

Table S1. Detailed information on the patients with AFF in the non-BP group

| | Case 1 | Case 2 ^a | Case 3 ^b | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 | Case 9 |
|---|-----------|--|--|--------------|---------------------------------|-----------------|------------------------|---------------------------|--|
| Age | 83 | 78 | 64 | 60 | 62 | 84 | 63 | 50 | 82 |
| Sex | Female | Male | Male | Female | Female | Female | Male | Male | Female |
| Bisphosphonate treatment | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Single dose of Zoledronic acid |
| Indication | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | Suspected Paget's disease of bone |
| Treatment duration, years | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Single infusion 25 months prior to surgery |
| Relevant comorbidities | NA | Diabetes mellitus Vitamin D deficiency Secondary hyperparathyroidism Vasculitis | AMI CKD stage 5 Prostate cancer Anemia CHF | Osteoporosis | Hypothyroidism Breast cancer | Rectal cancer | Dilated cardiomyopathy | X-linked hypophosphatemia | Paget's disease of the bone |
| Fracture location | Mid shaft | Subtrochanteric | Mid-shaft | Mid-shaft | Mid-shaft | Subtrochanteric | Mid-shaft | Subtrochanteric | Mid-shaft |
| Bilateral fractures | No | No | No | No | Yes | Yes | No | No | No |
| Bone resorption around fracture line | Yes | Yes | No | Yes | No | Yes | No | Yes | Yes |
| Multiple lesions | No | No | Yes | No | Yes | Yes | No | No | Yes |
| Number of lesions | 1 | 1 | >1 (5) | 1 | >1 (2) | >1 (2) | 1 | 1 | >1 (4) |
| Displacement | No | No | No | No | No | No | No | No | No |

^a Previously published case.

^b Died within 1 year of the index surgery.

AMI = acute myocardial infarction; CKD = chronic kidney disease; CHF = congestive heart failure.

Table S2. Detailed information for patients in the BP group with AFF

| | Case 10 ^a | Case 11 ^a | Case 12 ^a | Case 13 | Case 14 | Case 15 | Case 16 | Case 17 | Case 18 | Case 19 |
|--|---|-------------------------------------|----------------------------------|--|--------------------------------|---------------------------------|-------------------------------------|---------------------------------|---------------------------------|---|
| Age | 80 | 57 | 81 | 92 | 81 | 65 | 76 | 79 | 90 | 73 |
| Sex | Female | Female | Female | Female | Female | Female | Female | Female | Male | Female |
| Bisphosphonate | Alendronic acid | Alendronic acid/ risedronic acid | Alendronic acid | Alendronic acid | Alendronic acid | Alendronic acid | Alendronic acid/ zoledronic acid | Alendronic acid | Alendronic acid | Alendronic acid |
| Indication | Corticoid treatment | Corticoid treatment | Osteoporotic fractures | Osteoporosis | Osteoporosis | Osteoporosis | Osteoporosis | Osteoporosis | Osteoporotic fracture | Osteoporosis |
| Treatment duration, years | 5 | 6 | 21 | 5 | 9 | 5 | 7 | 2 | 3 | 4 |
| Discontinuation of bisphosphonate treatment | At the time of index surgery | At the time of index surgery | 1.5 years prior to index surgery | At the time of index surgery | 2 years prior to index surgery | 5 months prior to index surgery | 2 months prior to index surgery | At the time of index surgery | At the time of index surgery | At the time of index surgery |
| Relevant comorbidities | Graves' disease Diabetes mellitus PMR | Rheumatoid arthritis | Bullous pemphigoid | Congestive heart failure Ischemic heart disease | Hypo-thyroidism Smoker | Smoker Diabetes mellitus | No relevant comorbidities | Hypertension Hyper-lipidemia | Hypertension BPH Glaucoma | Postoperatively diagnosed with hypoparathyroidism |
| Fracture location | Mid-shaft | Subtrochanteric | Mid-shaft | Mid-shaft | Mid-shaft | Mid-shaft | Mid-shaft (bilaterally) | Mid-shaft | Mid-shaft | Mid-shaft |
| Bilateral fractures | No | Yes | No | No | Yes | Yes | No | No | No | No |
| Bone resorption around fracture line | No | No | No | No | No | No | No | No | No | No |
| Multiple lesions | No | No | No | No | Yes | Yes | No | No | No | No |
| Number of lesions | 1 | 1 | 1 | 1 | >1 (3) | >1 (4) | 1 | 1 | 1 | 1 |
| Displacement | No | No | No | No | No | No | No | No | No | No |

^a Previously published case.

PMR = polymyalgia rheumatica; BPH = benign prostatic hyperplasia.

Table S3. Radiologic follow-up for the non-BP group

| | General assessment | 0–2 months | 3–4 months | 5–8 months | 12–15 months | >15 months |
|---------------|--|-------------------|-----------------------------|--------------------------------|--|--|
| Case 1 | Cortical irregularities Extensive lateral femoral bowing Healed uneventfully | N/A | Faint callus | Bridging callus | Continuity of cortical bone | N/A |
| Case 2 | Cortical irregularities Coxa vara Healed uneventfully | N/A | N/A | Bridging callus | N/A | M17: Continuity of cortical bone |
| Case 3 | Cortical irregularities Healed uneventfully | N/A | N/A | N/A | Proximal biopsy shows continuity of cortical bone, biopsy 2 shows incomplete cortical continuity | N/A |
| Case 4 | Biopsy hole did not heal completely; resulted in complete AFF 4.5 years after index surgery. | N/A | Discrete callus | N/A | Bridging callus | M31: Radiolucent line at the fracture site |
| Case 5 | Fracture crack appeared to originate endosteally. 2–3 lesions with extensive edema on contralateral femur. Healed uneventfully | No callus | Bridging callus | N/A | N/A | M20: Continuity of cortical bone |
| Case 6 | Healed uneventfully | Faint callus | N/A | N/A | Continuity of cortical bone | N/A |
| Case 7 | Healed uneventfully | N/A | Continuity of cortical bone | N/A | N/A | N/A |
| Case 8 | Healed uneventfully | N/A | Bridging callus | Incomplete cortical continuity | Continuity of cortical bone | N/A |
| Case 9 | Multiple stress lesions in Paget’s disease-transformed bone Healed uneventfully | Bridging callus | N/A | N/A | Continuity of cortical bone | N/A |

Table S4. Radiologic follow-up for the BP group

| | General assessment | 0–2 months | 3–4 months | 5–8 months | 12–15 months | >15 months |
|----------------|--|-------------------|---|-----------------------------|--------------------------------------|----------------------------------|
| Case 10 | Healed uneventfully | N/A | N/A | N/A | N/A | M39: Continuity of cortical bone |
| Case 11 | Healed uneventfully | Faint callus | Bridging callus | Continuity of cortical bone | N/A | N/A |
| Case 12 | Healed uneventfully | N/A | Faint callus | Continuity of cortical bone | N/A | |
| Case 13 | Healed uneventfully | N/A | Discrete callus | Bridging callus | N/A | M26: Continuity of cortical bone |
| Case 14 | Healed uneventfully | N/A | No callus | No callus | Bridging callus | N/A |
| Case 15 | Extensive anterior and lateral bow Coxa vara Healed uneventfully; Later sustained complete AFF on the same side proximal to the previous fracture level | Faint callus | Faint callus | N/A | Complete continuity of cortical bone | N/A |
| Case 16 | Bilateral incomplete AFF. Healed uneventfully | N/A | Right: discrete callus. Left: discrete callus. | N/A | N/A | N/A |
| Case 17 | Extensive anterior and lateral bow Coxa vara Healed uneventfully | Faint callus | Bridging callus | N/A | Completely healed | N/A |
| Case 18 | Healed uneventfully | Faint callus | Bridging callus | N/A | Bridging callus | N/A |
| Case 19 | Healed uneventfully | N/A | N/A | N/A | Continuity of cortical bone | N/A |

Table S5. Micro CT-results for the 2 patient groups. Values are mean (SD)

| Micro CT | non-BP group (n = 7) | BP group (n = 7) | Mean difference (CI) |
|---|---------------------------------|-----------------------------|-----------------------------|
| Percent bone volume/Bone volume fraction, BV/TV (%) | 47 (17) | 65 (11) | -18 (-35 to -1.2) |
| Bone surface density, BS/TV (1/mm) | 35 (7.8) | 29 (5.7) | 5.7 (-2.2 to 14) |
| Bone surface:volume ratio, BS/BV (1/mm) | 80 (37) | 45 (9.0) | 35 (0.9 to 70) |
| Trabecular thickness, Tb.Th (mm) | 0.05 (0.02) | 0.06 (0.01) | -0.02 (-0.03 to 0) |
| Trabecular number, Tb.N (1/mm) | 11 (2.2) | 11 (2.7) | -0.03 (-2.9 to 2.8) |
| Trabecular separation, Tb.Sp (mm) | 0.09 (0.04) | 0.07 (0.03) | 0.02 (-0.02 to 0.06) |

Table S7. Results of the histologic analyses for the BP group

| Histologic feature | Case 10 | Case 11 | Case 12 | Case 13 | Case 14 | Case 15 | Case 16 | Case 17 | Case 18 | Case 19 |
|---|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Mean width of the fracture gap, μm | 154 | 119 | 145 | 202 | 187 | 257 | 235 | 111 | 353 | 66 |
| Loose bone fragments | Yes | No | Yes | No | No | No | Yes | No | No | No |
| Mainly empty osteocyte lacunae | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Osteocytes – viable, % | 54 | 34 | 43 | 42 | 36 | 14 | 28 | 31 | 16 | 42 |
| Woven bone close to the fracture line | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Cartilage adjacent to fracture line | Yes | Yes | No | No | No | Yes | No | No | No | No |
| Osteoclasts | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes |
| Giant osteoclasts | Yes | Yes | Yes | Yes | No | Yes | No | Yes | No | Yes |