ACUMED®

TECHNICAL MONOGRAPH

CALLOS®

Calcium Phosphate Cement

Overview

Callos is available in two forms:
Callos Impact® - moldable cement
Callos Inject® - injectable cement

- Biocompatible
- Easy to mix and deliver
- Can be drilled and interted with screws
- Replaced by bone via cell mediated remodeling
- Fast-setting, sets in a wet environment, no wash-out
- Enhanced mechanical properties
    - Increased tensile strength
    - Increased flexural strength
    - Increased fracture toughness
- Haemostatic

Mineral Phase of Bone

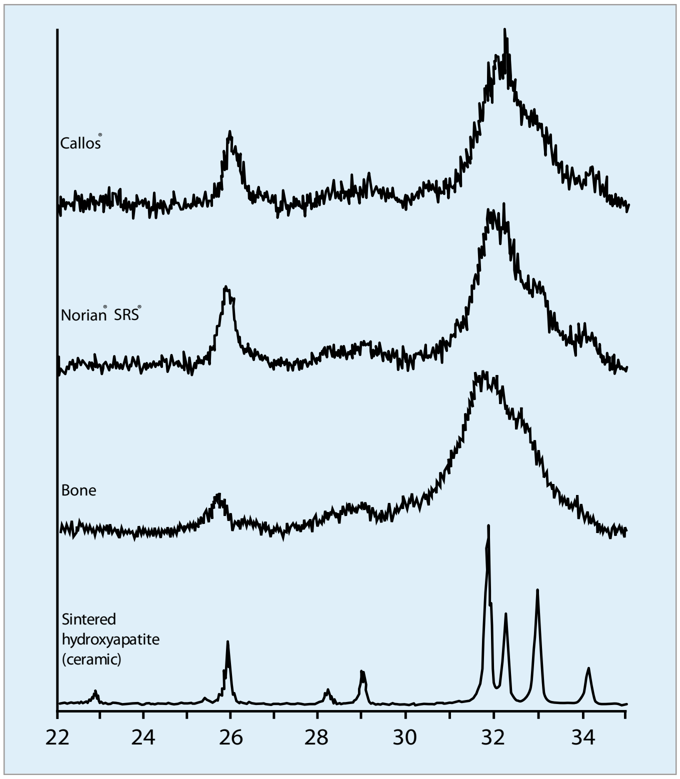


Figure 1. XRD patterns for Callos®, Norian®SRS®, bone and sintered hydroxyapatite. Callos and Norian SRS were both explanted and analyzed following four weeks in vivo implantation.

X-ray diffraction (XRD) allows identification of the mineral phase of materials. Figure 1 illustrates the XRD patterns for Callos®, Norian® SRS®, bone and sintered hydroxyapatite (ceramic). The diffraction pattern of the Callos and Norian SRS materials are considerably broader than the sintered hydroxyapatite material and more closely resemble the diffraction pattern of bone due to their similar crystallinity.

Fourier Transform Infrared Spectroscopy (FTIR) is used to evaluate additional aspects of the crystallographic and chemical make-up of the implant. Both Callos and Norian SRS are poorly crystalline apatites, similar to the native mineral phase of bone (Figure 2). These FTIR spectra indicate that they share similar characteristic differences from "ceramic" or sintered hydroxyapatite in that they incorporate carbonate and acidic phosphate groups with their crystalline structure, leading to their poor crystallinity and enhanced solubility relative to highly crystalline 'ceramic' or sintered hydroxyapatite calcium phosphate.

The relative solubility of calcium phosphate bone void fillers was measured at 37°C in a physiologic solution with a pH=7.4. Figure 3 shows increasing concentrations of dissolved calcium for both Norian SRS and Callos over the initial 24 hours. Calcium values begin to level off to an apparent equilibrium value of about 11 ppm after 5 days for Norian SRS and 9 ppm for Callos. These values are similar to those published previously for poorly crystalline apatite materials with similar chemical compositions and crystallographic structures.[1,2] The solubility curves for Callos® and Norian® SRS® show similar solubilities in vitro, which reflects their chemical and crystallographic similarities. Based on their similar in vitro solubility and dissolution rates at physiologic temperature and pH, Norian SRS and Callos are anticipated to have similar in vivo stability and remodeling rates.

Calcium sulfate (gypsum) or Plaster-of-Paris could not be plotted on this curve because its solubility is many orders of magnitude higher. This is why gypsum simply dissolves (autodegrades) rapidly in vivo, leaving a void before bone can infill a defect.[3] The promotionally advertised initial mechanical strength of Plaster-of-Paris cements is clinically irrelevant because they dissolve so rapidly in vivo. Strength is lost exponentially within a very short period of time, even though the radiographic disappearance of gypsum appears linear, giving a false sense that it remains mechanically intact.

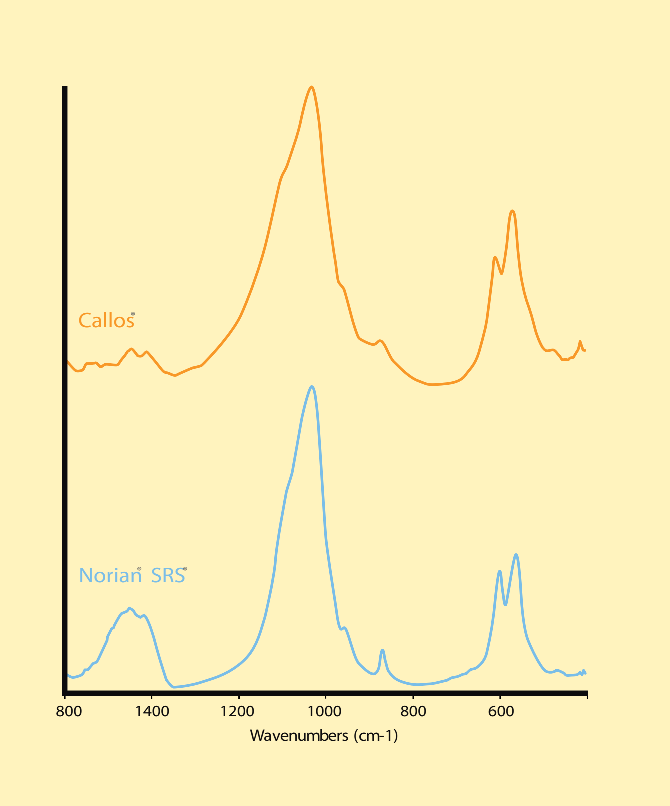


Figure 2. The Fourier Transform Infrared (FTIR) spectra for Callos® and Norian® SRS® show that both form carbonated hydroxyapatite in vivo, similar to the native mineral phase of bone. Callos and Norian SRS were both explanted and analyzed following four weeks in vivo implantation.

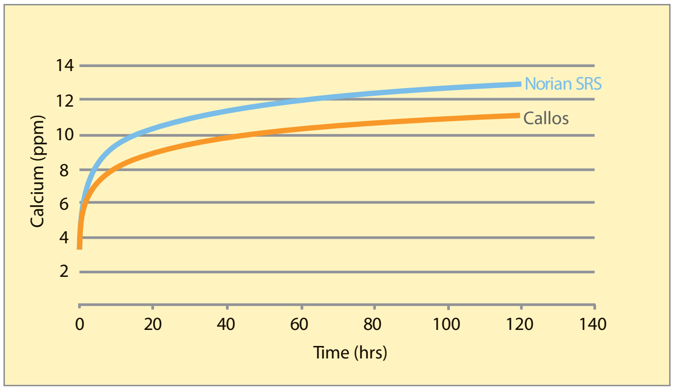


Figure 3. In vitro solubility measurements at 37°C, pH=7.4 phosphate buffered saline.

Pathology and Radiographic Interpretation

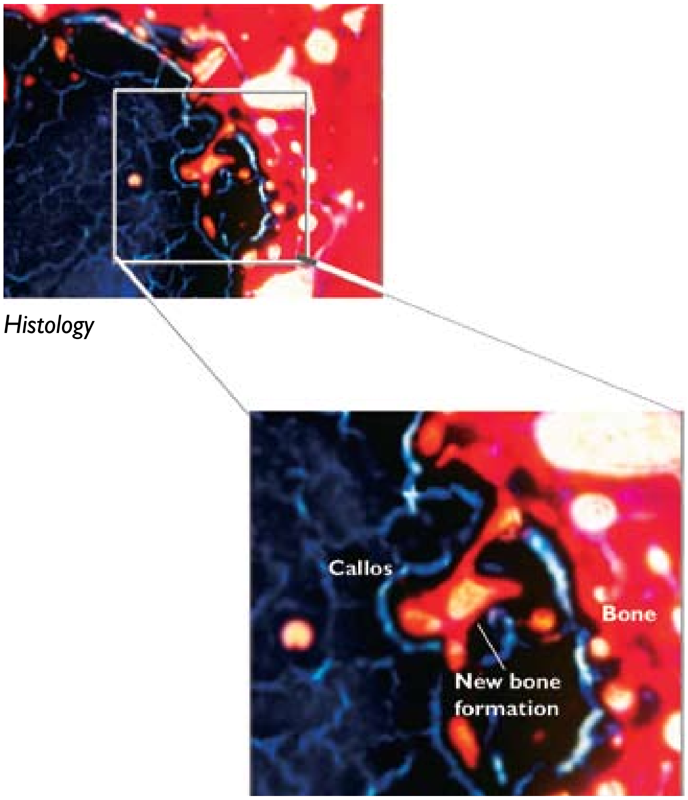


Figure 4. Low magnification and High magnification

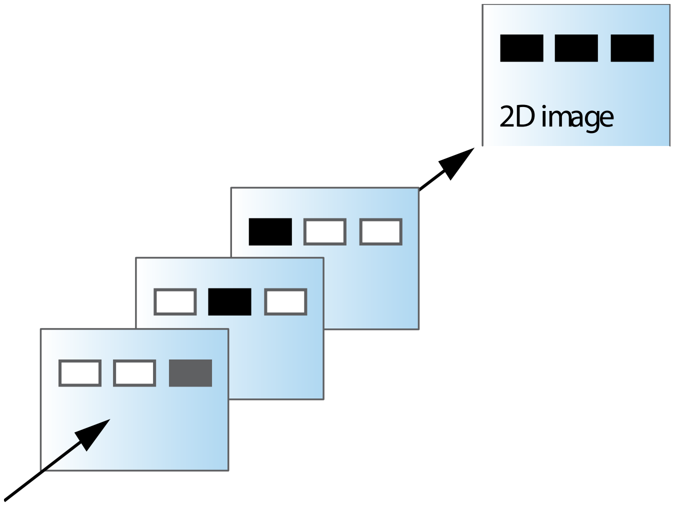


Figure 5. The white blocks are areas that have completely remodeled and the black blocks are areas not remodeled. The 2-D image, which is produced by radiographic means, shows only the localized areas of sections that have not remodeled, represented as black boxes. These 'black box' areas need only be about 5-10mm in thickness to appear radio-opaque on a clinical x-ray.

Histological analysis demonstrated that Callos® is highly biocompatible and osteoconductive. Figure 4 shows histological analysis following four and six weeks in vivo and showed extensive bone apposition with no adverse tissue reaction. Normal bone remodeling by localized osteoclastic, cell-mediated resorption coupled with new bone formation within the implanted area was a consistent finding in areas implanted with Callos.

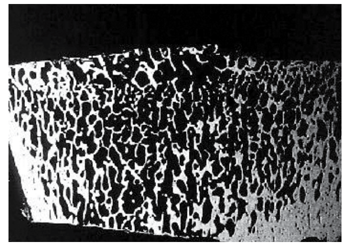
Over the last decade, reports in peer-reviewed literature and results from the above study have demonstrated that calcium phosphate cements remodel via osteoclastic cell-mediated resorption coupled with new bone formation.[4,5,6,7,8,9] It is important to note, that the use of standard radiographic imaging is limited in its capacity to show the progress of remodeling. A clinical radiograph takes a 3-D structure and produces a 2-D image. Figure 5 illustrates the "stacking" effect, which results during radiographic analysis of a 3-D structure.

Figures 6A & 6B are low power back-scattered scanning electron micrographs of tibial plateau sections from an in vivo canine study at 4.5 years from the same animal. 6A shows complete remodeling of the calcium phosphate cement, yet 6B, a different cross-section of the same sample, shows areas still comprised of cement. The radiograph, 6C, taken prior to sectioning the proximal tibia, illustrates the "stacking" effect seen when a 2-D image is produced from a 3-D structure. Although the micrographs show extensive remodeling, standard clinical radiographic analysis continues to show the presence of cement even at minimal levels and is not an effective means of measuring the extent of Callos cement remodeling.

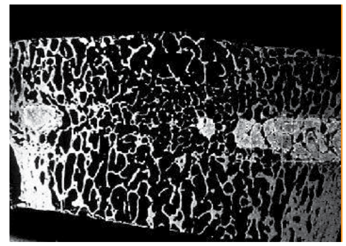
Figure 7 illustrates the limitations of simple radiographic analysis for accurate follow-up evaluation and interpretation of osteoclastic cellmediated remodeling and revascularization of the implanted area. Callos® was injected into cylindrical samples covering a range of thicknesses from 30mm down to 2mm and cured in vitro.

These samples were then x-rayed using standard radiographic technique for a distal radius fracture (54 Kv @ 7mA). The resulting radiograph highlights that one cannot easily distinguish the difference between cement bodies over 10-20mm in thickness. This shows that even with a significant decrease in the amount of the Callos implant, it is difficult to see any radiographic change, i.e. assuming no resorption and replacement by bone. With the added effects of remodeling native bone, bare implants alone show little evidence of radiographic significance as the implant remodels. As a result, especially in a clinical radiograph where both bone cement and new bone are present, the additive effect of the cement and bone render the radiograph completely radiopaque.

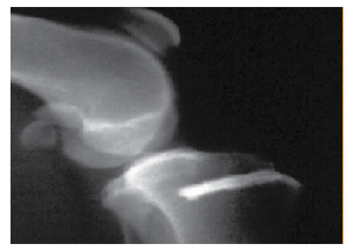
This misinterpretation in radiographic analysis has lead to the false interpretation that calcium phosphate cements are not remodeled even though all the histologic evidence demonstrates that they become completely replaced by bone in a mechanical stress-directed fashion.[4,5,6,7,8,9]



6A



6B



6C

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Figure 6. Electron micrographs of tibial plateau samples.

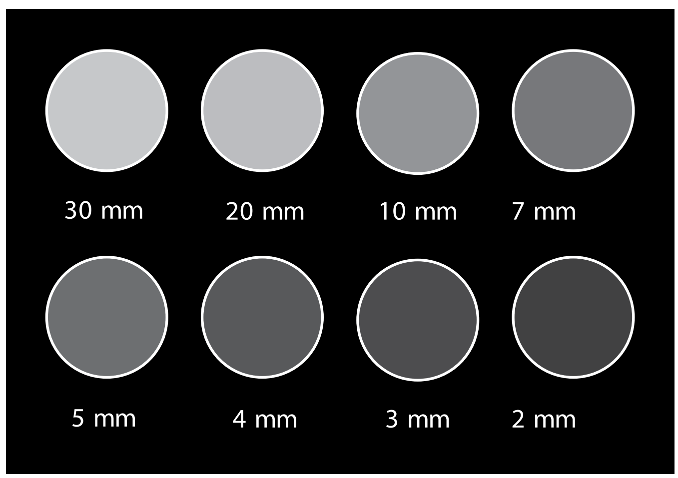

Figure 7. Radiograph samples in the following thicknesses: 30mm, 20mm, 10mm, 7mm, 5mm, 4mm, 3mm, and 2mm.

Strength Maintenance Over Time

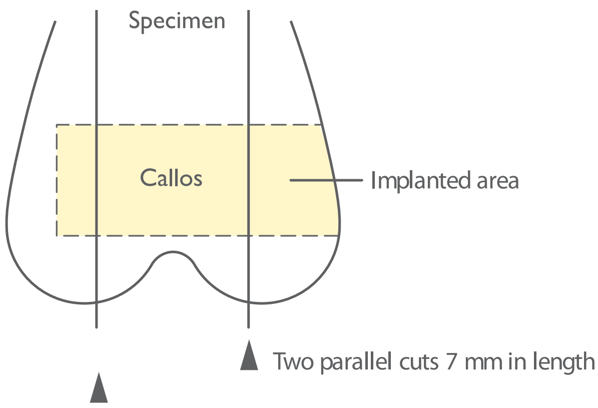

Figure 8. Two parallel cuts were made on biomechanical specimens.

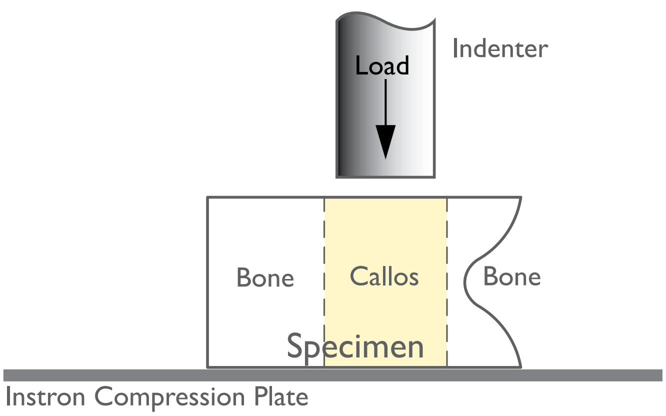

Figure 9. An indenter was used to apply compression force at a rate of 0.1 mm/sec for 2.5 mm on the implanted area.

A clinically relevant understanding of the long-term strength of defects treated with calcium phosphate bone void fillers (or any other bioactive material) are appropriately evaluated only in vivo. An in vivo biomechanical study was performed at four weeks and six months post-implantation to assess the in vivo strength of cancellous bone defects treated with Callos® or Norian® SRS® bone void filler during replacement by native cancellous bone.

Materials and Methods: Following sacrifice, distal femora were cut perpendicular to the axis of the cylindrical implants as shown in Figure 8. The mid section of the samples (7 mm in length) were utilized for biomechanical testing. The mid sections were loaded to failure by the use of an indenter to evaluate the strength of the implanted area.

Results: Implanted areas were tested after remodeling over a period of four weeks and a period of six months. Both time points had samples composed of new bone and implanted cement. The relative strengths of the implanted areas at four weeks were 278 N (±153) and 253 N (±157) and at six months were 318 N (±133) and 287 N (±129) for Callos and Norian SRS bone void fillers, respectively (Figure 10). The strength of the cancellous bone control specimens of the same implantation area were found to be 130 N (±37).

Conclusions: After both the four week and six month periods post implantation, the implanted regions of both Callos and Norian SRS demonstrated newly formed cement-bone constructs in the treated defect. These new constructs were approximately twice the strength of the cancellous bone control.[10]

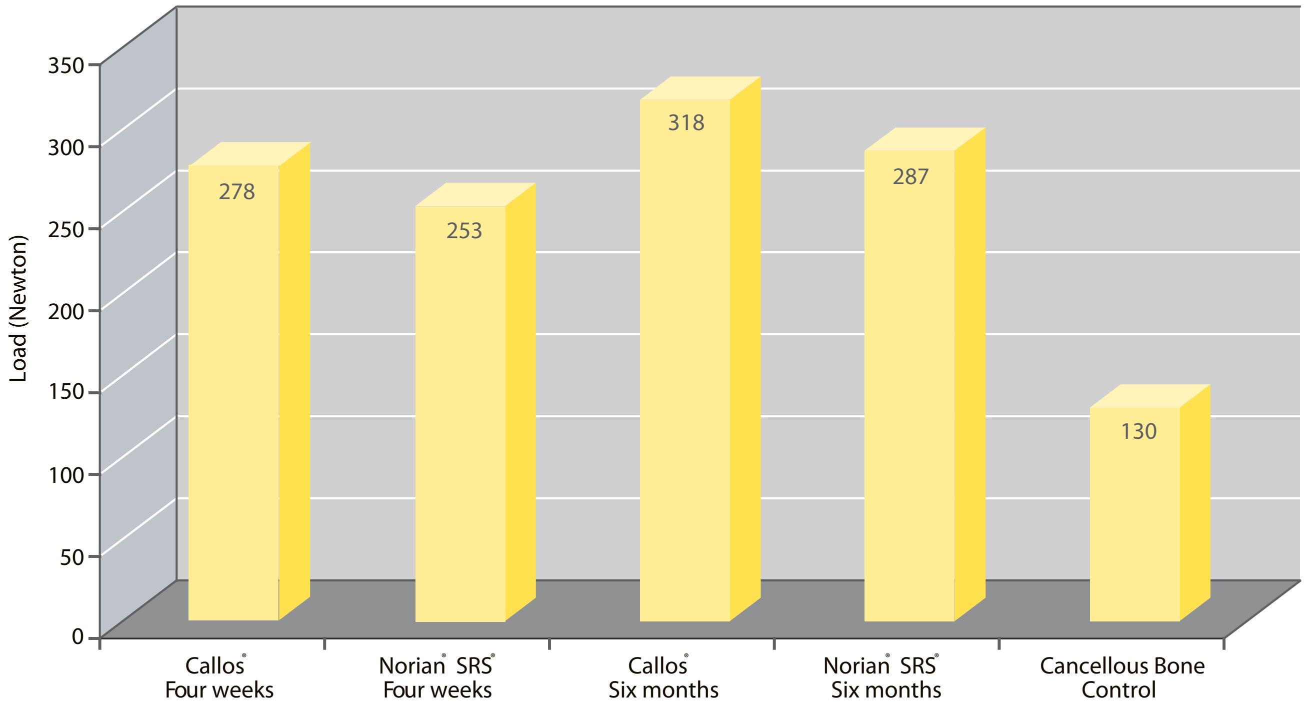

Figure 10. The strength of implanted Callos®, Norian® SRS® compared to cancellous bone at two time periods: Four weeks and six months.

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