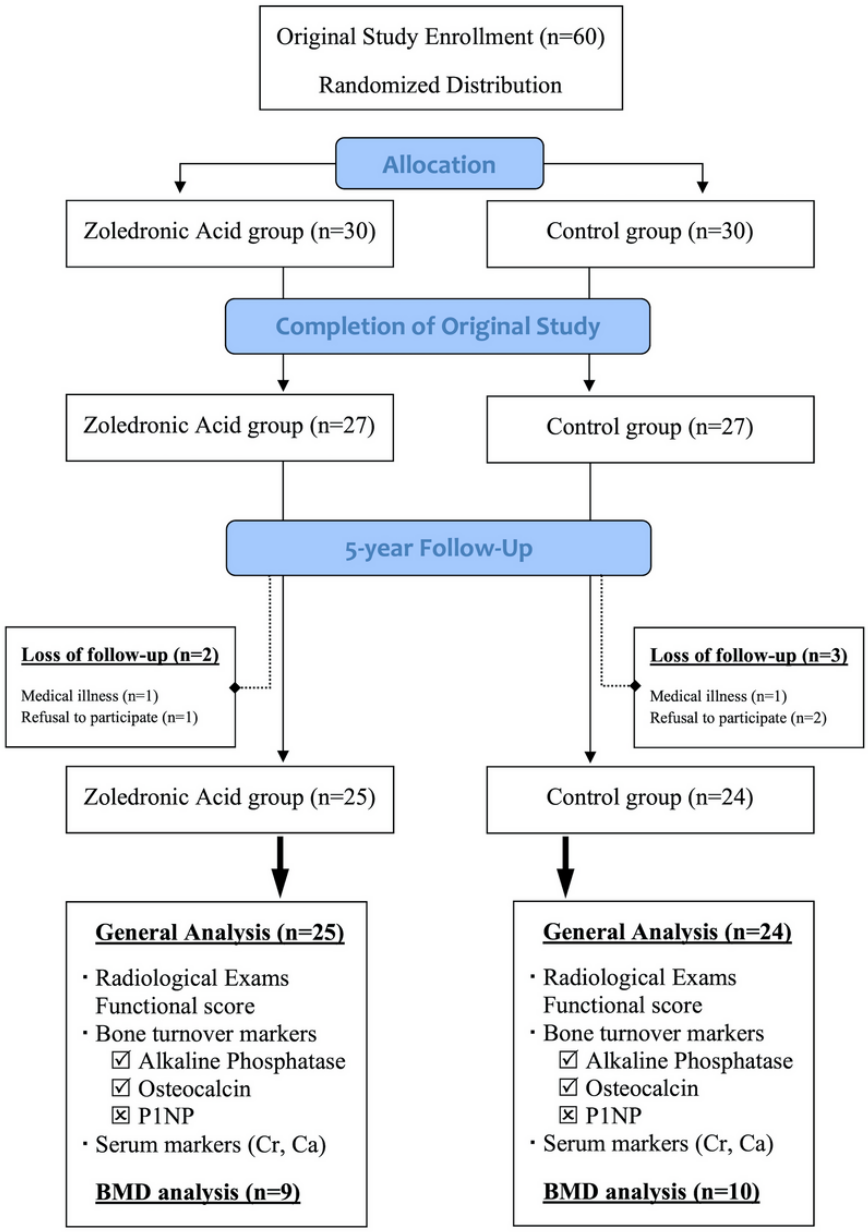

Figure 1

Patient enrollment is shown in Figure.