TABLE E-1 Ex Vivo Peripheral Quantitative Computed Tomography Measurements of Mineral Density of the Core Defect, the Trabecular Bone Surrounding the Core Defect, and the Corresponding Region in the Contralateral Femora at Twenty-four Weeks After Surgery*

| | Core-Defect Mineral Density† *(mg/cm$^3$)* | Contralateral Mineral Density *(mg/cm$^3$)* | Surrounding Trabecular Mineral Density *(mg/cm$^3$)* | Contralateral Mineral Density *(mg/cm$^3$)* |
|---|---|---|---|---|
| Phase 1: Treatment with rhBMP-2/ACS, ACS alone, and no treatment in proximal femoral core defects compared with proximal part of the contralateral, normal femora | | | | |
| rhBMP-2/ACS | 345.5 ± 60.6[a] | 427.2 ± 70.2‡ | 495.0 ± 74.6 | 443.3 ± 75.0‡ |
| ACS alone | 195.8 ± 68.3[b] | 364.2 ± 52.3‡ | 310.6 ± 38.1 | 296.1 ± 42.8 |
| Untreated | 74.7 ± 37.5[c] | 377.6 ± 42.5‡ | 409.3 ± 25.4 | 394.1 ± 19.2 |
| Phase 2: Treatment with rhBMP-2/ACS in distal femoral core defects compared with ACS alone in contralateral distal femoral core defects | | | | |
| rhBMP-2/ACS | 382.6 ± 81.4 | 219.9 ± 51.5‡ | 427.6 ± 99.0 | 367.0 ± 73.4‡ |

*The values are given as the mean and the standard deviation. The values within the core defect density column that share the same letter are not significantly different. ACS = absorbable collagen sponge. †Group effect for proximal femoral core defect density is $p < 0.0001$. ‡A significant difference was found between core defect compared with the corresponding contralateral mineral density and surrounding mineral density compared with corresponding contralateral mineral density ($p < 0.05$, with specific p values given in text).

TABLE E-2 Histological Measurements of the Core-Defect Region and the Corresponding Region in the Contralateral Femora at Twenty-four Weeks After Surgery*

| | Trabecular Volume† *(%)* | Contralateral Trabecular Volume *(%)* | Trabecular Thickness† *(μm)* | Contralateral Trabecular Thickness *(μm)* | Trabecular Number† *(no./mm)* | Contralateral Trabecular Number *(no./mm)* |
|---|---|---|---|---|---|---|
| Phase 1: Treatment with rhBMP-2/ACS, ACS alone, and no treatment in proximal femoral core defects compared with proximal part of the contralateral, normal femora | | | | | | |
| rhBMP-2/ACS | 27.8 ± 7.6 | 29.7 ± 7.1 | 109.3 ± 12.3 | 161.2 ± 17.4‡ | 2.55 ± 0.57 | 1.79 ± 0.30‡ |
| ACS alone | 10.2 ± 3.2 | 28.4 ± 1.3‡ | 75.1 ± 5.4 | 147.9 ± 2.6‡ | 1.13 ± 0.49 | 1.78 ± 0.10‡ |
| Untreated | 8.5 ± 4.2 | 27.8 ± 4.2‡ | 68.1 ± 9.8 | 140.9 ± 8.0‡ | 1.03 ± 0.28 | 1.69 ± 0.23‡ |
| Phase 2: Treatment with rhBMP-2/ACS in distal femoral core defects compared with ACS alone in contralateral distal femoral core defects | | | | | | |
| rhBMP-2/ACS | 40.3 ± 13.2 | 20.9 ± 7.7‡ | 188.8 ± 62.3 | 130.3 ± 44.7‡ | 2.12 ± 0.34 | 1.38 ± 0.22‡ |

*The values are given as the mean and the standard deviation. ACS = absorbable collagen sponge. †Group effect for Phase-1 proximal femoral core defect trabecular volume, trabecular thickness, and trabecular number is $p < 0.0001$, $p = 0.0001$, and $p = 0.0002$, respectively. ‡A significant difference was found between core defect and corresponding contralateral values ($p < 0.05$).

TABLE E-3 Histological Measurements of the Trabecular Bone Region Surrounding the Core Defects and the Corresponding Region in the Contralateral Femora at Twenty-four Weeks After Surgery*

| | Trabecular Volume *(%)* | Contralateral Trabecular Volume *(%)* | Trabecular Thickness *(μm)* | Contralateral Trabecular Thickness *(μm)* | Trabecular Number *(no./mm)* | Contralateral Trabecular Number *(no./mm)* |
|---|---|---|---|---|---|---|
| Phase 1: Treatment with rhBMP-2/ACS, ACS alone, and no treatment in proximal femoral core defects compared with proximal part of the contralateral, normal femora | | | | | | |
| rhBMP-2/ACS | 42.9 ± 7.2 | 36.6 ± 7.1† | 225.5 ± 23.9 | 193.2 ± 27.4† | 5.2 ± 1.0 | 5.3 ± 0.8 |
| ACS alone | 32.0 ± 3.2 | 29.7 ± 1.3 | 163.0 ± 16.7 | 158.9 ± 3.5 | 6.5 ± 0.7 | 6.4 ± 0.1 |
| Untreated | 32.8 ± 5.3 | 30.7 ± 4.1 | 175.2 ± 26.0 | 165.1 ± 8.5 | 5.9 ± 1.3 | 6.0 ± 0.4 |
| Phase 2: Treatment with rhBMP-2/ACS in distal femoral core defects compared with ACS alone in contralateral distal femoral core defects | | | | | | |
| rhBMP-2/ACS | 32.6 ± 7.3 | 27.7 ± 4.2† | 216.3 ± 46.9 | 186.0 ± 25.1 | 1.50 ± 0.14 | 1.49 ± 0.23 |

*The values are given as the mean and the standard deviation. ACS = absorbable collagen sponge. †A significant difference was found between surrounding and corresponding contralateral values ($p < 0.05$).

TABLE E-4 Measurements of the Trabecular Bone Region Surrounding the Core Defects and the Corresponding Region in the Contralateral Femora at Twenty-four Weeks After Surgery*

| | Mineralized Surface *(%)* | Contralateral Mineralized Surface *(%)* | Mineral Apposition Rate *(μm/day)* | Contralateral Mineral Apposition Rate *(μm/day)* | Bone Formation Rate *(%/yr)* | Contralateral Bone Formation Rate *(%/yr)* |
|---|---|---|---|---|---|---|
| rhBMP-2/ ACS | 23.9 ± 5.0 | 11.4 ± 4.7† | 2.46 ± 0.72 | 1.20 ± 0.48† | 2049.3 ± 655.2 | 190.5 ± 48.8† |
| ACS alone | 6.0 ± 2.1 | 4.7 ± 1.7† | 0.94 ± 0.16 | 0.81 ± 0.13† | 96.6 ± 15.3 | 71.6 ± 18.4† |
| Untreated | 6.3 ± 1.2 | 4.5 ± 0.7† | 1.02 ± 0.23 | 0.79 ± 0.11† | 85.0 ± 19.3 | 66.5 ± 16.6† |

*The values are given as the mean and the standard deviation. ACS = absorbable collagen sponge. †A significant difference was found between surrounding and corresponding contralateral values ($p < 0.05$).

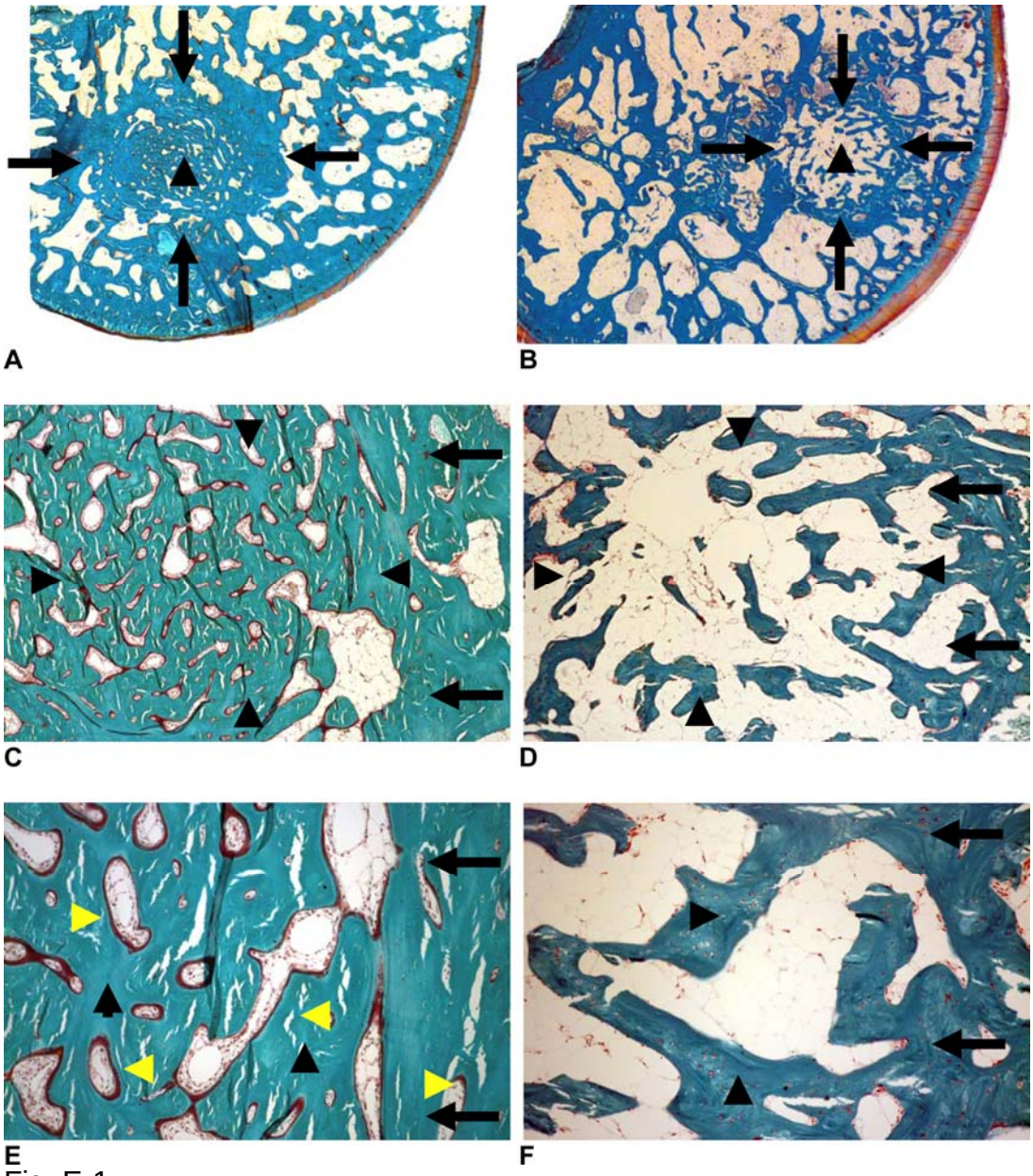


Fig. E-1

Histological appearance of the distal part of a femur with a core defect (arrows in A, C, and E) treated with rhBMP-2/absorbable collagen sponge (ACS) compared with the distal part of the contralateral femur with a core defect treated with ACS alone (arrows in B, D, and F) at twenty-four weeks after surgery. New thin, closely packed trabecular bone is contained within the defects (black arrowheads). Nonmineralized osteoid is present on the surface of the new trabecular bone (yellow arrowheads in E) (Goldner trichrome stain, ×1 for A and B, ×4 for C and D, ×10 for E and F).

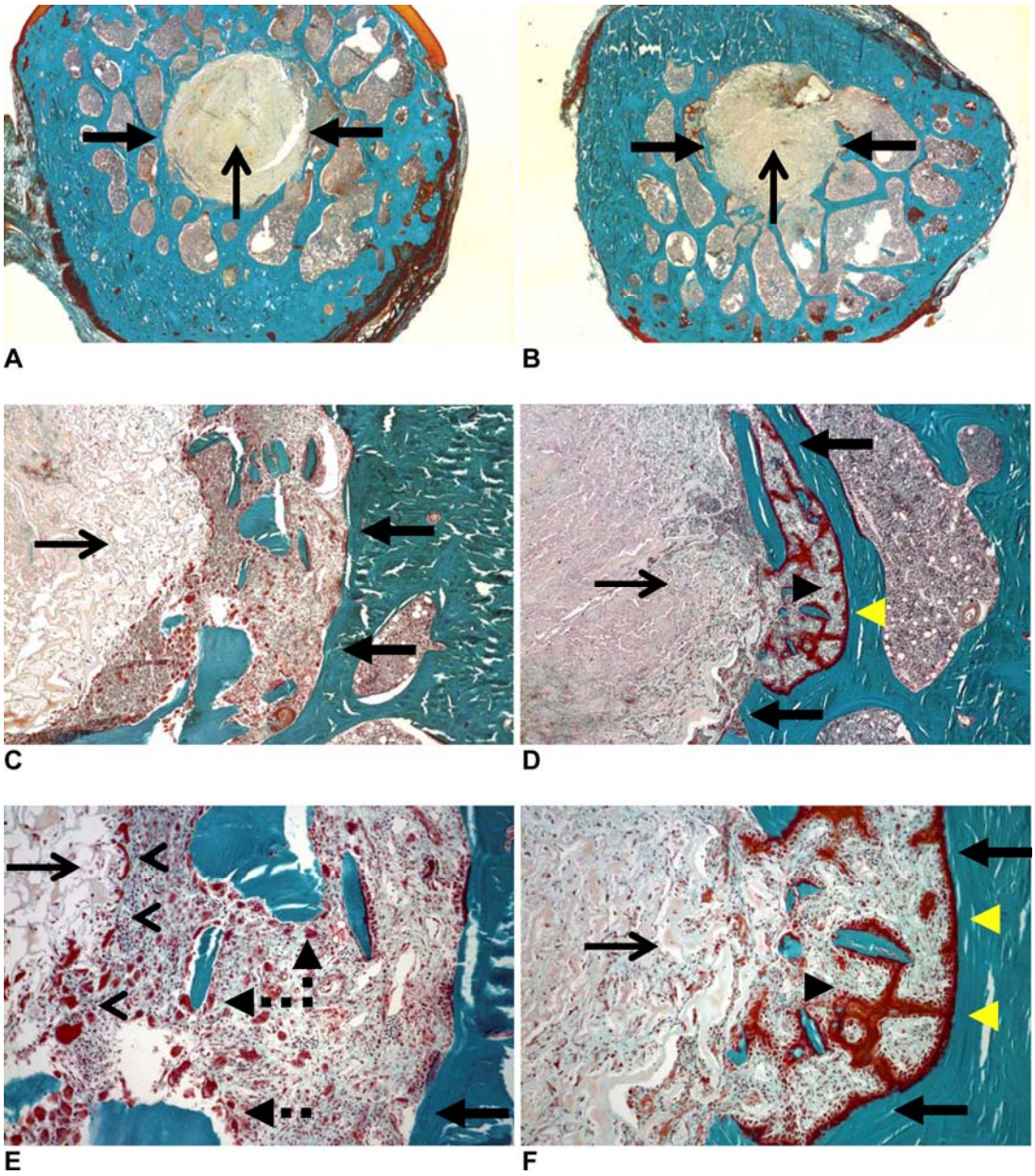


Fig. E-2

Histological appearance of a femoral neck with a core defect (closed arrows in A, C, and E) treated with rhBMP-2/absorbable collagen sponge (ACS) (open arrows in A, C, and E) compared with the contralateral femoral neck with a core defect (closed arrows in B, D, and F) treated with ACS alone (open arrows in B, D, and F) at one week after surgery. Multinucleated cells are initiating resorption of trabecular bone at the periphery of the core defect (dotted arrows in E). Multinucleated cells are also actively degrading the perimeter of the collagen sponge (C and open arrowheads in E). New trabecular bone formation (black arrowheads in D and F) and appositional bone formation (yellow arrowheads in D and F) on existing bone surfaces are present at the periphery of the core defects treated with ACS alone. Minimal degradation of the collagen sponge is evident at one week (Goldner trichrome stain, ×1 for A and B; ×4 for C and D; and ×10 for E and F).

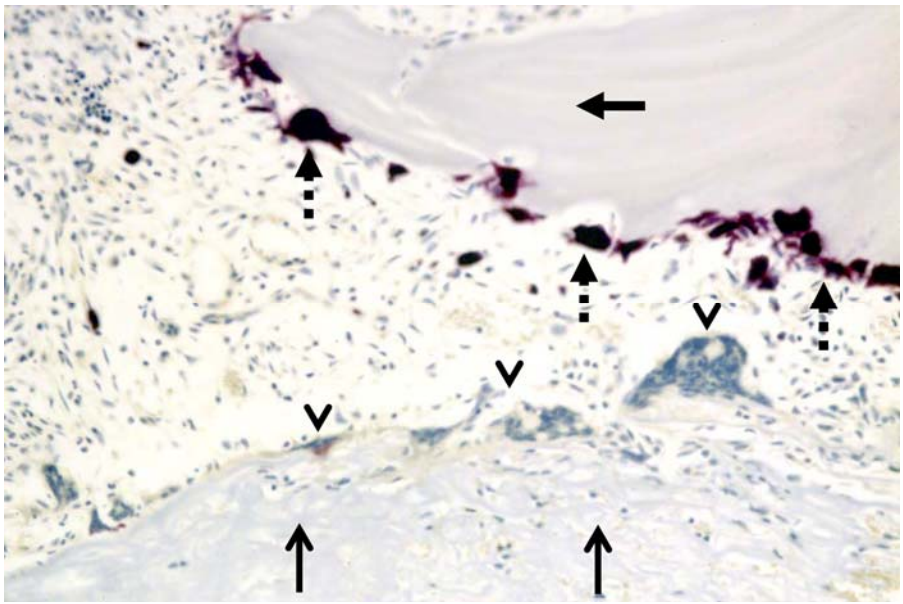

Fig. E-3
Histological appearance of tartrate-resistant acid phosphatase (TRAP)-positive stained multinucleated cells (dotted arrows) initiating resorption of trabecular bone (closed arrow) and TRAP-negative stained multinucleated cells (arrowheads) initiating resorption of the absorbable collagen sponge (ACS; open arrows) in a core defect treated with rhBMP-2/ACS at one week after surgery. Highly cellular and vascularized granulation tissue is present surrounding the resorbing bone and collagen sponge (hematoxylin stain, ×20).

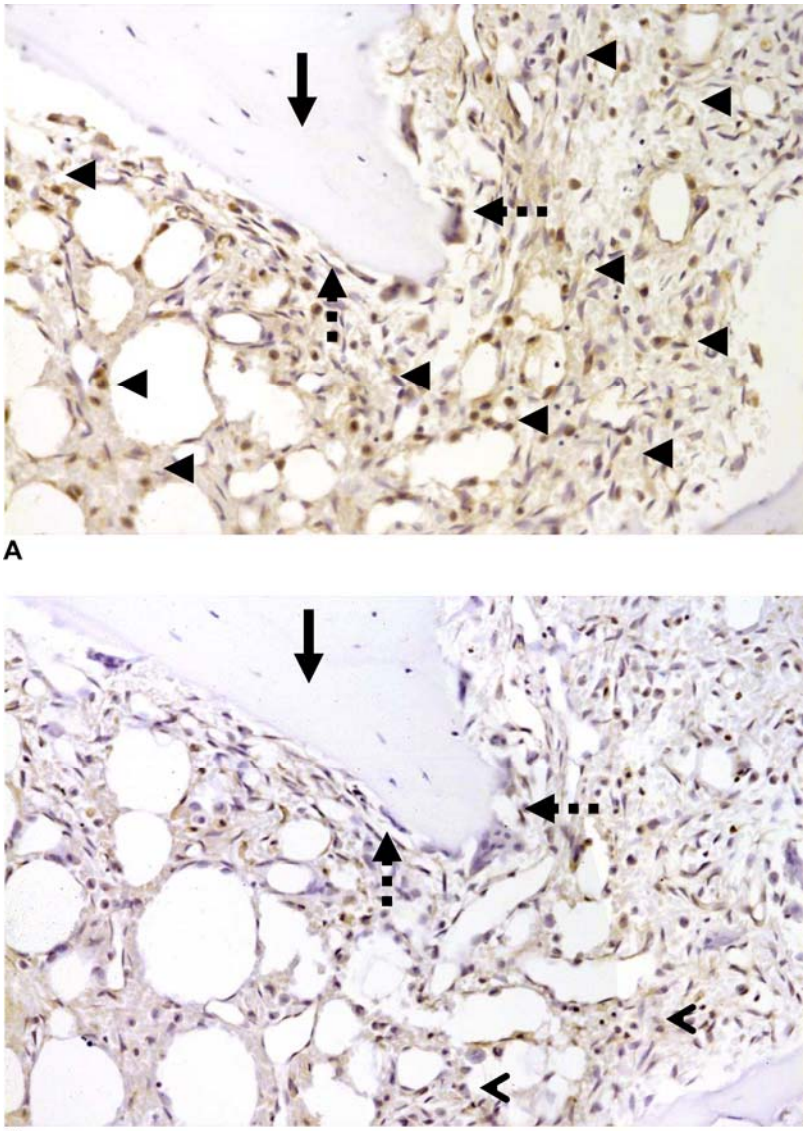

Fig. E-4
Histological appearance of a femoral neck core defect treated with rhBMP-2/absorbable collagen sponge at one week after surgery, demonstrating numerous receptor activator of nuclear factor-κB ligand (RANKL)-positive stained spindle-shaped cells (closed arrowheads) in the marrow space adjacent to trabecular bone (closed arrow) at the perimeter of the defect being resorbed by multinucleated cells (dotted arrows in A). Few osteoprotegerin-positive stained cells (open arrowheads) are visible in a histological section from the same location (B) (hematoxylin stain, ×20).

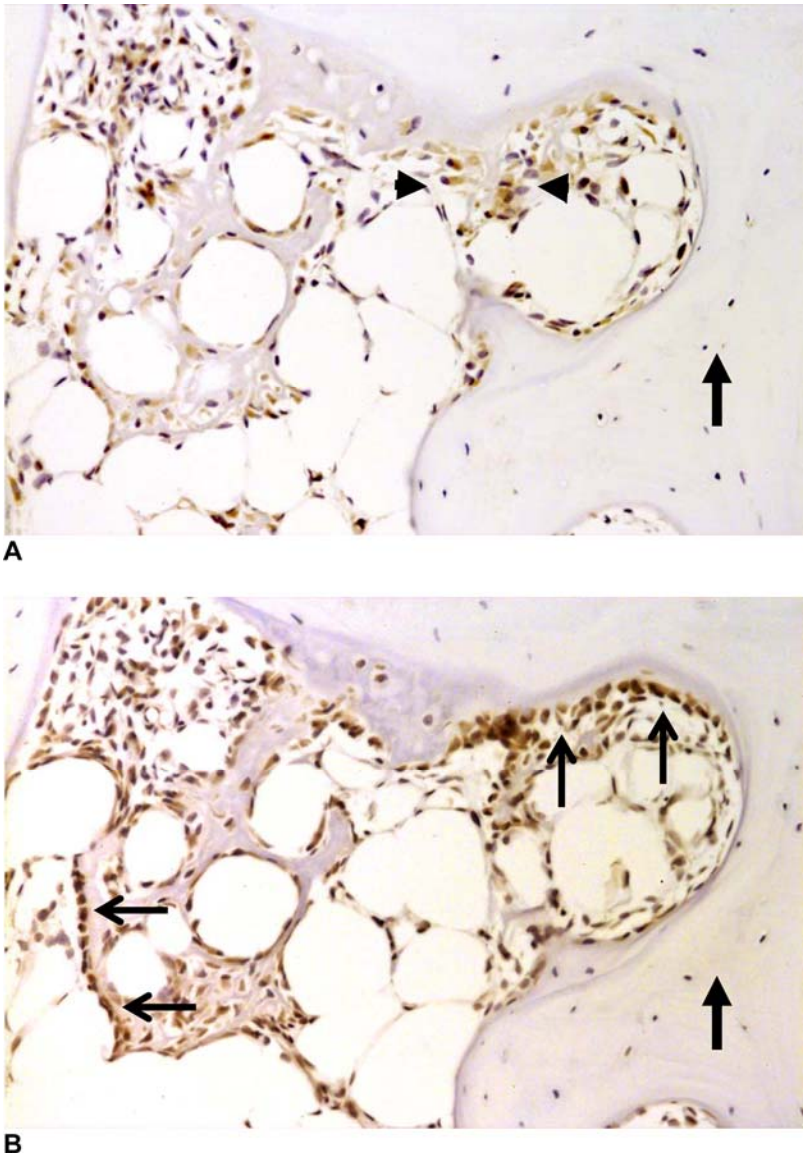


Fig. E-5

Histological appearance of a femoral neck with a core defect treated with collagen sponge alone at one week after surgery, demonstrating sporadic receptor activator of nuclear factor-κB ligand (RANKL)-positive stained spindle-shaped cells (arrowheads) in the marrow space adjacent to trabecular bone (arrow) at the perimeter of the defect (A). Numerous osteoprotegerin-positive stained cells (open arrows) are visible lining the trabecular bone at the perimeter of the defect in a histological section from the same location (B) (hematoxylin stain, ×20).

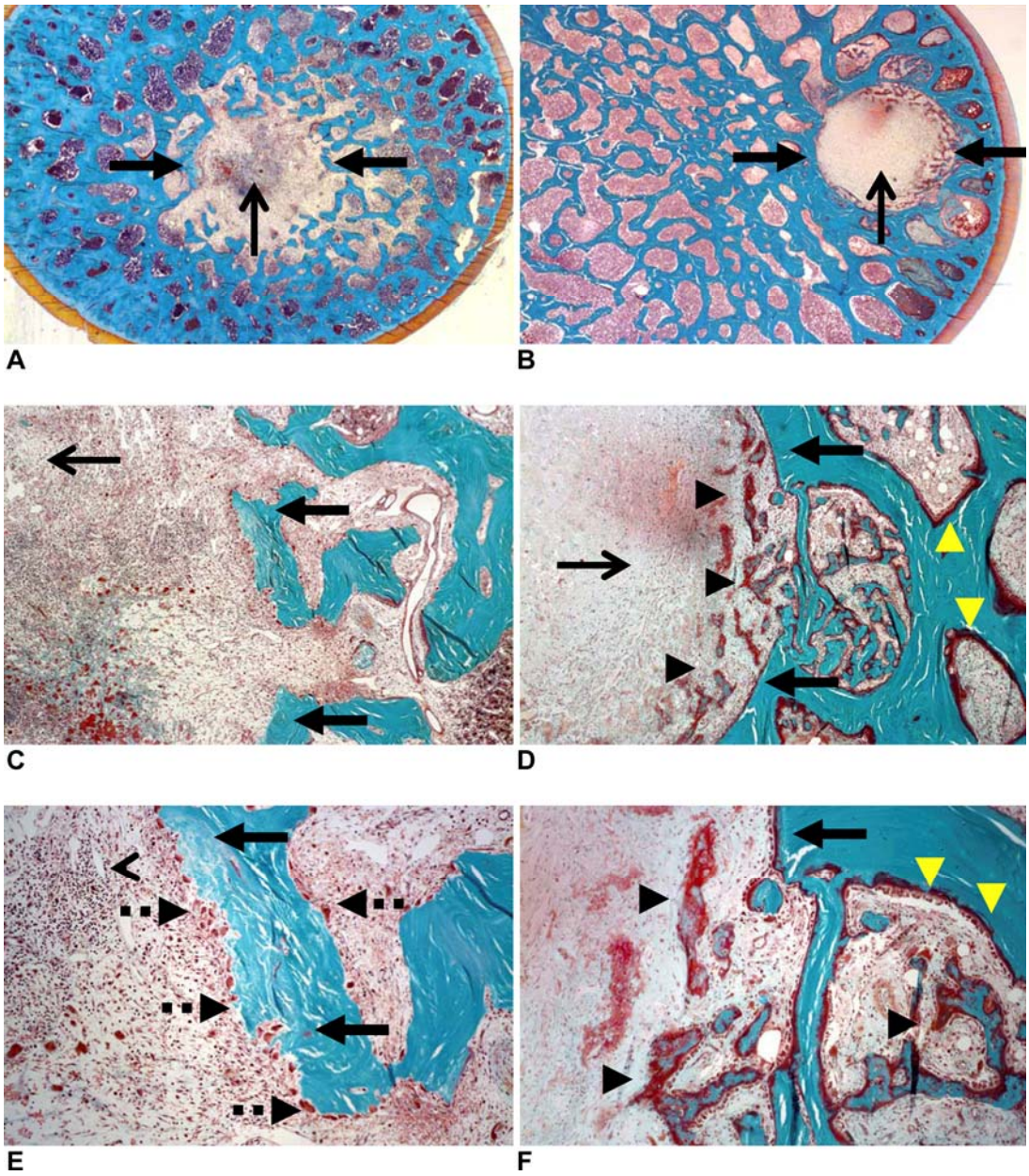


Fig. E-6

Histological appearance of a femoral neck with a core defect (closed arrows in A, C, and E) treated with rhBMP-2/absorbable collagen sponge (ACS; open arrows in A and C) compared with the contralateral femoral neck with a core defect (closed arrows in B, D, and F) treated with ACS alone (open arrows in B and D) at two weeks after surgery. Multinucleated cells are resorbing trabecular bone (dotted arrows in E). New trabecular bone formation (black arrowheads in D and F) and appositional bone formation (yellow arrowheads in D and F) on existing bone surfaces are present at the rim of the core defects treated with ACS alone (Goldner trichrome stain, ×1 for A and B; ×4 for C and D; and ×10 for E and F).

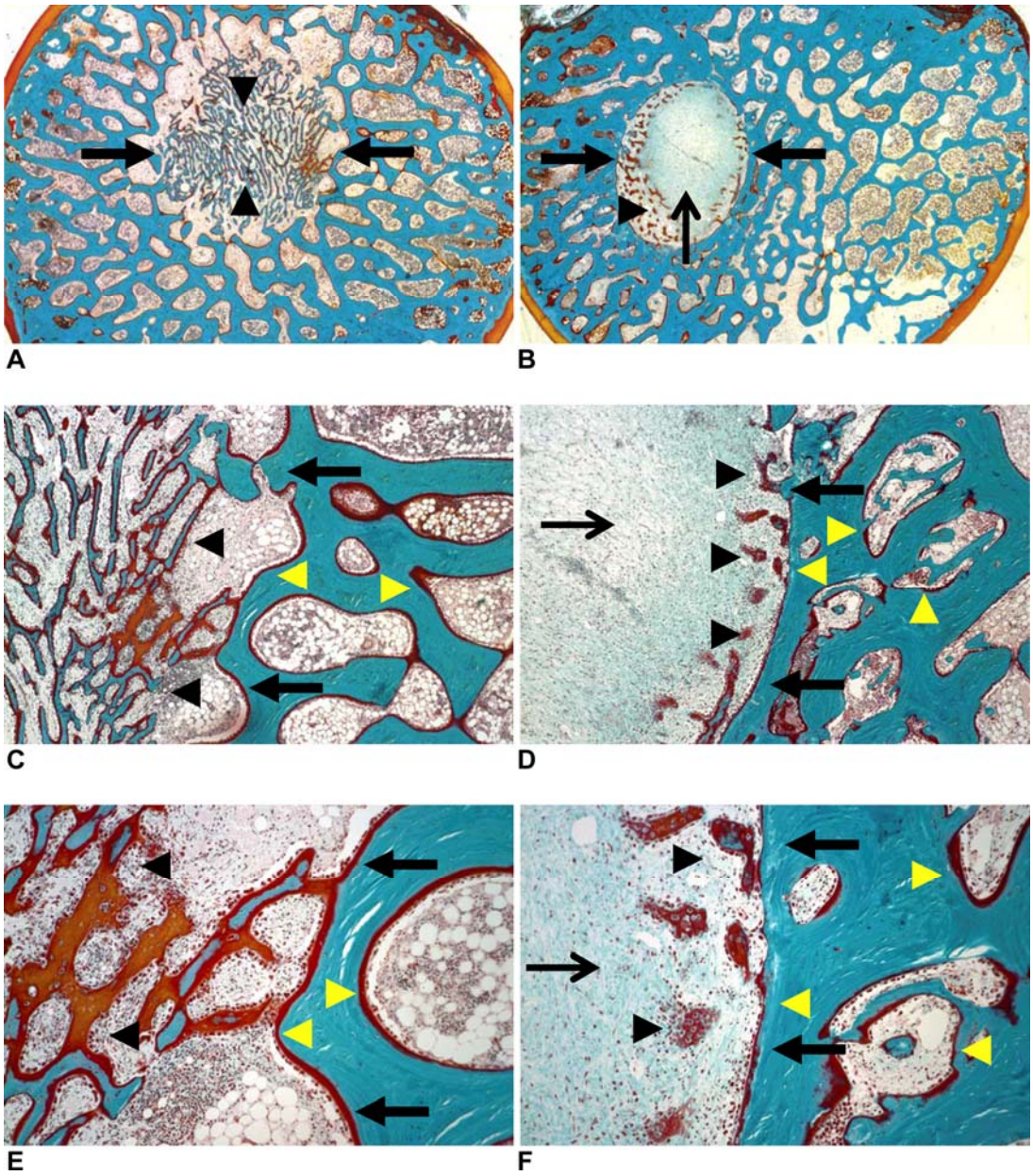


Fig. E-7

Histological appearance of a femoral neck with a core defect (closed arrows in A, C, and E) treated with rhBMP-2/absorbable collagen sponge (ACS) compared with the contralateral femoral neck with a core defect (closed arrows in B, D, and F) treated with ACS alone (open arrows in B, D, and F) at four weeks after surgery. New thin, closely packed trabecular bone (black arrowheads in A, C and E) continues to fill the core defects. Appositional bone formation (yellow arrowheads in C and E) is present on new trabecular bone surfaces within the core defect and on preexisting bone surfaces at the rim of the core defects treated with rhBMP-2/ACS. New bone formation within the core defect (black arrowheads in D and F) and appositional bone formation (yellow arrowheads in D and F) on existing trabecular bone surfaces is confined to the rim of the core defect. Residual collagen sponge is also readily visible at four weeks in the core defects treated with ACS alone (Goldner trichrome stain, ×1 for A and B; ×4 for C and D; and ×10 for E and F).

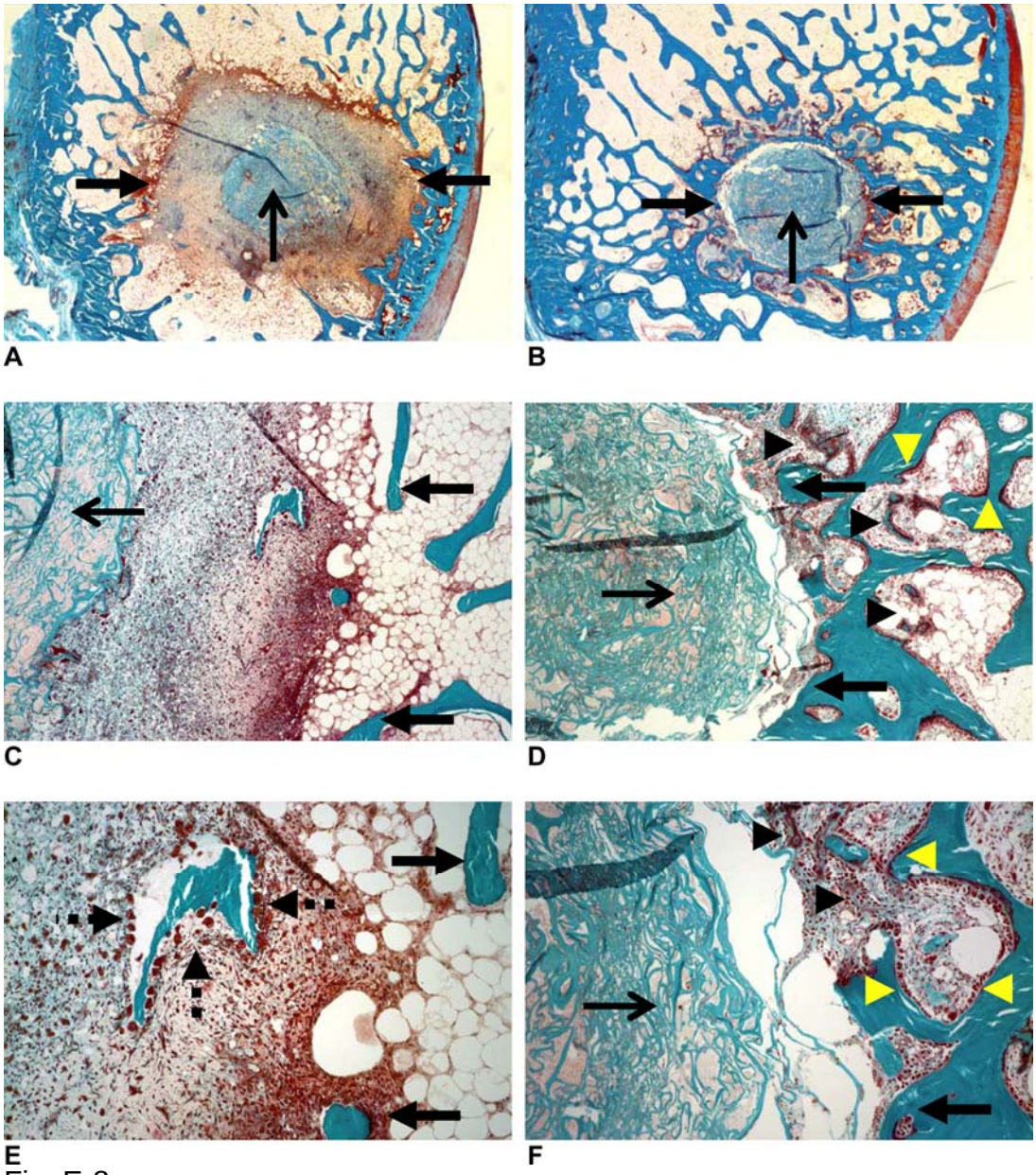


Fig. E-8

Histological appearance of the distal part of a femur with a core defect (closed arrows in A, C, and E) treated with rhBMP-2/absorbable collagen sponge (ACS; open arrows in A and C) compared with the core defect in the distal part of the contralateral femur (closed arrows in B, D, and F) treated with ACS alone (open arrows in B, D, and F) at two weeks after surgery. Multinucleated cells are resorbing trabecular bone (dotted arrows in E). New trabecular bone formation (black arrowheads in D and F) and appositional bone formation (yellow arrowheads in D and F) on existing bone surfaces are present at the rim of the core defects treated with ACS alone (Goldner trichrome stain, ×1 for A and B; ×4 for C and D; and ×10 for E and F).