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## Injectable Phosphate Cements – A Review

**Sune Larsson MD, PhD, Professor**, Department of Orthopaedic Surgery, Uppsala University Hospital  
Uppsala, Sweden

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Corresponding Author: Professor Sune Larsson  
Department of Orthopedics  
Uppsala University Hospital  
S-751 85 Uppsala, Sweden  
Phone (dir) + 46 18 6114470  
(secr) + 46 18 6114467  
Fax + 46 18 509427

sune.larsson@ortopedi.uu.se

### ABSTRACT

Surgical treatment of fractures close to joints, especially in osteoporotic patients, is often associated with problems to obtain adequate strength of the bone-implant construct as well as sufficient purchase for screws in the weak bone. One way to address this increasing problem is through the development of new metal implants specifically designed for fixation of fractures in osteoporotic bone. An alternative strategy is to develop methods for augmentation of the weak bone that surrounds the metal implant. Such reinforcement of the bone can be achieved by injectable cement. Conventional polymethylmethacrylate (PMMA) provides good strength but due to several drawbacks it has never gained general acceptance for fracture augmentation. More recently injectable osteoconductive cements based on calcium phosphate or calcium sulphate have been introduced as an adjunct to internal fixation for selected fractures. Based on clinical studies, cement augmentation can shorten the rehabilitation time compared with conventional metal implants alone, and also replace bone graft. The purpose of this paper is to review injectable osteoconductive cements with special reference to the development of a novel calcium phosphate cement, HydroSet™, designed to overcome drawbacks seen in the first generation phosphate based cements.

### Introduction

Internal fixation of metaphyseal fractures may be difficult because of the low strength in the cancellous bone that makes up the major part of the metaphysis. This is particularly true in the growing number of patients with compromised bone strength due to osteoporosis. In addition, the fragment closest to the joint is often short, and the fracture frequently also has an intra-articular component. Despite the technical difficulties introduced by these problems, internal fixation is usually recommended because good fracture stability is a prerequisite for early return to adequate joint function. Good fracture stabilization is especially important in elderly patients, who may suffer from general weakness that prevents them from reducing the load on their injured extremity during healing.

Unfortunately, two factors frequently complicate the stabilization of metaphyseal fractures. The first is the crushing of subchondral cancellous bone by depressed articular fragments at the time of injury. Reducing the fracture during surgery creates a metaphyseal defect that must be filled to prevent the joint surface from subsiding when the bone is subjected to loading. Most commonly, the subchondral void is filled with autologous bone graft. However, this procedure carries serious drawbacks such as

donor site morbidity and the limited immediate mechanical stability afforded by cancellous autograft. The second factor that complicates the stabilization of such fractures is the presence of osteoporosis, which increases the risk that the fracture will become displaced before it heals.

Problems related to internal fixation of fractures in osteoporotic bone usually have been addressed by developing new metal implants. An alternate strategy is to develop methods that will reinforce the weak cancellous bone surrounding the metal implant. A few clinical studies have suggested that **a c r y l i c b o n e c e m e n t** (polymethylmethacrylate or PMMA) enhances fracture stability in osteoporotic patients [1,26,30]. However, PMMA has not gained wide acceptance in fracture treatment, because of its exothermic reaction during curing, the inability of the cement to be remodelled, the risk of inhibiting fracture healing if the PMMA is interposed between fracture surfaces, and difficulty in removing if revision surgery becomes necessary.

The solution to many of the problems encountered when fixing fractures involving crushed cancellous and osteoporotic bone may lie in injectable bioactive cements. In recent years several such cements have therefore been developed as potential tools for augmenting hardware during fracture surgery [5,11,18]. Cement that provides immediate fracture stability and is strong enough to allow early and active rehabilitation will facilitate function to be restored more rapidly. Apart from mechanical competence, ideal cement would also be gradually resorbed over time and replaced by host bone. The rate of cement resorption should be balanced with the rate of new bone formation to avoid collapse at the fracture site, which might occur if resorption is too fast.

The purpose of this paper is to provide a review on different aspects of injectable calcium phosphate and calcium sulphate cements when used for fracture treatment. Special emphasis will be focused on the

development of a new calcium phosphate cement (HydroSet™), intended to provide improved mechanical and handling characteristics compared with the first generation calcium phosphate products.

### **General appearance**

Based on composition, at least two types of injectable calcium based cements are at present commercially available. The first, and by far the larger of the two groups, includes different calcium phosphate compounds, while the second group consists of calcium sulphate products. The injectable calcium based cements are all delivered as two or three components including one or two dry powders and a fluid, which are mixed in the operating room either manually or with the use of a mixing machine. After mixing, the paste like cement is injectable and malleable for a few minutes, depending on the type of cement, temperature, etc. Most commonly, real time fluoroscopy is used during injection to ensure an adequate positioning of the cement. Following injection the cement hardens in situ to form a solid structure with mechanical integrity that will contribute to the strength of the bone-implant construct.

### **Calcium phosphate**

#### **Composition**

The powder is usually a mix of different calcium phosphate salts where almost all products contain one or several of the following components; amorphous calcium phosphate (ACP), dicalcium phosphate dihydrate (DCPD), dicalcium phosphate anhydrous (DCPA),  $\alpha$ -tricalcium phosphate ( $\alpha$ -TCP), dicalcium phosphate (DCP), tetracalcium phosphate (TTCP), monocalcium phosphate monohydrate (MCPM) and calcium carbonate (CC), while the fluid usually is a sodium phosphate solution. In table 1, the major components of some of the injectable calcium phosphate products have been listed.

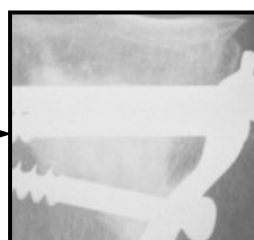
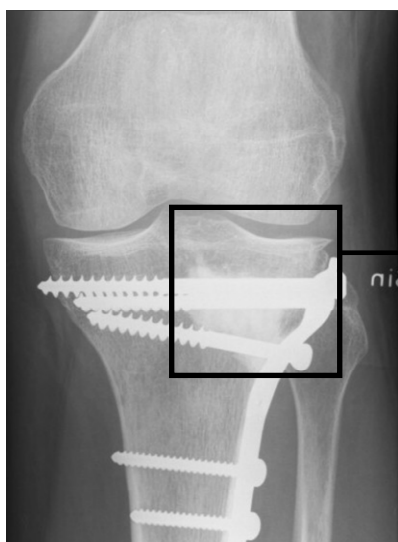
Product	Components	End product	Resorbable	References
$\alpha$ -BSM	ACD, DCPD	PHA	Yes	Vereecke & Lemaitre 1990 [36]
Biobon	ACD, DCPD	PHA	Yes	Sarkar et al 2001 [29]
Bone-Source	TTCP, DCPA	PHA	Slow	Constantino et al 1996 [4]
Calcibon	$\alpha$ -TCP, DCP, CC, PHA	CAP	Slow	Driessens et al 1994 [7]
ChronOS inject	$\alpha$ -TCP, MCPM	DCPD	No	Lemaitre et al 1987 [21]
Norian <sup>TM</sup> SRS	$\alpha$ -TCP, CC, MCPM	CAP	Slow	Constantz et al 1995 [5]

**Table 1. Calcium phosphate bone substitutes that set in situ.**

After injection, the paste hardens within minutes to form a precipitated hydroxyapatite (PTH) or a carbonated apatite (CAP) of low crystalline order and small crystal size, very similar to the mineral phase of bone. The solubility of the injectable calcium phosphate cement is expected to be similar to that of bone mineral. This means that it will be relatively insoluble at neutral pH and increasingly soluble as pH decreases, an important characteristic of normal bone mineral that facilitates controlled dissolution by osteoclasts as the cells causes a local lowering of the pH at the site where bone will be dissolved. PHA and CAP have been shown to resorb slightly more rapidly than high temperature treated HA but the resorption rate is still very slow.

Most of the calcium phosphate based bone substitutes will remain, at least in part, several years after implantation.

Due to the high content of calcium salts the products will have inherently high radiographic attenuation, i.e. be naturally visible on radiographs without adding contrast medium to the product. A bone region implanted with calcium phosphate cement therefore appears quite radiopaque on conventional radiographic films (Figure 1). As the cement undergoes remodelling one would expect to see a proportionate change in the radiopacity. However, due to the low resolution and limitations of conventional radiographs this change is usually not visible until a substantial part of the material has been replaced by bone. In vitro it has been shown that as much as 50% of the material can be taken away until the difference is detectable on radiographs.



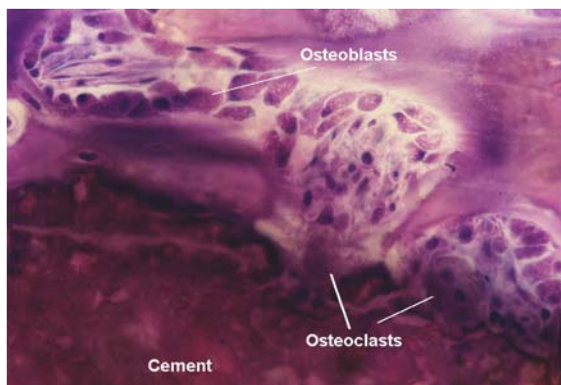
**Figure 1.** Elderly women with osteoporosis operated with conventional internal fixation combined with calcium phosphate cement for filling of subchondral void following a displaced lateral tibia plateau fracture. The cement having an inherently high radiographic attenuation.

### Mechanical characteristics

As the injected calcium phosphate paste cures, the cement physically interdigitates with adjacent bone, forming a solid structure that is more mechanically stable than either cancellous bone graft or the pellets or blocks of hydroxyapatite, calcium phosphate or calcium sulfate often used to fill bone voids [8,35,38,39,40]. For most products it is important to avoid movement of the material during the initial minutes as it sets, to avoid disturbing the final mechanical characteristics. The strength improves slightly within minutes after the injection during the initial course of crystallization. Most products will reach close to the maximal strength within 4-8 hours and the full strength within 24 hours. In general, calcium phosphate cements will, fully cured, have a compressive strength between that of good cancellous and cortical bone, but tensile and shear strength will be much lower than those of cancellous bone.

### Histology

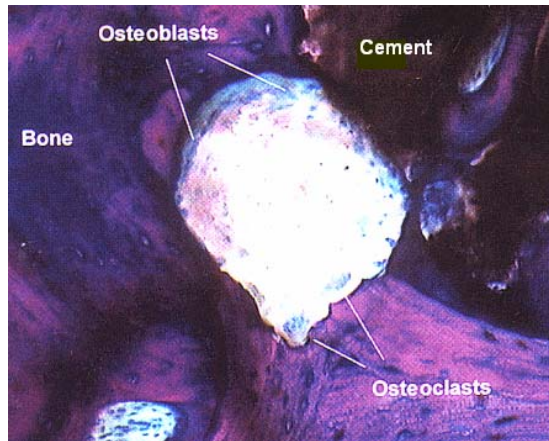
Preclinical animal studies have shown that calcium phosphate is osteoconductive and undergoes gradual remodelling over time, mainly through a cell mediated surface process involving osteoclasts and osteoblasts. There seems to be osteoclastic resorption of the cement, vascular penetration, and bone formation through osteoblasts in a pattern that suggests remodelling similar to that of normal bone. In a canine study, a bone defect created in the proximal tibia and filled with cement showed prominent bone apposition as early as 2 weeks (Figure 2) [9].



the interface between calcium phosphate cement and the bone at two weeks after implantation in a defect in the distal femora of a canine. Osteoclasts and osteoblasts indicating remodelling and no intervening connective tissue (courtesy Dr Thomas W. Bauer).

There have also been a few reports of the histology in humans. Schildhauer and co-workers described the use of injectable calcium phosphate in augmenting internal fixation of calcaneal fractures [31]. Biopsies were obtained from 7 patients at the time of hardware removal, more than 1 year after injury. The biopsies showed almost complete bone apposition to the residual calcium phosphate cement. Resorption was evident in the vicinity of osteoclasts and was often accompanied by new bone formation that appeared qualitatively similar to normal bone remodelling. Vascular ingrowth into the cement was evident, and there was no fibrous tissue. In a study on proximal femoral fractures in humans, calcium phosphate cement was used for augmentation around cannulated screws and sliding hip screws used for internal fixation [23,24]. Retrievals from several of the patients from 6 to 28 months revealed areas with extensive bone apposition to the cement without intervening fibrous tissue, and in other areas, the bone marrow contained macrophages with fragments of cement that had been phagocytosed. In specimens taken from unstable areas that had undergone motion, fragmented cement and macrophages were prominent [19].

**Figure 2.** Photomicrograph demonstrating Overall, the histologic features in human biopsies have illustrated processes of remodeling identical to those previously reported in animal studies and similar to those seen in normal bone (Figure 3).



**Figure 3.** Photomicrograph demonstrating a focus of osteoclastic resorption and new bone formation associated with both bone and calcium phosphate cement in a biopsy obtained from an elderly patient more than 9 months after treatment with cement to reinforce an internal fixation of a proximal femoral fracture. (Larsson et al [19]).

### Calcium sulphate

Calcium sulphate has been used as a synthetic bone graft material for more than one hundred years [6]. In earlier studies the material used varied in structure and properties and it was not until the last decade that the first surgical grade calcium sulphate based products were developed. Until very recently calcium sulphate products have only been available as preformed pellets or tablets, although at present there are also a few injectable calcium sulphate cements that will harden in situ following injection (e.g. MIIG 115, MIIG X3).

Calcium sulphate is highly biocompatible and it resorbs or dissolves fairly quickly. The dissolution rate makes it possible to be used for drug release, such as antibiotics, while the mechanical characteristics for most calcium sulphate compounds, except MIIG X3, show low compressive strength and a brittle appearance. The low mechanical strength limits the potential use for augmentation and most calcium sulphate products should therefore be considered mainly as bone void fillers. The rapid dissolution that proceeds without a cell-mediated regu-

lation, as seen for calcium phosphate products, can exceed the ability for new bone formation.

### **Composition**

Calcium sulphate exists naturally in the dihydrate form. Dehydration of the dihydrate by heating produces the hemihydrate form which sets to a solid material when mixed with water. Depending on the method of heating,  $\alpha$ - or  $\beta$ -form hemihydrate is obtained. The  $\alpha$ -form shows large, rectangular shaped crystals that are compact and well formed while the  $\beta$ -form shows flaky very small crystals. The  $\alpha$ -form has a higher density, it is less soluble and stronger than the  $\beta$ -form. Conventional plaster of Paris is in fact  $\beta$ -calcium sulphate hemihydrate.

### **Mechanical characteristics**

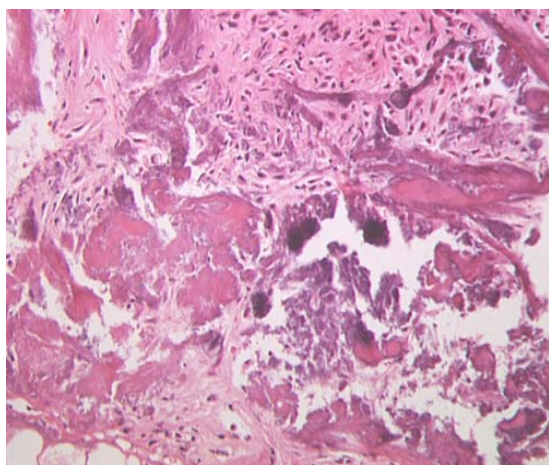
Calcium sulphate products are in general brittle and weak although the strength is also highly dependent on the form of calcium sulphate hemihydrate used to form the dihydrate. The  $\alpha$ -form provides a stronger product than the  $\beta$ -form, mainly due to differences in the density. Moisture also affects the strength. By wetting set calcium sulphate dihydrate as much as half of the strength might be lost. This is because the friction between the needles in the structure decreases which means that the crystals are able to slide more easily against each other and therefore the strength decreases. As a consequence, when measuring strength of calcium sulphate compounds over time, the results will be highly depending on whether the cured product has been stored in a dry or a wet environment.

### **Histology**

Animal studies have shown a good contact between calcium sulphate and the surrounding bone tissue with no or little inflammatory reaction. A common finding is a precipitated layer of a biological apatite on the material surface. It has been suggested that this layer might enhance cell attachment to the material. Once the material is implanted in a bone defect it starts to degrade. A process mainly described as a passive dissoluti-

on, commonly referred as a bulk erosion, caused by ion exchange with the body fluid (Figure 4). The speed of the degradation depends on defect size and location, but is generally in the range of 40-70 days. As there is no known cell-mediated regulatory connection between the passive degradation of calcium sulphate and the formation of new bone, there is a risk that the degradation might be too rapid. If so, new bone tissue will not grow in and remodel the defect and a new void will then appear before new bone has developed and filled out the defect. This complication has been described in clinical series, especially when using calcium sulphate to fill larger bone defects [15, 37].

**Figure 4.** Photomicrograph demonstrating degradation of calcium sulphate cement at



two weeks after implantation in a defect in canine (courtesy Dr Thomas W. Bauer).

## HydroSet™

In a recent project a new calcium phosphate based injectable cement, HydroSet™, was developed. The overall design criteria included improved curing and mechanical characteristics, improved handling and application properties, as well as improved acceptance of hardware when compared with existing calcium phosphate compounds such as BoneSource™ and Norian SRST™, two of the major products on the market.

## Chemical composition

HydroSet™ consists of three blended powder subcomponents (tetracalcium phosphate, dicalcium phosphate dihydrate and trisodium citrate) and a liquid solution (sodium phosphate, polyvinylpyrrolidone and water). The powder and the solution are hand mixed for 45 seconds using the supplied bowl and spatula after which the formed paste is transferred to a syringe that is held by a specifically designed device at an angle to ensure that the amount of trapped air in the cement is kept to a minimum (Figure 5). Such a consistent transfer process, from bowl to syringe, will ensure predictable viscosity and time to curing. Variables that are very important for the user in order to feel confident with the material.



**Figure 5.** The cement delivery syringe placed at an angle to aid cement transfer from mixing bowl to syringe. The cement paste can run slowly down the barrel without trapping air inside the syringe and thereby create a more consistent end product.

Once the powder and the solution are mixed the crystallization process starts. This process does not create any exothermic reaction. The curing speed is temperature sensitive but within normal temperature limits expected in an operating room, the material will be injectable up to about 4 minutes after mixing. The subsequent setting time lasts for about another 4 minutes after which the material has a “tap hard” texture when touched. HydroSet™ can be manipulated post-implantation giving surgeons the opportunity to refine the construction, including adding hardware with or without predrilling.

Once the material is fully cured, *in vitro* studies have shown that the material has got a slight expansion, of approximately 0.7%, compared with the volume directly after mixing [33]. This is very favourable when used for augmentation as the material through this slight and controlled expansion will add a slight additional pressure and support to the surrounding bone when used for bone void filling.

### **Mechanical characteristics**

*In vitro* testing have shown that HydroSet™ reaches about 55% of its final strength at 30 minutes after mixing and about 75% at 4 hours.

The compressive strength when fully cured at 24 hours is about 17 MPa, to be compared with the strength of cancellous bone that is in the range 2-12 MPa. Compared with the predecessor BoneSource™, the present material gain strength faster and thereby the risk for early secondary fracture displacement will be reduced. The strength when fully cured is more than doubled compared with the strength seen in BoneSource™. A summary of the compression strength *in vitro* for different injectable cement types is given in table 2. It should be noted that these samples were allowed set without any applied external force during the setting period so as to simulate the *in vivo* environment. When evaluating *in vitro* results for cement types that will undergo some type of degradation *in vivo*, it is important to remember that *in vitro* results can

not be taken as a prediction for the strength *in vivo* over time. A reasonable prediction of the strength to be expected when used in a clinical setting can only be obtained through well designed animal studies, i.e. *in vivo*, where the material is subjected to a biological environment, including normal cell activity. When trying to foresee the mechanical strength over time *in vivo*, there are reasons to believe that CaS compounds, such as MIIG X3, might dissolve rather quickly and thereby lose the mechanical strength more rapidly than what can be expected for the CaP products [27].

### **Preclinical animal studies**

In two animal studies using adult mongrel dogs a subchondral defect of about 2x1.5x1.5 cm was created in the proximal tibia through a lateral incision. Following irrigation and cleaning of the defect, HydroSet™ was hand mixed and transferred to a syringe, after which it was injected to fill out the defect. The main priority of these animal studies was to validate critical aspects of the cement design using surgeon feedback and to validate specific handling characteristics as well as assess potential risks as defined through a previous risk analysis.

The tests revealed that the handling characteristics were considered as very good by the participating surgeons. The main advantages compared with similar products on the market included a very good injectability and a reliable handling in a wet environment with a low tendency for washout. During the early phase of the study the setting time varied between tests. By refining the mixing procedure into a more stringent and consistent way of mixing this potential problem was solved. As a minor part of this study the ability for the material to be used for screw augmentation was examined. Following injection of the cement a 2.5 mm drill was used to create a hole through the cement once it had cured for a few minutes. A 3.5 mm self threaded cortical screw was then inserted after which the holding power was assessed through manual traction. A common finding was that the drilled canal

Product	Lot No.	Time	Compressive Strength (MPa)			
			Batch 1 (n=5)	Batch 2 (n=5)	Batch 3 (n=5)	Mean
HydroSet™	BT010510 BT010310	30mins	9.25	13.73	11.13	11.20
		4hr	13.07	15.82	17.01	15.30
		24hr	17.43	13.98	16.28	15.90
		2weeks	10.34	11.74	8.72	10.27
B o n e - Source™	BS05266	30mins	1.17	1.43	1.53	1.38
		4hr	4.24	4.57	3.59	4.13
		24hr	8.82	8.54	6.89	8.08
		2weeks	16.86	17.69	17.67	17.41
a-BSM™	ZK7LH400 0	30mins	5.14	4.19	5.65	4.99
		4hr	5.30	4.11	5.99	5.13
		24hr	2.99	1.75	2.74	2.50
		2weeks	1.09	1.89	1.55	1.51
MIIG X3™	124155498 025177386	30mins	21.72	23.63	27.12	24.16
		4hr	24.51	26.88	23.64	25.01
		24hr	30.15	26.27	22.78	26.37
		2weeks	18.33	16.66	16.38	16.52
N o r i a n SRS™	N519101 N519103 N633101 N644802	30mins	10.80	9.65	8.52	9.66
		4hr	11.27	13.36	13.53	12.72
		24hr	16.62	17.00	22.39	18.67
		2weeks	13.90	21.97	20.05	15.64

**Table 2.** Average compressive strength (MPa) in vitro for injectable cement cylinders following incubation in sodium phosphate buffer at 37°.

Failure occurred by shear through the cement at the periphery of the threads.

In summary, the participating surgeons assessed that the product had very good handling characteristics and a very favorable risk profile when used for filling of bone voids as well as when used for augmentation of screws in animal models.

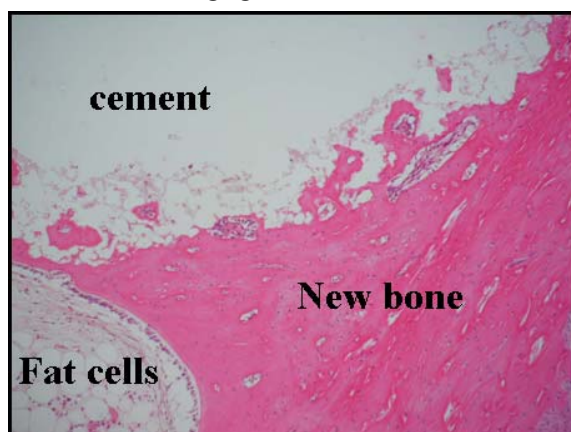
(\*The FDA and CE notified bodies have currently not cleared this cement for the screw augmentation use described here.)

In an animal model performed with New Zealand white rabbits, HydroSet™ was compared with two well established injectable calcium phosphate cements, Bone-

Source™ (Stryker inc) and Norian SRS™ (Synthes inc). Following predrilling in the femoral condyle, cement was injected after which the cortical opening was closed with a threaded plug. Evaluation was performed after 24 hrs (XRD analysis) and after 6 weeks (histology) and 26 weeks (histology and XRD analysis). The main questions to be addressed were: 1) will the cements initiate an adverse biological response, 2) will the cements convert to hydroxyapatite and 3) will it resorb over time?

The study showed a good penetration of HydroSet™ into the cancellous bone surrounding the drilled canal with no signs of

disintegration. All three cements tested were highly biocompatible with no adverse effects on tissues or recruitment of inflammatory cells in any of the specimens. The XRD analysis showed a conversion of all cements into crystalline hydroxyapatite. TRAP-positive cells were found indicating that the resorption of the cements occurred by a cell mediated process, although quantitative measurements showed that the resorption of all cements between 6 and 26 weeks was negligible.



**Figure 6:** Photomicrograph demonstrating good tissue response at the interface between HydroSet™ and bone at 6 months after implantation in a defect in the distal femora of a rabbit.

### Discussion

Over the last decades there has been a shift in the orthopaedic community in favour of operative treatment followed by active rehabilitation for many fracture types that previously were treated conservatively with plaster, braces or traction in bed. There are many reasons for this shift including development of improved internal and external implants that makes it possible to achieve stable bone-implant constructs that will allow early active rehabilitation and a favourable outcome. A second main factor that is driving this trend towards a more active fracture treatment is the pressure applied from patients, independent of age, to regain the prefracture level of function as fast as possible. For many fracture types the advancements in the implant technology combined with improved less invasive surgical techniques and peroperative imaging makes

it possible to fulfil these goals. However, this is especially true for midshaft fractures in long bones in patients with normal bone quality. Within the rapidly increasing group of patients with reduced bone strength due to osteoporosis, fixation of shaft fractures as well as fractures close to joints still present a frequent challenge to the surgeon, i.e. the standard of care can be improved. The classic way to address this increasing problem has been by the development of new metal implants. An additional or alternate strategy has been to develop methods for augmentation of the weak bone that surrounds the metal implant.

With the recent introduction of injectable osteoconductive calcium phosphate cements a new treatment strategy has become possible for treating selected fractures especially in the metaphyseal region of long bones. These cements harden without producing heat, develop reasonable compressive strength, and are slowly remodelled in vivo through a cell-mediated process. The main purpose of the cement is to fill voids in metaphyseal bone and thereby reduce the need for bone graft, but osteoconductive cements may also improve the holding strength around metal devices and then especially around screws when used in osteoporotic bone.

Until now the available cement types, i.e. the first generation bioactive cements, have got limitations including limited strength especially in shear, an important mechanical variable when treating fractures, as well as suboptimal handling and application characteristics. The limitations for the first generation of cements have restricted their use to non weight bearing indications.

With the development of HydroSet™, the second generation of bioactive cement types can be seen. The handling properties, the earlier development of mechanical strength, the ease of flow during injection and the resistance to wash-out in a wet environment have been extensively improved. Factors that will provide the surgeon with a product that is far more consistent and predictable

compared with the first generation of cements. The improved strength, especially in shear, combined with the slow cell-mediated remodelling will ensure a good efficacy. Based on the known properties, this cement will most likely work very well also in weight bearing indications, although so far there are no clinical data available to support this.

The goal with respect to mechanical strength when developing a bioactive cement is not necessarily to create a "maximal" strength. Instead the goal must be to create a cement that is so strong that it will not become the weak link in the bone-implant construct that the surgeon is creating when fixing a fracture. It therefore seems more appropriate to discuss adequate mechanical properties rather than "maximal" strength, including also the stiffness or the modulus of elasticity. If the cement is too stiff, there might at least theoretically be a risk for local overloading of the cartilage when the cement is being used for filling of subchondral voids.

Apart from adequate strength in compression and shear immediately after surgery, it is of outmost importance that the cement can provide adequate mechanical support not only during the initial phase following surgery but all the way until the bone healing process has restored the mechanical integrity to the bone. Due to the slow remodelling process seen with HydroSet™ the mechanical strength will remain intact for a period that exceeds the bone healing. There is therefore no risk for a too rapid dissolution that might occur when using calcium sulphate compounds. As HydroSet™ undergoes a cell-mediated remodelling the resorption speed can not exceed the bone forming capacity. This is especially important when treating elderly osteoporotic patients who might have a slower bone forming capacity compared with younger individuals.

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