

Fig. E-1

Fluoroscopic images illustrating the procedure used to create a 3.5-mm core defect in the distal part of the radius. The distal part of the radius was first positioned over the image intensifier (A). A 1.25-mm Kirschner wire was placed through the lateral cortex of the distal part of the radius, and correct positioning was verified on orthogonal views (B, C). A 3.5-mm cannulated drill was then placed into a soft-tissue protector and over the Kirschner wire (D) to create the core defect in the distal part of the radius (E, F). The appropriate treatment was administered with an 18-gauge spinal needle that was placed into the core defect following soft-tissue closure (G). The radiodense calcium phosphate matrix could be visualized within the core defects (white arrows; G, H, I) and in some cases within the soft tissue adjacent to the core defect entry portal (black arrows; G, H, I).



Fig. E-2

Radiographic appearance of a proximal femoral site containing a core defect treated with 1.5-mg/mL rhBMP-2/CPM (A) and the contralateral proximal femoral site containing a core defect treated with 4.5-mg/mL rhBMP-2/CPM (B), compared with a proximal femoral site containing a core defect treated with CPM alone (C) and the contralateral proximal femoral site containing an untreated core defect (D, arrowhead) immediately after surgery. The radiodense CPM can be visualized within the core defects of the rhBMP-2/CPM and CPM-alone-treated femora (black arrows, A, B, C) and within the soft tissue adjacent to the core defect entry portal in the rhBMP-2/CPM-treated proximal femoral sites immediately after surgery (white arrows, A, B).

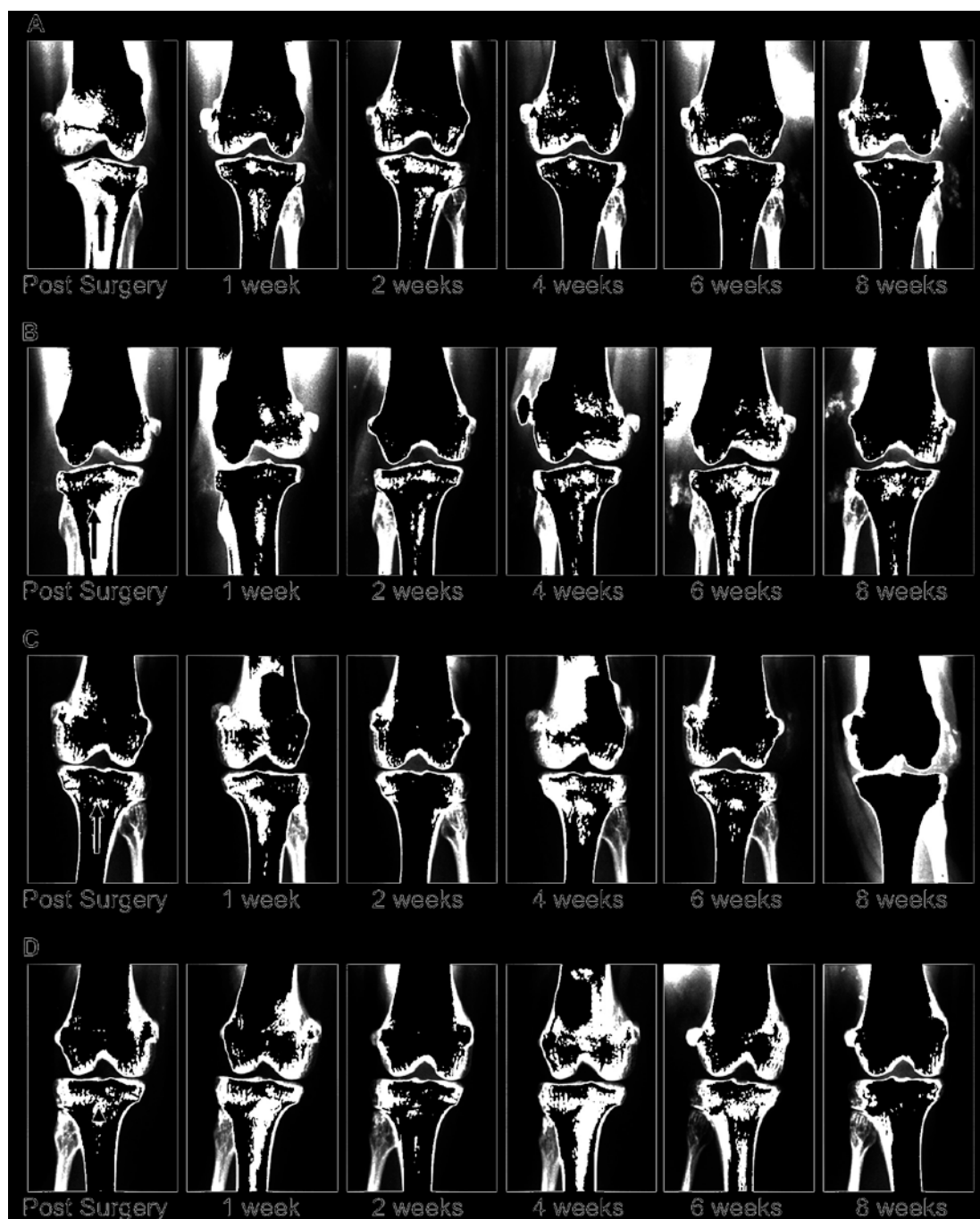


Fig. E-3

Radiographic appearance of proximal tibial site containing a core defect treated with 1.5-mg/mL rhBMP-2/CPM (A) and the contralateral proximal tibial site containing a core defect treated with 4.5-mg/mL rhBMP-2/CPM (B), compared with a proximal tibial site containing a core defect treated with CPM alone (C) and the contralateral proximal tibial site containing an untreated core defect (D, arrowhead) immediately after surgery. The radiodense CPM can be visualized within the rhBMP-2/CPM and CPM alone-treated core defects immediately after surgery (black arrows, A, B, C).

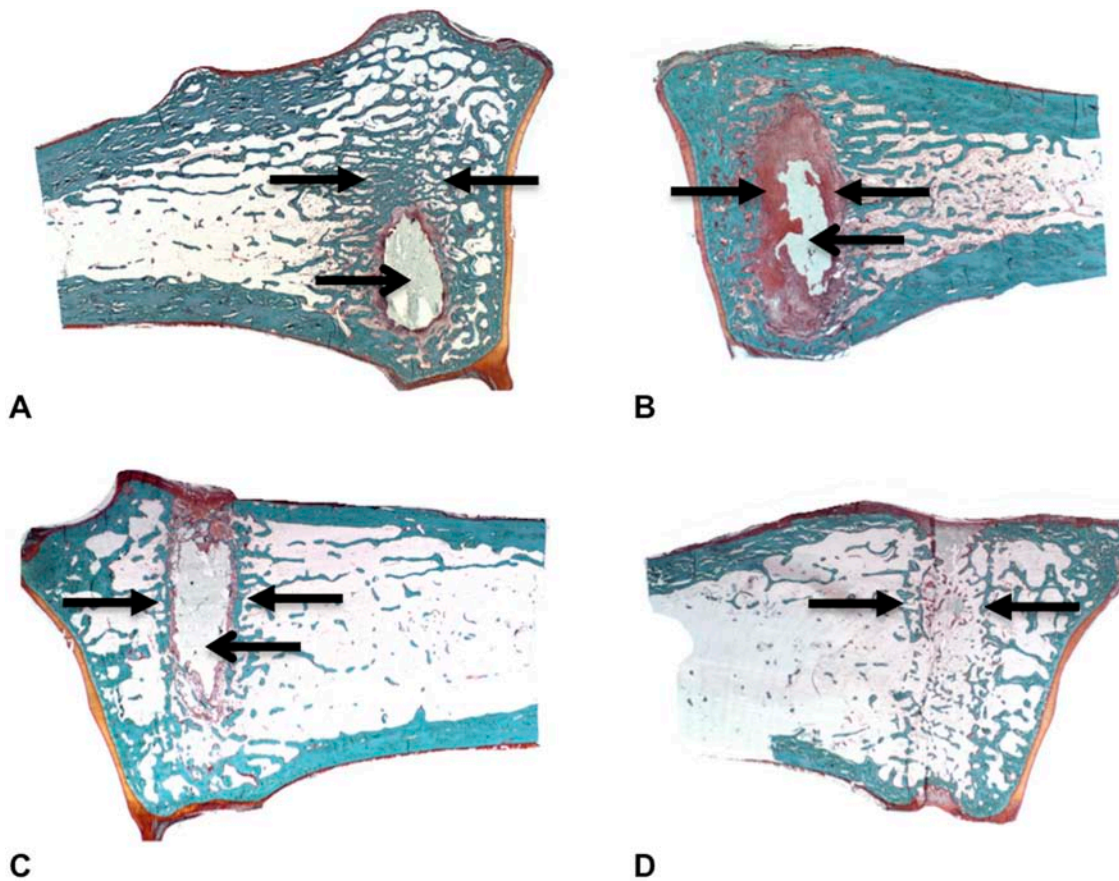


Fig. E-4

Histologic appearance of the distal part of a radius containing a core defect treated with 1.5-mg/mL rhBMP-2/CPM (A) and the distal part of the contralateral radius containing a core defect treated with 4.5-mg/mL rhBMP-2/CPM (B) compared with the distal part of a radius containing a core defect treated with calcium phosphate matrix alone (C) and the distal part of the contralateral radius containing an untreated core defect (D) at eight weeks after surgery. The arrows with closed arrowheads designate the location of the core defect. Residual CPM is visible within the rhBMP-2/CPM and CPM alone-treated core defects (arrows with open arrowheads, A, B, C) ($\times 0.5$ Goldner trichrome).

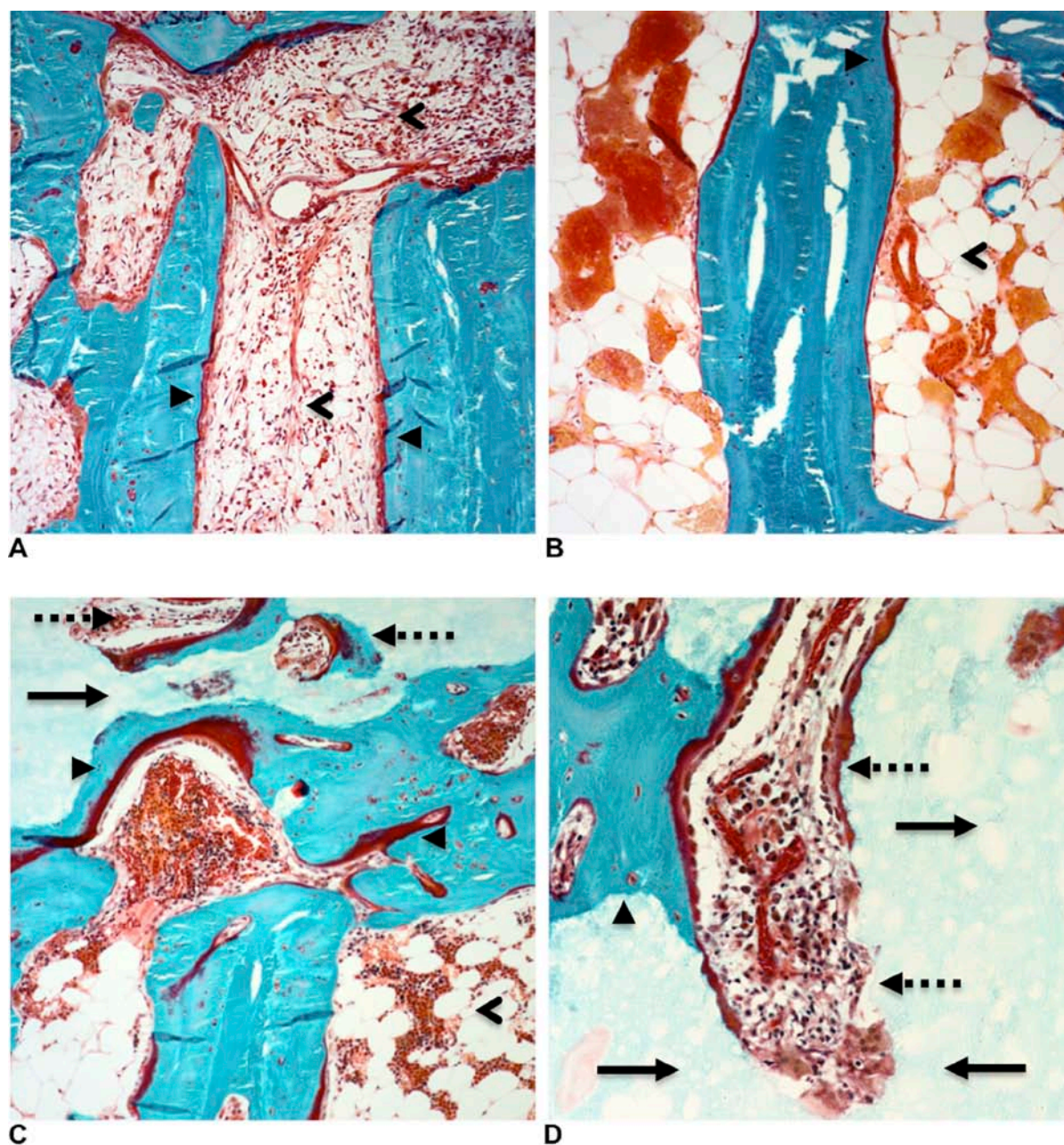


Fig. E-5

Histological appearance of the marrow and trabeculae immediately surrounding a core defect in the distal part of a radius treated with 1.5-mg/mL rhBMP-2/CPM (A), a similar area in the distal part of a radius containing an untreated core defect (B), and the distal part of a radius containing a core defect treated with CPM alone (C, D) at eight weeks after surgery. Marrow spaces are indicated by the open arrowheads (A, B, C). Appositional bone formation on existing trabeculae and residual CPM is indicated by arrows with closed arrowheads (C, D). Bone formation resulting from penetrating cutting cones (dotted arrows) is visible within the residual CPM in the CPM alone-treated core defects (C, D) (x4; Goldner trichrome).

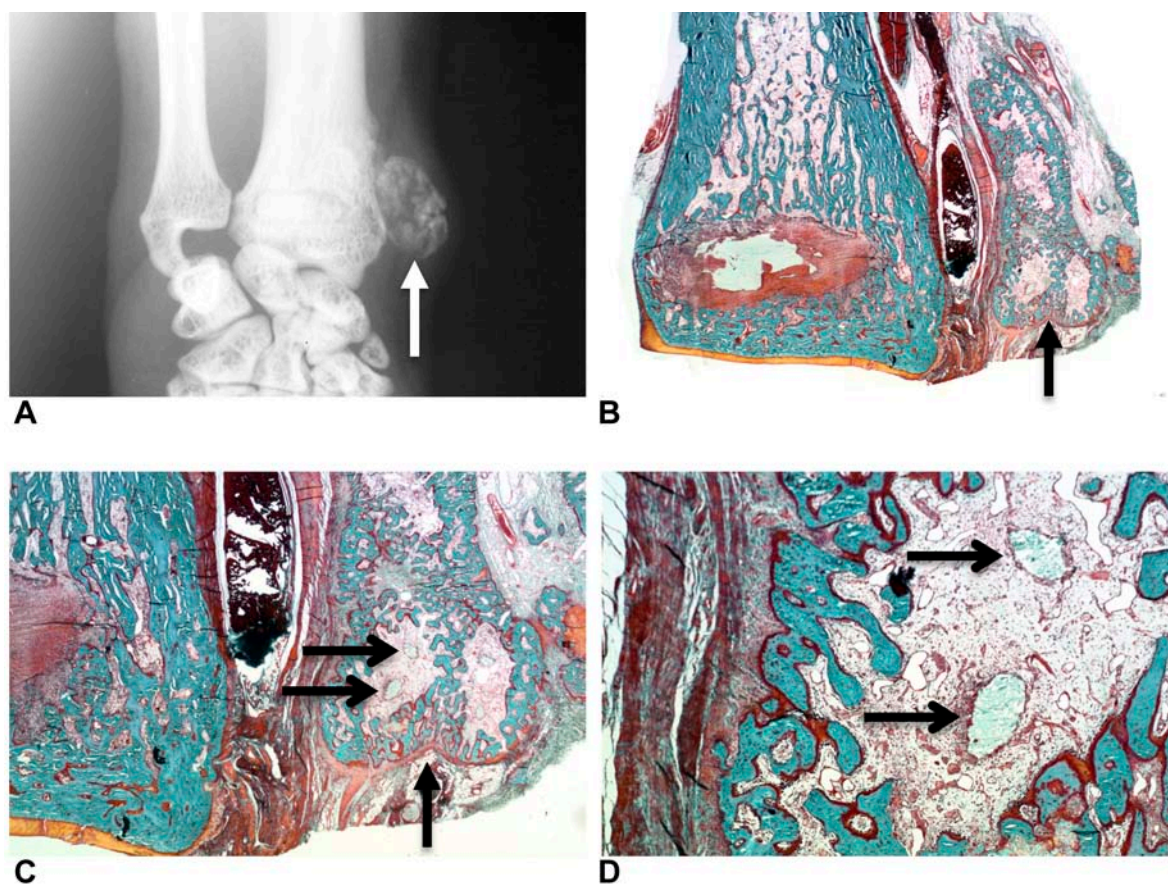


Fig. E-6

Radiographic appearance (A) and histological appearance (B, C, D) of the distal part of a radius containing a core defect treated with 4.5-mg/mL rhBMP-2/CPM at eight weeks after surgery. Heterotopic bone formation (A, white arrow with closed arrowhead; B, C, black arrows with closed arrowheads) surrounded resorbing rhBMP-2/CPM (C, D, black arrows with open arrowheads) is visible where the test material extruded into the soft tissues from the core defect entry portal after treatment ($\times 0.5$ for B, $\times 4$ for C, and $\times 10$ for D; Goldner trichrome).

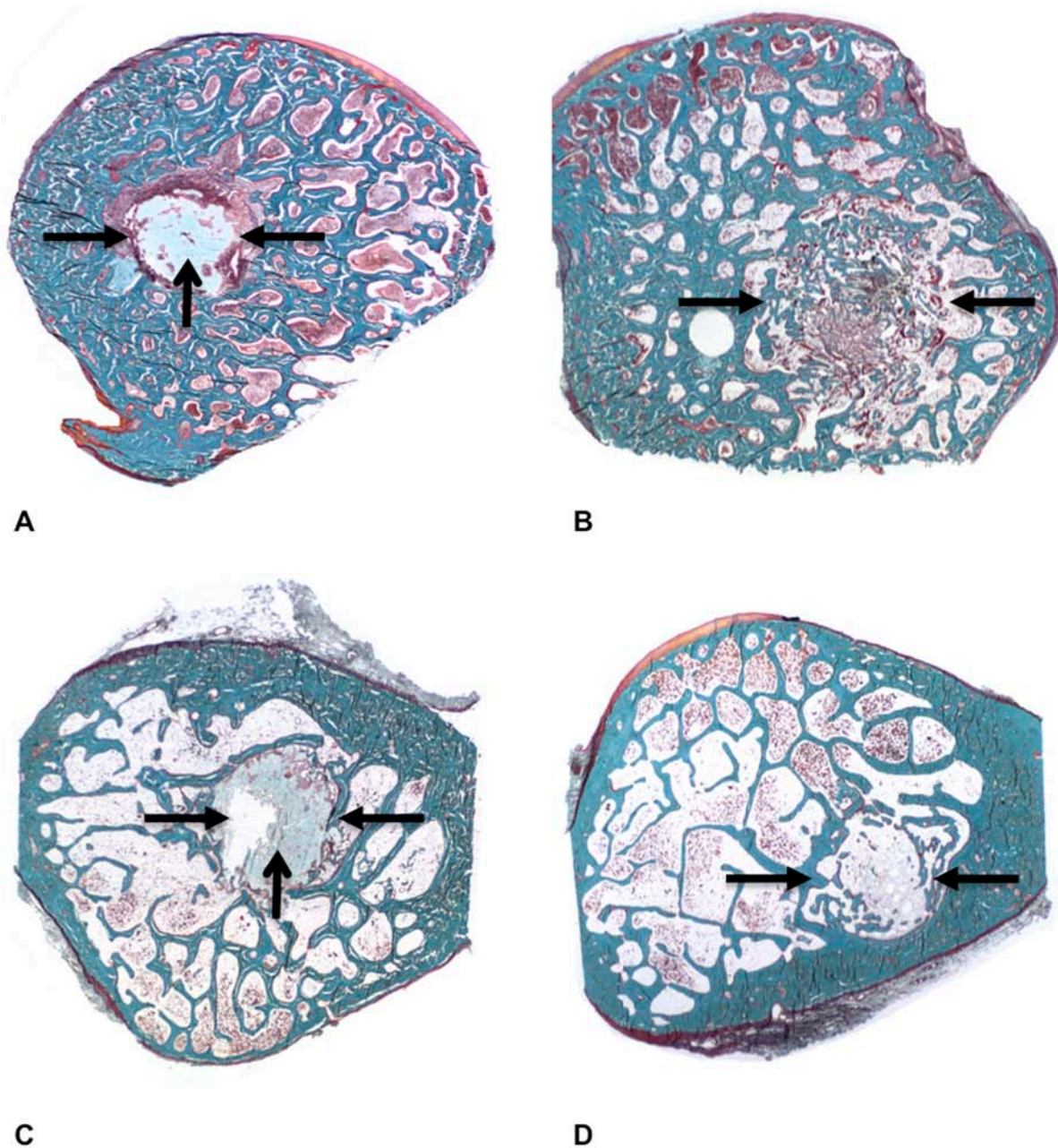


Fig. E-7

Histological appearance of a femoral neck containing a core defect treated with 1.5-mg/mL rhBMP-2/CPM (A) and the contralateral femoral neck containing a core defect treated with 4.5-mg/mL rhBMP-2/CPM (B) compared with the distal part of a radius containing a core defect treated with CPM alone (C) and the distal part of the contralateral radius containing an untreated core defect (D) eight weeks after surgery. The arrows with closed arrowheads designate the location of the core defect. Residual CPM is visible within the rhBMP-2/CPM and CPM alone-treated core defects (arrows with open arrowheads, A, C) ($\times 0.5$; Goldner trichrome).

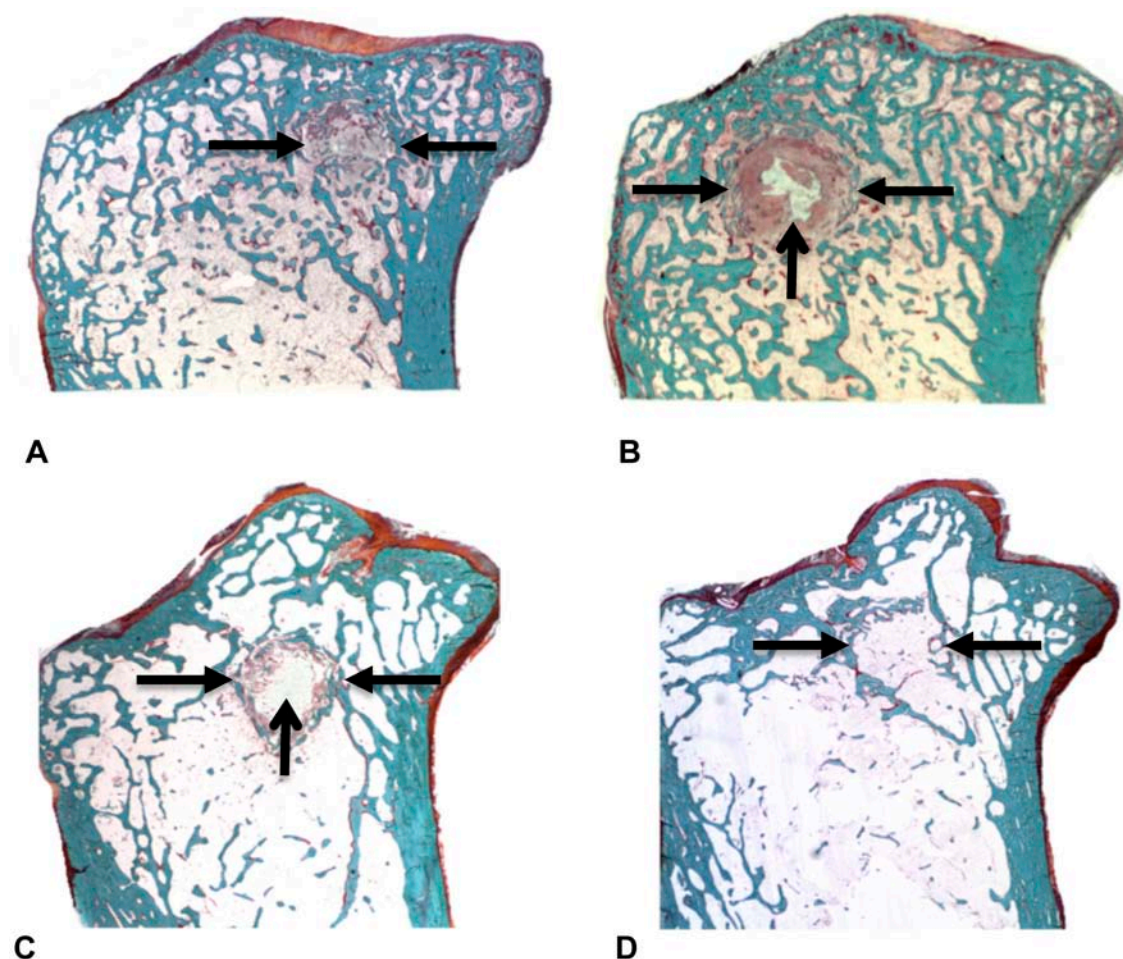


Fig. E-8

Histological appearance of the proximal part of a tibia containing a core defect treated with 1.5-mg/mL rhBMP-2/CPM (A), the proximal part of the contralateral tibia containing a core defect treated with 4.5-mg/mL rhBMP-2/CPM (B), the proximal part of a tibia containing a core defect treated with CPM alone (C), and the proximal part of the contralateral tibia containing an untreated core defect (D) at eight weeks after surgery. The arrows with closed arrowheads designate the location of the core defect. Residual CPM is visible within the rhBMP-2/CPM and CPM alone-treated core defects (arrows with open arrowheads, B, C) ($\times 0.5$; Goldner trichrome).

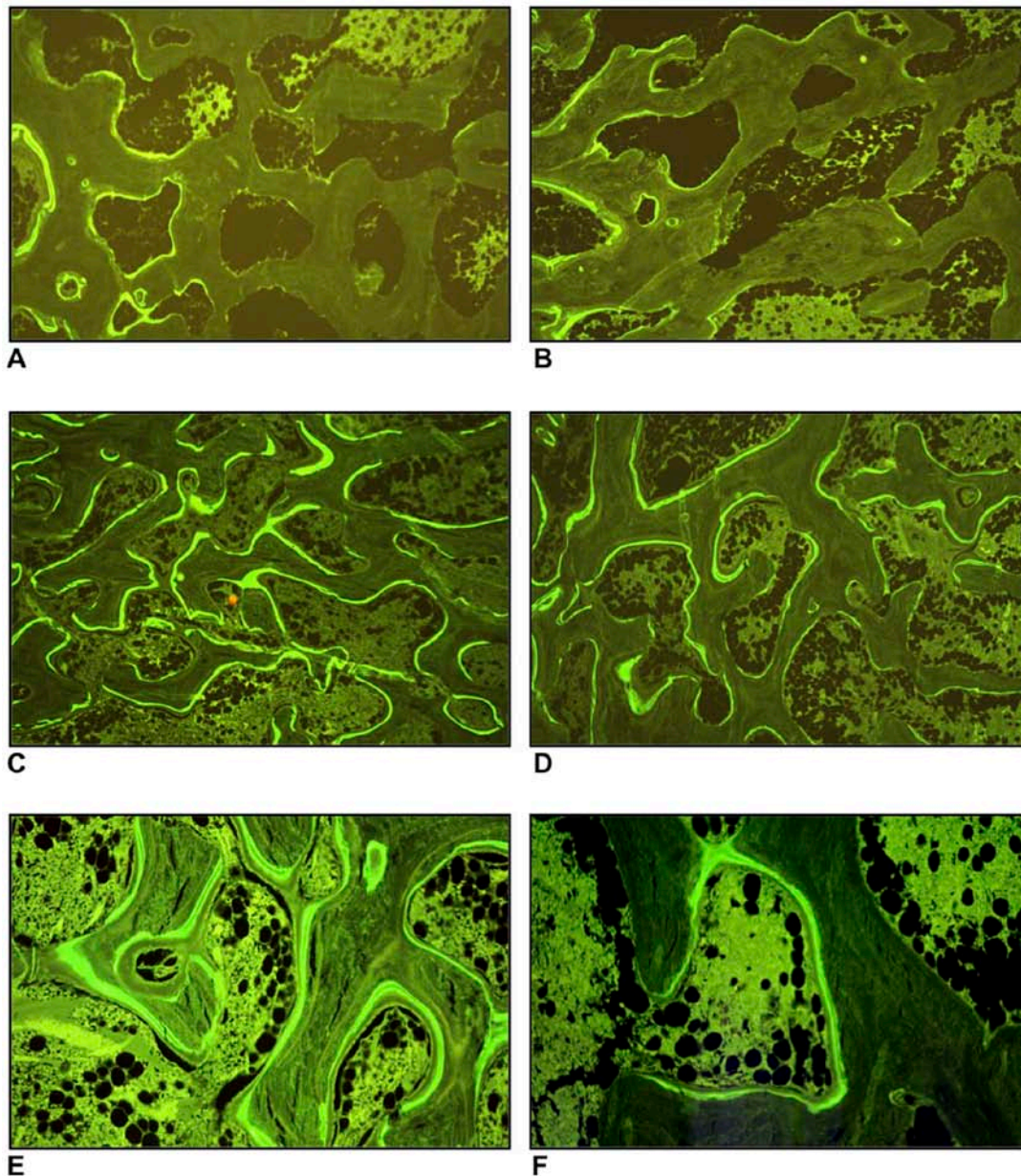


Fig. E-9

Histological appearance of fluorochromium-labeled trabecular bone surrounding an untreated core defect in the distal part of a radius (A) and surrounding the radial core defect treated with CPM alone in the contralateral limb (B), compared with trabecular bone surrounding a core defect treated with 1.5-mg/mL rhBMP-2/CPM in one limb (C) and 4.5-mg/mL rhBMP-2/CPM in the contralateral limb (D) at eight weeks after surgery. Calcein label appears green. Labeled surface was increased in the BMP-treated animals compared with the untreated and CPM-alone-treated animals. The higher-power magnification demonstrates the increased distance between calcein labels administered fourteen days and three days before the animals were killed in the 1.5-mg/mL rhBMP-2/CPM-treated core defect (E) compared with the untreated core defect (F) (x4 for A, B, C, and D, x20 for E and F; unstained, ultraviolet fluorescence).

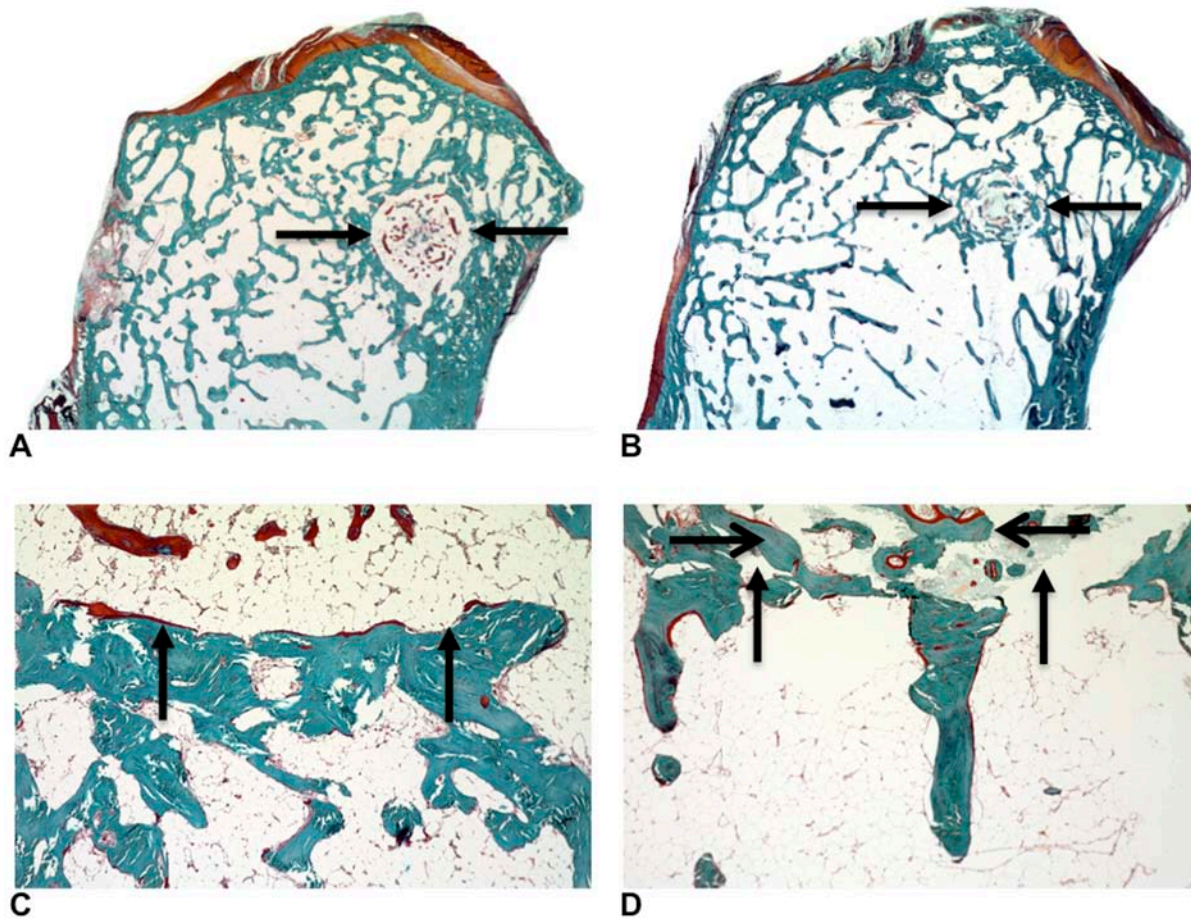


Fig. E-10

Histological appearance of the proximal part of a tibia containing a core defect treated with 1.5-mg/mL rhBMP-2/CPM (A, C) compared with the proximal part of the contralateral tibia containing a core defect treated with CPM alone (B, D) at six months after surgery. The arrows with closed arrowheads designate the locations of the core defects. Appositional bone formation can be seen both on and within the residual CPM carrier within the core defects of the CPM alone-treated proximal tibiae (arrows with open arrowheads, D). (x0.5 for A and B, x4 for C and D; Goldner trichrome).

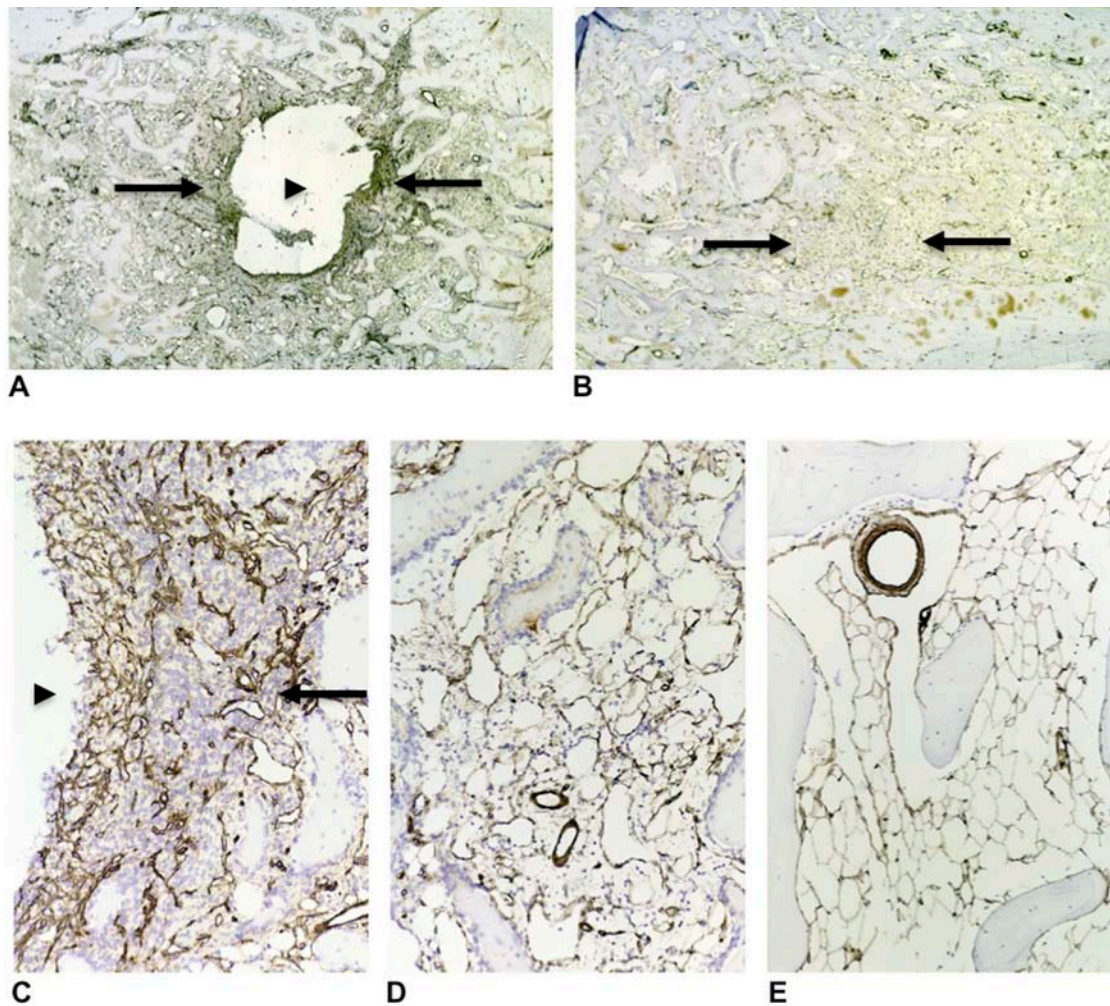


Fig. E-11

Histological appearance of the distal part of a radius containing a core defect treated with 1.5-mg/mL rhBMP-2/CPM (A, arrows with closed arrowheads) compared with the distal part of the contralateral radius containing an untreated core defect (B, arrows with closed arrowheads) at two weeks after surgery. Positive immunohistochemical staining for type-IV collagen (brown) identified increased marrow vascularity immediately adjacent to the residual rhBMP-2/CPM (A, C arrowhead) within the core defects (C, arrow with closed arrowhead) as well as the trabecular region surrounding the core defect (D) compared with a similar region in the distal part of the contralateral radius adjacent to the untreated core defect (E) (x1 for A and B, x10 for C, D and E; hematoxylin/collagen type-IV stain).

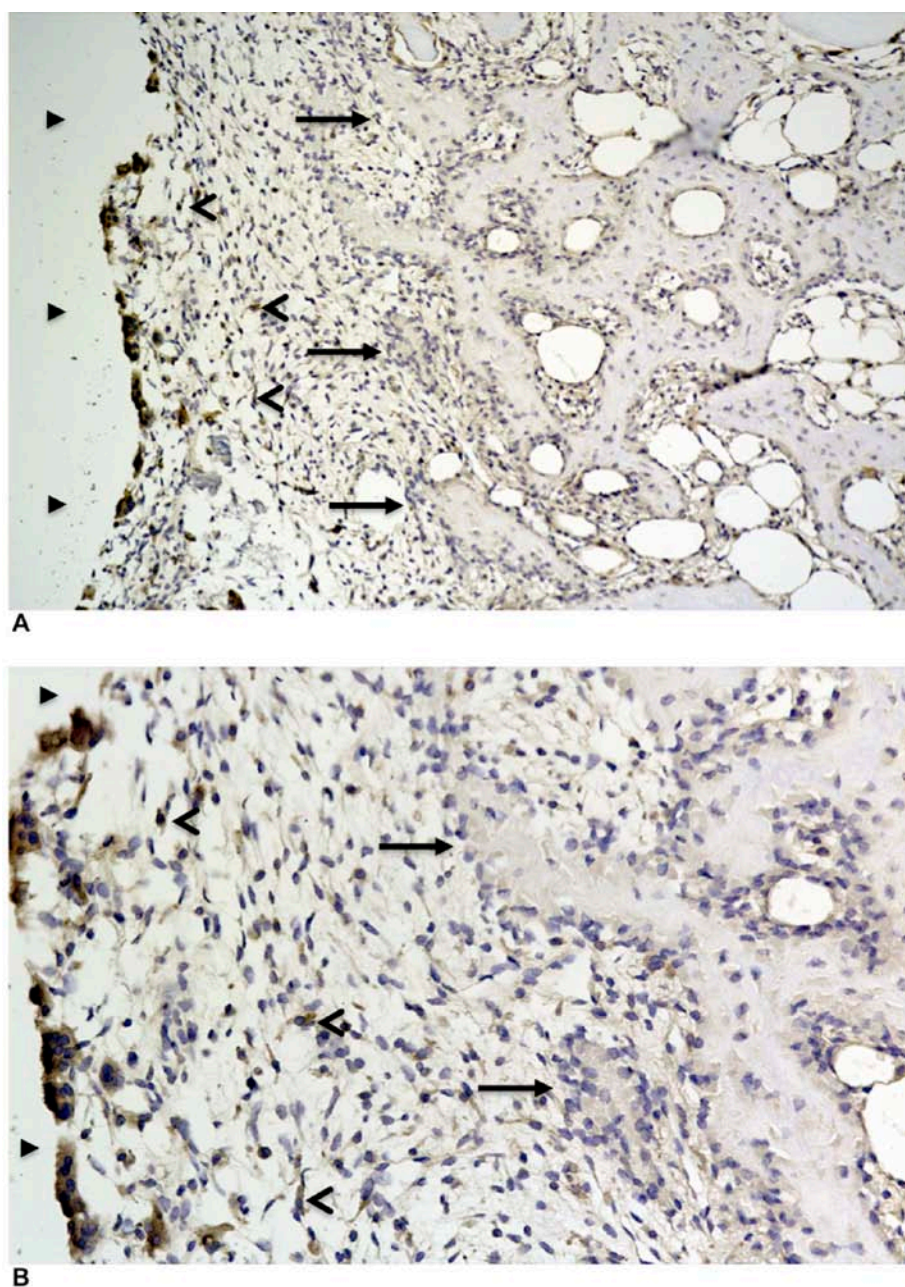


Fig. E-12

Histological appearance of the distal part of a radius containing a core defect treated with 1.5-mg/mL rhBMP-2/CPM (A, B, perimeter of the core defect indicated by arrows with closed arrowheads) Spindle-shaped cells in the region between the residual CPM in the core defect (closed arrowheads) and adjacent trabecular bone (arrows with closed arrowheads) exhibit positive (brown) cytoplasmic staining for RANKL (open arrowheads, A, B). Osteoclasts on the surface of the residual CPM in core defect also exhibit positive cytoplasmic staining for RANKL. In contrast, osteoblasts on the surface of adjacent trabeculae exhibit negative cytoplasmic staining for RANKL (×10 for A, ×20 for B; hematoxylin/RANKL stain).

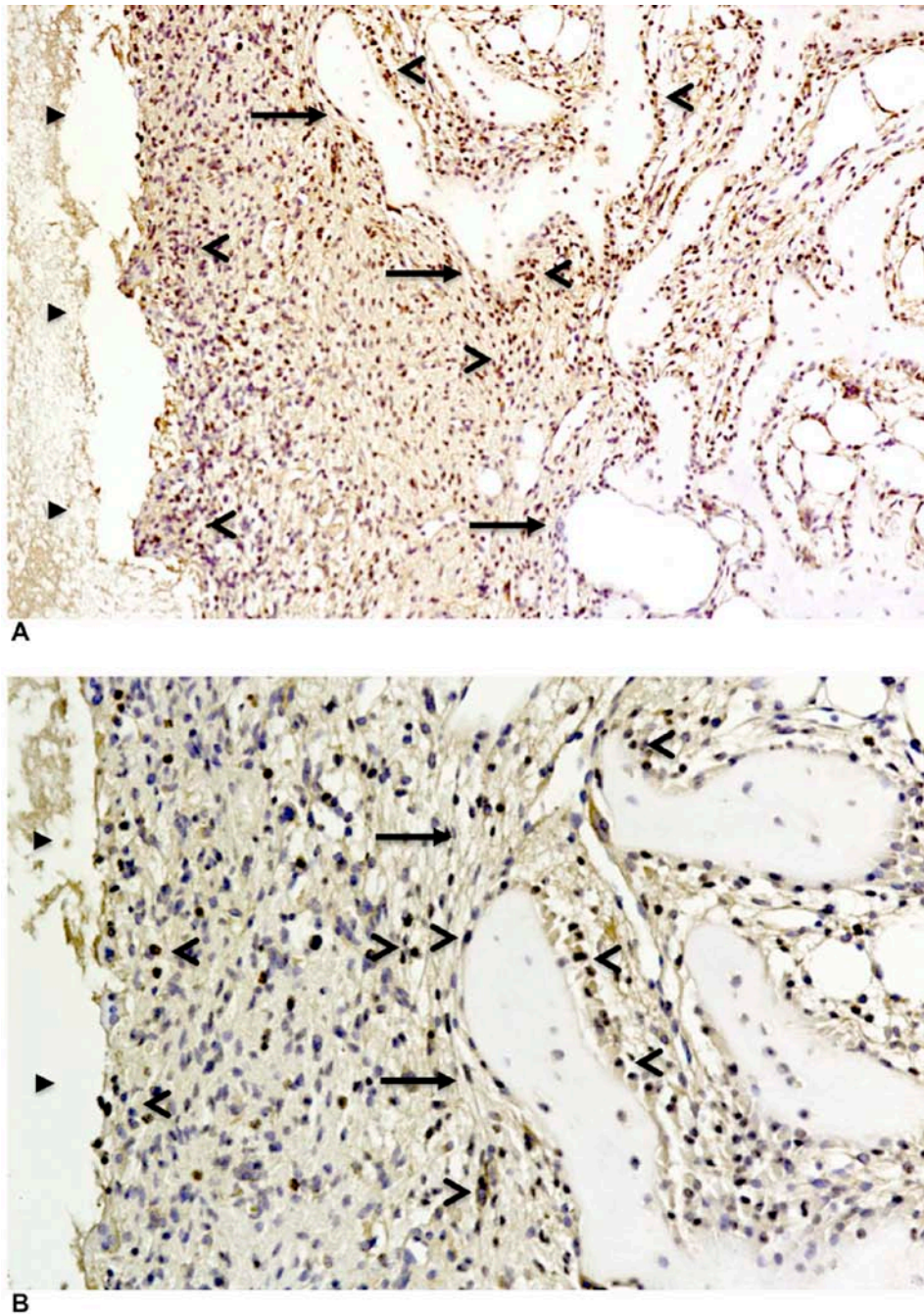


Fig. E-13

Histological appearance of the distal part of a radius containing a core defect treated with 1.5-mg/mL rhBMP-2/CPM (A, B, perimeter of the core defect indicated by arrows with closed arrowheads) at two weeks after surgery. Large numbers of spindle-shaped cells in the region between the residual CPM in the core defect (closed arrowheads) and adjacent trabecular bone (arrows with closed arrowheads) exhibit positive (brown) nuclear staining for CBFA1 (open arrowheads, A, B). Mature osteoblasts on the surface of adjacent trabeculae also exhibit positive nuclear staining for CBFA1 ($\times 10$ for A, $\times 20$ for B; hematoxylin/CBFA1 stain).

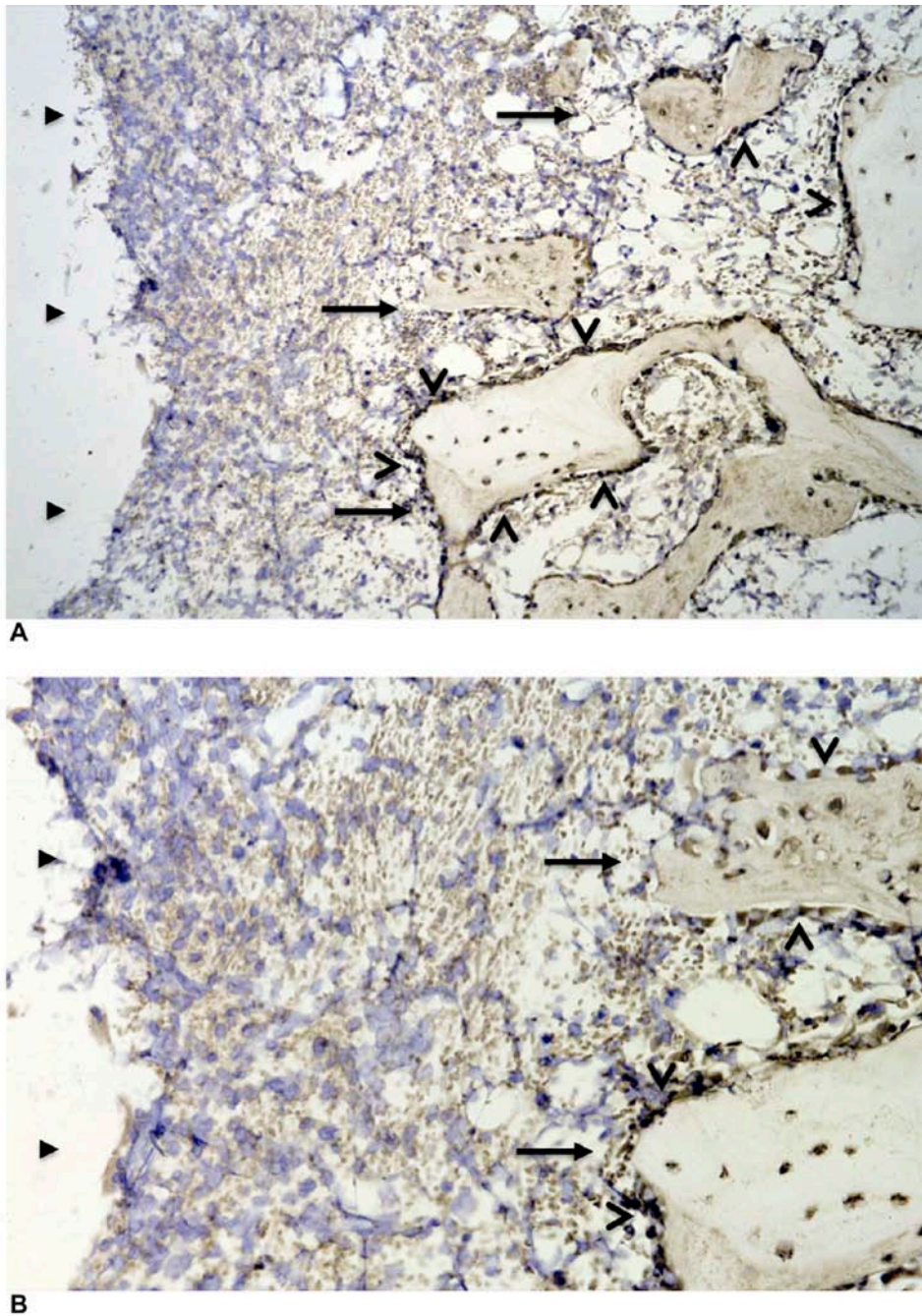


Fig. E-14

Histological appearance of the distal part of a radius containing a core defect treated with 1.5-mg/mL rhBMP-2/CPM (A, B, perimeter of the core defect indicated by arrows with closed arrowheads) at two weeks after surgery. Spindle-shaped cells in the region between the residual CPM in the core defect (closed arrowheads) and adjacent trabecular bone (arrows with closed arrowheads) exhibit negative (brown) cytoplasmic staining for osteocalcin (A, B). In contrast, osteoblasts on the surface of adjacent trabeculae exhibit positive cytoplasmic staining for osteocalcin (open arrowheads) (x10 for A, x20 for B; hematoxylin/osteocalcin stain).

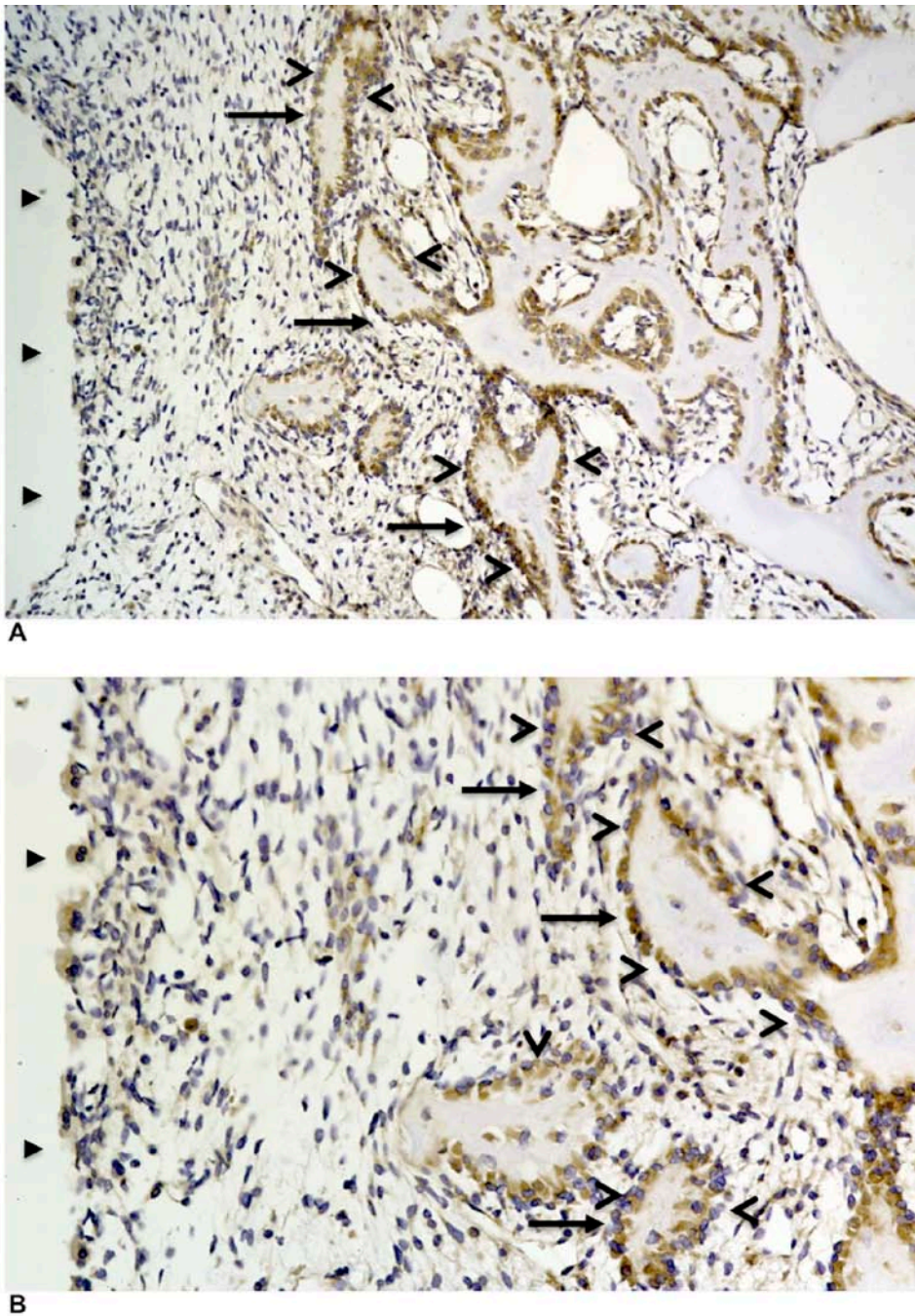


Fig. E-15

Histological appearance of the distal part of a radius containing a core defect treated with 1.5-mg/mL rhBMP-2/CPM (A, B, perimeter of the core defect indicated by arrows with closed arrowheads) at two weeks after surgery. Spindle-shaped cells in the region between the residual CPM in the core defect (closed arrowheads) and adjacent trabecular bone (arrows with closed arrowheads) exhibit negative (brown) cytoplasmic staining for OPG (A, B). In contrast, osteoblasts on the surface of adjacent trabeculae exhibit positive cytoplasmic staining for OPG (open arrowheads) (x10 for A, x20 for B; hematoxylin/OPG stain).

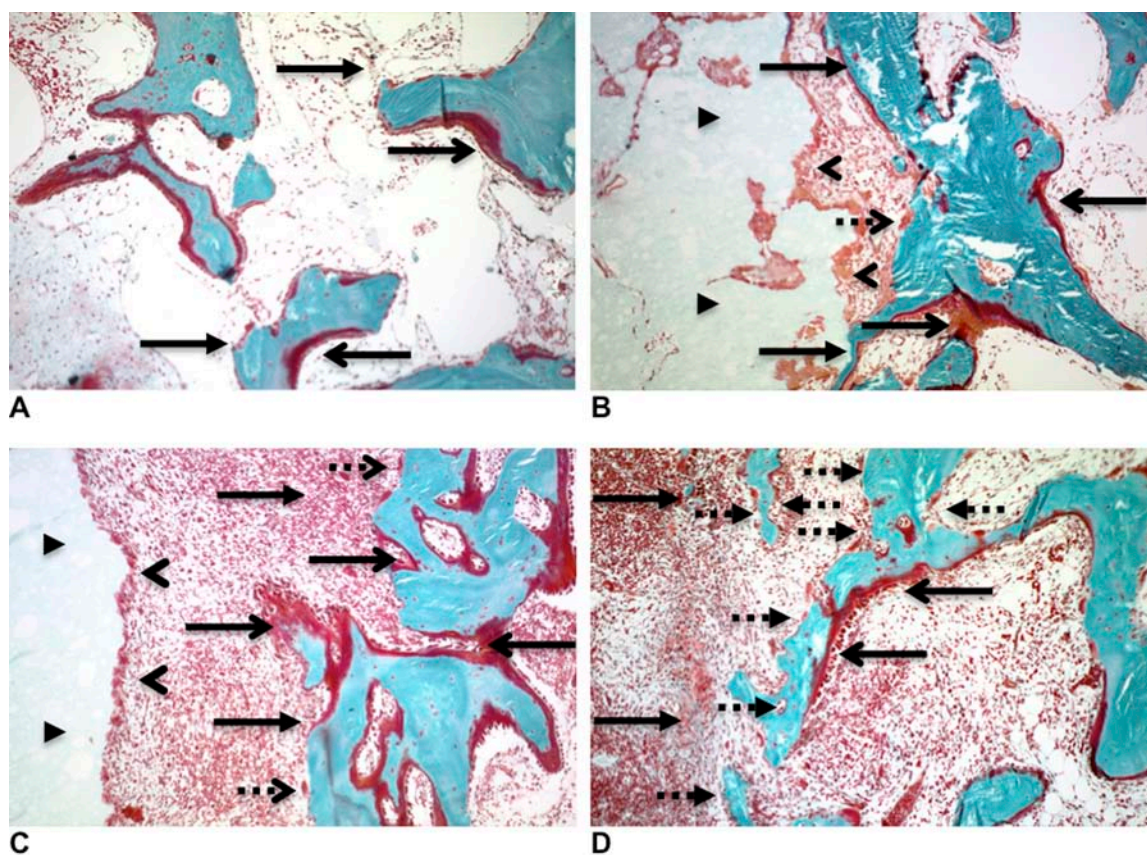


Fig. E-16

Histologic appearance of the distal part of a femur containing an untreated core defect (A), the distal part of a femur containing a core defect treated with CPM alone (B), the distal part of a femur containing a core defect treated with 1.5-mg/mL rhBMP-2/CPM (C), and the distal part of a femur containing a core defect treated with 4.5-mg/mL rhBMP-2/CPM (D) at four weeks after surgery. Arrows with closed arrowheads indicate the perimeter of the core defects. Arrows with open arrowheads indicate appositional bone formation on existing trabeculae adjacent to the core defects. Osteoclasts (B, C, open arrowheads) resorbing the residual CPM carrier (closed arrowheads) are visible within two of the treated core defects (B, C). Occasional osteoclasts (dotted arrows with open arrowheads) are visible resorbing the surface of trabecular bone adjacent to the core defects in the CPM-alone and 1.5-mg/mL rhBMP-2/CPM-treated core defects (B, C). Resorption of preexisting trabeculae by osteoclasts (D, dotted arrows with closed arrowheads) is apparent only in core defects treated with 4.5-mg/mL rhBMP-2/CPM (D) (×10; Goldner trichrome).

TABLE E-1 Phase 1: Retention of ^{125}I -rhBMP-2 in Distal Part of Radius Using Gamma Scintigraphy and Evaluation of Bone Formation Using Radiographic and Histological Analysis Over an Eight-Week Time Period

	Right (μL of test material injected, mg/mL rhBMP-2 injected, μg rhBMP-2 injected)	Left (μL of test material injected, mg/mL rhBMP-2 injected, μg rhBMP-2 injected)	Time (wk)
rhBMP-2/calcium phosphate matrix (n = 6*)			8
Distal part of the radius	150 μL , 1.5 mg/mL, 225 μg	150 μL , 4.5 mg/mL, 675 μg	
Proximal part of the tibia	200 μL , 1.5 mg/mL, 300 μg	200 μL , 4.5 mg/mL, 900 μg	
Proximal part of the femur	300 μL , 1.5 mg/mL, 450 μg	300 μL , 4.5 mg/mL, 1350 μg	
Calcium phosphate matrix alone (n = 6*)			8
Distal part of the radius	150 μL CPM alone	No treatment	
Proximal part of the tibia	200 μL CPM alone	No treatment	
Proximal part of the femur	300 μL CPM alone	No treatment	

*Animals used for Phases 1 and 4.

TABLE E-2 Phase 2: Evaluation of Bone Formation Using Radiographs, Peripheral Quantitative Computed Tomography, and Histological Analysis Over a Twenty-four-Week Time Period

	Right (μL of test material injected, mg/mL rhBMP-2 injected, μg rhBMP-2 injected)	Left (μL of test material injected, mg/mL rhBMP-2 injected, μg rhBMP-2 injected)	Time (wk)
Proximal part of the tibia (n = 6*)	200 μL , 1.5 mg/mL, 300 μg	200 μL , 0.0 mg/mL, 0.0 μg	24

*Animals used in Phases 2, 3, and 4.

TABLE E-3 Phase 3: Evaluation of Response to Treatment at Early Time-Points Using Histology

	Right (μL of test material injected, mg/mL rhBMP-2 injected, μg rhBMP-2 injected)	Left	Time (wk)
Distal part of the radius (n = 2*)	150 μL , 1.5 mg/mL, 225 μg	No treatment	1
Distal part of the radius (n = 2*)	200 μL , 1.5 mg/mL, 300 μg	No treatment	2
Distal part of the radius (n = 2*)	300 μL , 1.5 mg/mL, 450 μg	No treatment	4

*Animals used in Phases 2, 3, and 4.

TABLE E-4 Phase 4: Dose Ranging Evaluation of Transient Bone Resorption at Four Weeks Using Histological Analysis

	Right (μL of test material injected, mg/mL rhBMP-2 injected, μg rhBMP-2 injected)	Left (μL of test material injected, mg/mL rhBMP-2 injected, μg rhBMP-2 injected)	Time (wk)
rhBMP-2/calcium phosphate matrix			
Distal part of the femur (n = 6*)	300 μL , 1.5 mg/mL, 450 μg	300 μL , 4.5 mg/mL, 1350 μg	4
Distal part of the femur (n = 6*)	300 μL , 2.0 mg/mL, 600 μg	300 μL , 3.0 mg/mL, 900 μg	4
Calcium phosphate matrix alone			
Distal part of the femur (n = 6†)	300 μL , 0.0 mg/mL, 0.0 μg	No treatment	4

*Animals used in Phases 1 and 4. †Animals used in Phases 2, 3, and 4.

TABLE E-5 Histological Measurements of the Core Defect Region in the Distal Part of the Radius, Proximal Part of the Femur, and Proximal Part of the Tibia at Eight Weeks After Surgery*

Group	Trabecular Volume Fraction (%)	Osteoid Volume Fraction (%)	Matrix Volume (%)
Distal part of the radius			
No treatment	$6.8 \pm 4.8^{\dagger}$	6.3 ± 4.1	NA
CPM alone	$4.2 \pm 1.9^{\dagger}$	7.5 ± 3.8	$70.0 \pm 16.1^{\dagger}$
1.5-mg/mL rhBMP-2/CPM	$12.6 \pm 4.9^{\ddagger}$	14.7 ± 14.5	$49.2 \pm 20.1^{\ddagger}$
4.5-mg/mL rhBMP-2/CPM	$14.1 \pm 1.9^{\ddagger}$	9.1 ± 9.6	$40.0 \pm 12.6^{\ddagger}$
P value			
Group effect	<0.0004	>0.41	<0.02
1.5 rhBMP-2/CPM versus CPM alone	<0.0007		<0.04
4.5-mg/mL rhBMP-2/CPM versus CPM alone	<0.0001		<0.006
1.5 rhBMP-2/CPM versus no treatment	<0.02		NA
4.5-mg/mL rhBMP-2/CPM versus no treatment	<0.003		NA
1.5 versus 4.5-mg/mL rhBMP-2/CPM	>0.52		>0.35
CPM alone versus no treatment	>0.23		NA
Proximal part of the femur			
No treatment	$6.7 \pm 1.3^{\dagger}$	$1.8 \pm 0.7^{\dagger}$	NA
CPM alone	$4.9 \pm 3.2^{\dagger}$	$1.6 \pm 1.2^{\dagger}$	$63.4 \pm 13.1^{\dagger}$
1.5-mg/mL rhBMP-2/CPM	$13.2 \pm 3.9^{\ddagger}$	$5.5 \pm 3.9^{\ddagger}$	$13.2 \pm 17.5^{\ddagger}$
4.5-mg/mL rhBMP-2/CPM	$15.7 \pm 6.5^{\ddagger}$	$6.4 \pm 4.3^{\ddagger}$	$6.9 \pm 13.7^{\ddagger}$
P value			
Group effect	<0.0004	<0.02	<0.0001
1.5 rhBMP-2/CPM versus CPM alone	<0.002	<0.03	<0.0001
4.5-mg/mL rhBMP-2/CPM versus CPM alone	<0.0002	<0.01	<0.0001
1.5 rhBMP-2/CPM versus no treatment	<0.02	<0.04	NA
4.5-mg/mL rhBMP-2/CPM versus no treatment	<0.002	<0.02	NA
1.5 versus 4.5-mg/mL rhBMP-2/CPM	>0.32	>0.62	>0.47
CPM alone versus no treatment	>0.44	>0.69	NA
Proximal part of the tibia			
No treatment	$6.3 \pm 4.1^{\dagger}$	$1.3 \pm 0.8^{\dagger}$	NA
CPM alone	$13.9 \pm 5.4^{\dagger}$	$1.8 \pm 0.8^{\dagger}$	$68.3 \pm 15.1^{\dagger}$
1.5-mg/mL rhBMP-2/CPM	$31.4 \pm 10.8^{\ddagger}$	$5.3 \pm 4.3^{\ddagger}$	$32.5 \pm 18.6^{\ddagger}$
4.5-mg/mL rhBMP-2/CPM	$28.4 \pm 7.6^{\ddagger}$	$6.0 \pm 4.4^{\ddagger}$	$16.3 \pm 14.9^{\ddagger}$
P value			
Group effect	<0.0001	< 0.04	<0.0002
1.5 rhBMP-2/CPM versus CPM alone	<0.0005	<0.05	<0.0009
4.5-mg/mL rhBMP-2/CPM versus CPM alone	<0.003	<0.04	<0.0001
1.5 rhBMP-2/CPM versus no treatment	<0.0001	<0.04	NA
4.5-mg/mL rhBMP-2/CPM versus no treatment	<0.0001	<0.02	NA

1.5 versus 4.5-mg/mL rhBMP-2/CPM	>0.48	>0.91	>0.1
CPM alone versus no treatment	>0.1	>0.66	NA

*The values are given as the mean and the standard deviation. Between-group comparisons were not made when the p value for group effect was not significant. CPM = calcium phosphate matrix. NA = not applicable. †The values with each column that share the same symbol are not significantly different. ‡The values with each column that share the same symbol are not significantly different.

TABLE E-6 Histological Measurements of Trabecular Bone in the Region Surrounding the Core Defects in Distal Part of the Radius, Proximal Part of the Femur, and Proximal Part of the Tibia at Eight Weeks After Surgery*

Group	Trabecular Volume Fraction (%)	Trabecular Thickness (μm)	Trabecular Number (#/mm)
Distal part of the radius			
No treatment	$18.5 \pm 3.4^\dagger$	91.0 ± 47.4	2.2 ± 0.9
CPM alone	$22.6 \pm 6.7^\dagger$	94.3 ± 47.1	2.3 ± 0.9
1.5-mg/mL rhBMP-2/CPM	$30.9 \pm 6.3^\ddagger$	145.1 ± 46.0	2.0 ± 0.2
4.5-mg/mL rhBMP-2/CPM	$36.6 \pm 6.5^\ddagger$	143.4 ± 39.7	2.3 ± 0.4
P value			
Group effect	<0.0002	>0.08	>0.77
1.5 rhBMP-2/CPM versus CPM alone	<0.02		
4.5-mg/mL rhBMP-2/CPM versus CPM alone	<0.001		
1.5 rhBMP-2/CPM versus no treatment	<0.001		
4.5-mg/mL rhBMP-2/CPM versus no treatment	<0.0001		
1.5 versus 4.5-mg/mL rhBMP-2/CPM	>0.13		
CPM alone versus no treatment	>0.25		
Proximal part of the femur			
No treatment	$28.5 \pm 5.0^\dagger$	$67.9 \pm 11.3^\dagger$	3.9 ± 0.6
CPM alone	$30.7 \pm 2.0^\dagger$	$72.8 \pm 16.4^\dagger$	4.1 ± 1.1
1.5-mg/mL rhBMP-2/CPM	$39.8 \pm 9.1^\ddagger$	$94.8 \pm 22.8^\ddagger$	4.5 ± 1.4
4.5-mg/mL rhBMP-2/CPM	$37.6 \pm 3.9^\ddagger$	$90.1 \pm 13.1^\ddagger$	4.4 ± 0.8
P value			
Group effect	<0.03	<0.013	>0.73
1.5 rhBMP-2/CPM versus CPM alone	<0.03	<0.02	
4.5-mg/mL rhBMP-2/CPM versus CPM alone	<0.05	<0.002	
1.5 rhBMP-2/CPM versus no treatment	<0.009	<0.005	
4.5-mg/mL rhBMP-2/CPM versus no treatment	<0.03	<0.001	
1.5 versus 4.5-mg/mL rhBMP-2/CPM	>0.59	>0.58	
CPM alone versus no treatment	>0.58	>0.57	
Proximal part of the tibia			
No treatment	$28.5 \pm 5.0^\dagger$	$67.9 \pm 11.3^\dagger$	3.9 ± 0.6
CPM alone	$30.7 \pm 2.0^\dagger$	$72.8 \pm 16.4^\dagger$	4.1 ± 1.1
1.5-mg/mL rhBMP-2/CPM	$39.8 \pm 9.1^\ddagger$	$94.8 \pm 22.8^\ddagger$	4.5 ± 1.4
4.5-mg/mL rhBMP-2/CPM	$37.6 \pm 3.9^\ddagger$	$90.1 \pm 13.1^\ddagger$	4.4 ± 0.8
P value			
Group effect	<0.0001	< 0.001	>0.97
1.5 rhBMP-2/CPM versus CPM alone	<0.002	<0.05	
4.5-mg/mL rhBMP-2/CPM versus CPM alone	<0.0001	<0.004	
1.5 rhBMP-2/CPM versus no treatment	<0.0001	<0.02	

4.5-mg/mL rhBMP-2/CPM versus no treatment	<0.0001	<0.002	
1.5 versus 4.5-mg/mL rhBMP-2/CPM	>0.44	>0.70	
CPM alone versus no treatment	>0.42	>0.75	

*The values are given as the mean and the standard deviation. Between-group comparisons were not made when the p value for group effect was not significant. CPM = calcium phosphate matrix. NA = not applicable. †The values with each column that share the same symbol are not significantly different. ‡The values with each column that share the same symbol are not significantly different.

TABLE E-7 Histological Measurements of Osteoid in the Region Surrounding the Core Defects in the Distal Part of the Radius, Proximal Part of the Femur, and Proximal Part of the Tibia at Eight Weeks After Surgery*

Group	Osteoid Volume Fraction (%)	Osteoid Thickness (μm)	Osteoid Surface (%)
Distal radius			
No treatment	$0.3 \pm 0.3^\dagger$	10.6 ± 2.3	$5.9 \pm 4.3^\dagger$
CPM alone	$0.4 \pm 0.3^\dagger$	11.7 ± 0.8	$10.0 \pm 8.3^\dagger$
1.5-mg/mL rhBMP-2/CPM	$2.6 \pm 1.1^\ddagger$	13.0 ± 2.4	$60.4 \pm 18.4^\ddagger$
4.5-mg/mL rhBMP-2/CPM	$3.3 \pm 1.8^\ddagger$	13.5 ± 1.9	$61.6 \pm 29.1^\ddagger$
P value			
Group effect	<0.0001	>0.07	<0.00001
1.5 rhBMP-2/CPM versus CPM alone	<0.002		<0.00007
4.5-mg/mL rhBMP-2/CPM versus CPM alone	<0.0001		<0.00005
1.5 rhBMP-2/CPM versus no treatment	<0.001		<0.00003
4.5-mg/mL rhBMP-2/CPM versus no treatment	<0.0001		<0.00002
1.5 versus 4.5-mg/mL rhBMP-2/CPM	>0.34		>0.91
CPM alone versus no treatment	>0.84		>0.69
Proximal femur			
No treatment	$1.1 \pm 1.0^\dagger$	11.4 ± 1.2	$15.1 \pm 11.2^\dagger$
CPM alone	$1.4 \pm 1.0^\dagger$	10.8 ± 2.4	$21.4 \pm 14.8^\dagger$
1.5-mg/mL rhBMP-2/CPM	$8.0 \pm 3.7^\ddagger$	13.0 ± 2.4	$75.6 \pm 10.2^\ddagger$
4.5-mg/mL rhBMP-2/CPM	$8.3 \pm 4.9^\ddagger$	13.8 ± 2.9	$76.4 \pm 23.1^\ddagger$
P value			
Group effect	<0.001	>0.43	<0.00001
1.5 rhBMP-2/CPM versus CPM alone	<0.002		<0.00006
4.5-mg/mL rhBMP-2/CPM versus CPM alone	<0.001		<0.00005
1.5 rhBMP-2/CPM versus no treatment	<0.001		<0.00002
4.5-mg/mL rhBMP-2/CPM versus no treatment	<0.001		<0.00001
1.5 versus 4.5-mg/mL rhBMP-2/CPM	>0.87		>0.94
CPM alone versus no treatment	>0.89		>0.50
Proximal tibia			
No treatment	$0.3 \pm 0.3^\dagger$	$12.4 \pm 0.9^\dagger$	$9.4 \pm 3.9^\dagger$
CPM alone	$0.6 \pm 0.5^\dagger$	$14.1 \pm 1.5^\dagger$	$16.0 \pm 8.5^\dagger$
1.5-mg/mL rhBMP-2/CPM	$2.8 \pm 1.1^\ddagger$	$20.4 \pm 4.1^\ddagger$	$50.2 \pm 10.1^\ddagger$
4.5-mg/mL rhBMP-2/CPM	$2.6 \pm 1.2^\ddagger$	$22.6 \pm 2.8^\ddagger$	$41.7 \pm 16.9^\ddagger$
P value			
Group effect	<0.0001	< 0.00001	< 0.00001
1.5 rhBMP-2/CPM versus CPM alone	<0.0001	<0.0004	<0.00002
4.5-mg/mL rhBMP-2/CPM versus CPM alone	<0.0001	<0.00001	<0.00005
1.5 rhBMP-2/CPM versus no treatment	<0.0001	<0.00003	<0.00001

4.5-mg/mL rhBMP-2/CPM versus no treatment	<0.0001	<0.00001	<0.00004
1.5 versus 4.5-mg/mL rhBMP-2/CPM	>0.70	>0.17	>0.18
CPM alone versus no treatment	>0.60	>0.23	>0.31

*The values are given as the mean and the standard deviation. Between-group comparisons were not made when the p value for group effect was not significant. CPM = calcium phosphate matrix. NA = not applicable.

†The values with each column that share the same symbol are not significantly different. ‡The values with each column that share the same symbol are not significantly different.

TABLE E-8 Histological Measurements of the Core Defect Region and the Region Surrounding the Core Defects in the Proximal Part of the Tibia at Six Months After Surgery*

Region	Trabecular Volume Fraction (%)	Osteoid Volume Fraction (%)	Matrix Volume Fraction (%)
Core defect region			
1.5-mg/mL rhBMP-2/CPM	19.2 ± 6.5†	6.4 ± 5.9†	0
CPM alone	11.0 ± 3.3‡	0.6 ± 0.8‡	24.9 ± 14.5
P value	p < 0.002	p < 0.002	p < 0.015
Surrounding region			
1.5-mg/mL rhBMP-2/CPM	22.2 ± 4.1†	0.4 ± 0.1†	
CPM alone	15.9 ± 1.3‡	0.2 ± 0.1‡	
P value	p < 0.0001	p < 0.0001	

*The values are given as the mean and the standard deviation. CPM = calcium phosphate matrix. †The values with each column that share the same symbol are not significantly different. ‡The values with each column that share the same symbol are not significantly different.