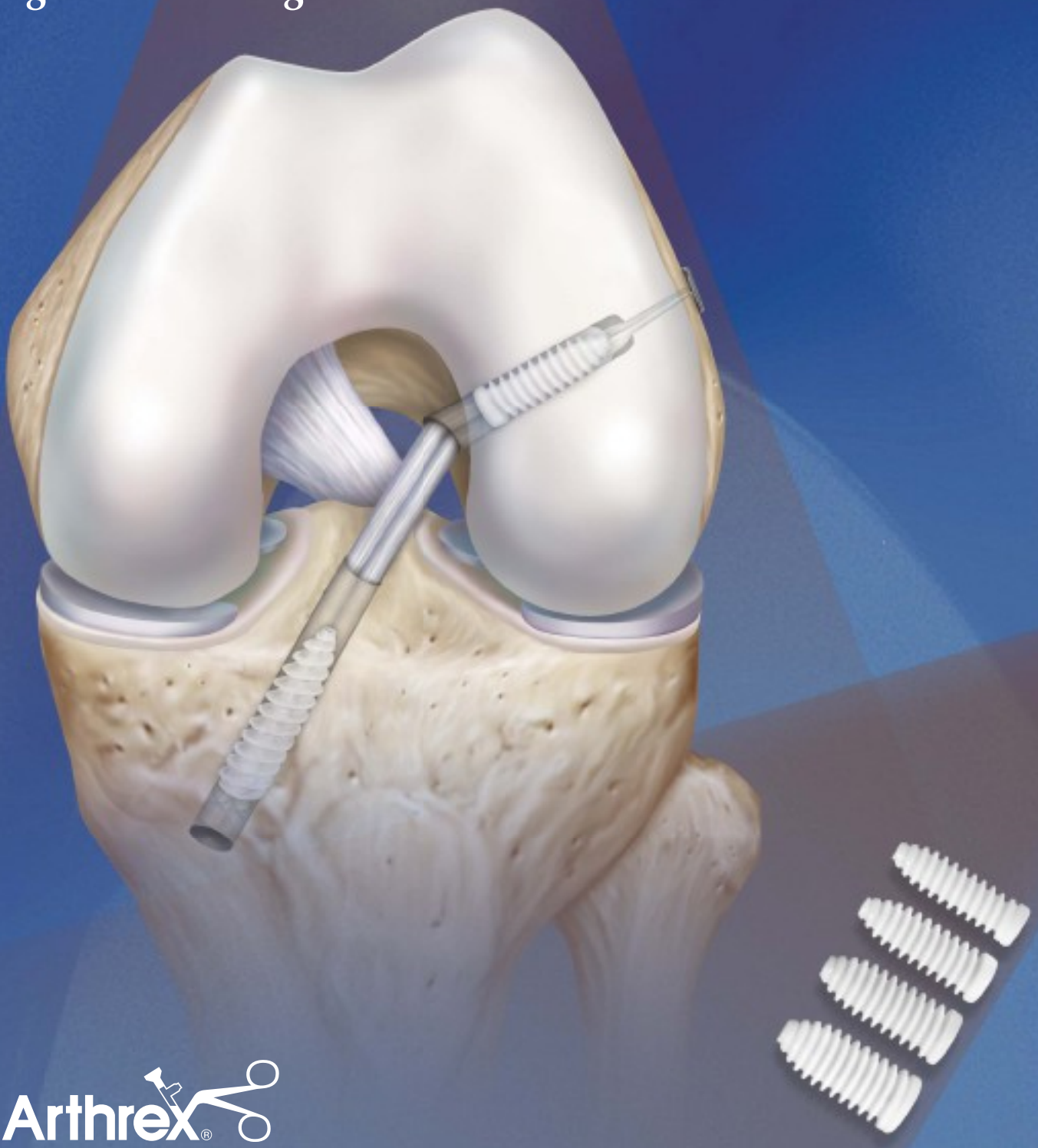
Vis d'Interférence BioComposite

La révolution dans les systèmes de fixation ligamentaire du genou



Arthrex®

Les Vis d'Interférence BioComposites

Les Vis d'Interférence BioComposites contiennent 30% de phosphate de calcium biphasé (BCP) et 70% de PLDLA. Elles ont été conçues comme système de fixation de transplants (tendon rotulien ou tendons de la patte d'oie) pour la chirurgie de reconstruction du LCA ou du LCP.
La méthode de fabrication et la technique de mélange des composants donnent une solidité accrue à l'implant en réduisant à leur minimum les zones de concentrations de contraintes. De plus, la matrice macro et micro poreuse ainsi produite facilite la colonisation osseuse, l'ostéointégration de l'implant, sa résorption ainsi que le remodelage osseux.
Le nouveau système canulé Hexalobe de la vis permet l'usage d'un tournevis unique quelle que soit la taille de la vis, et améliore de façon significative la résistance au couple de vissage. Le tournevis pénètre sur toute la longueur de la vis, et la surface de contact est augmentée.
Des publications cliniques ont montré que l'utilisation du phosphate de calcium biphasé est sûre et qu'elle est adaptée à la chirurgie orthopédique. D'autres études sur les produits de comblement osseux ont mis en évidence le lien étroit entre l'ostéogénèse précoce et les propriétés d'ostéoconductivité et de biorésorbabilité du BCP.

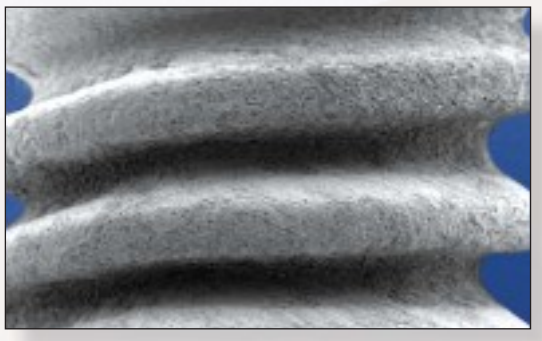
Caractéristiques et Avantages

Une combinaison optimale de matériaux

- **Phosphate de Calcium Biphasé (BCP)**
  - Matériau connu pour son ostéoconductivité
  - Ce mélange d'hydroxyapatite (HA) et de phosphate tricalcique ß (ß-TCP) permet un meilleur équilibre d'adhésion et de prolifération des ostéoblastes que ces deux matériaux utilisés séparément[1].
  - La solubilité maitrisée du BCP et le relâchement d'ions calcium favorisent une ostéogénèse naturelle et équilibrée[5,2]
  - Formation d'un lien solide et dynamique à son interface avec l'os[5,2]
  - Recul clinique important en tant que substitut osseux biorésorbable, étudié dans de nombreux articles scientifiques[4]

- **Polymère de PLDLA amorphe**
  - Cinétique de résorption prédictible et contrôlée[3]
  - Prévalence de lésions ostéolytiques très inférieure à des matériaux à absorption rapide tels que les polymères et co-polymères PGA
  - Pas de produits cristallins de dégradation relâchés sur le site de l'implant
  - Recul clinique important en tant que polymère biorésorbable d'utilisation sûre comme en attestent de nombreux articles scientifiques[4]
  - Meilleur potentiel d'ostéogénèse de tous les polymères disponibles[4]

Vis BioComposite de 23 mm



Grossissement 25 x

Une conception innovante

- **Vis d'Interférence BioComposite**
  - Le processus de mélange et de fabrication du matériau est optimisé pour augmenter la résistance mécanique sans que le matériau ne devienne cassant, résultant en un mélange homogène sur la totalité du volume de l'implant.
  - La structure micro et macro-poreuse formée favorise l'adhésion et la colonisation cellulaire.
  - Résistance incomparable du filetage aux forces de cisaillement[1].
  - Géométrie du filetage optimisée pour faciliter l'insertion de la vis tout en maximisant la fixation d'os comme de tissus mous dans de l'os cortical ou spongieux.
  - Le design progressif du filetage de la vis maximise le couple de vissage lorsque la vis est totalement insérée.
  - La résistance du matériau permet une implantation de la vis qui dans la majorité des cas, ne nécessite pas de taraudage préalable

- **Interface Hexalobe**
  - Nouveau système révolutionnaire qui maximise la surface de contact entre la vis et le tournevis éliminant le risque de rupture de la vis. Le tournevis s'engage sur toute la longueur de la vis pour une assise complète lors de l'insertion.
  - Le tournevis universel canulé est compatible avec toutes les tailles de vis et permet le vissage sur une broche guide.
  - Les marquages laser sur la tige du tournevis confirment visuellement la bonne assise de la vis sur toute sa longueur avant son insertion, et peuvent également servir comme mesureur de profondeur.
  - Tournevis, à cliquet ou non, existant en système à encliquetage rapide et en système monobloc

Design Hexalobe de la Vis BioComposite

Coupe d'une Vis BioComposite sur son tournevis

Tournevis à cliquet à encliquetage rapide

Informations & Références Produits

Vis d'interférence BioComposite

Vis d'interférence BioComposite, 7 mm x 23 mm	AR-1370C
Vis d'interférence BioComposite, 8 mm x 23 mm	AR-1380C
Vis d'interférence BioComposite, 9 mm x 23 mm	AR-1390C
Vis d'interférence BioComposite, 10 mm x 23 mm	AR-1400C
Vis d'interférence BioComposite, FT 7 mm x 28 mm	AR-1370TC
Vis d'interférence BioComposite, FT 8 mm x 28 mm	AR-1380TC
Vis d'interférence BioComposite, FT 9 mm x 28 mm	AR-1390TC
Vis d'interférence BioComposite, FT 10 mm x 28 mm	AR-1400TC
Vis d'interférence BioComposite, FT 11 mm x 28 mm	AR-1403TC
Vis d'interférence BioComposite, FT 12 mm x 28 mm	AR-1404TC
Vis d'interférence BioComposite, Tête ronde - Profil Delta 8 mm x 28 mm	AR-5028C-08
Vis d'interférence BioComposite, Tête ronde - Profil Delta 9 mm x 28 mm	AR-5028C-09
Vis d'interférence BioComposite, Tête ronde - Profil Delta 10 mm x 28 mm	AR-5028C-10
Vis d'interférence BioComposite, Tête ronde - Profil Delta 11 mm x 28 mm	AR-5028C-11
Vis d'interférence BioComposite, Profil Delta 9 mm x 35 mm	AR-5035TC-09
Vis d'interférence BioComposite, Profil Delta 10 mm x 35 mm	AR-5035TC-10
Vis d'interférence BioComposite, Profil Delta 11 mm x 35 mm	AR-5035TC-11
Vis d'interférence BioComposite, Profil Delta 12 mm x 35 mm	AR-5035TC-12

Instrumentation nécessaire

Tournevis monobloc pour Vis d'interférence BioComposite	AR-1996CD
Tige de tournevis à encliquetage rapide pour Vis BioComposite	AR-1996CD-1
Poignée pour tournevis à encliquetage rapide à cliquet	AR-1999
Poignée pour tournevis à encliquetage rapide standard	AR-1999NR
Pointeau pour encoche de tunnel pour Vis d'interférence biorésorbable	AR-1845
Dilatateur universel canulé pour vis biorésorbable	AR-1377M

Instruments optionnels

Tige de taraud à encliquetage rapide pour vis BioComposite, 7 mm	AR-1996CT-07
Tige de taraud à encliquetage rapide pour vis BioComposite, 8 mm	AR-1996CT-08
Tige de taraud à encliquetage rapide pour vis BioComposite, 9 mm	AR-1996CT-09
Tige de taraud à encliquetage rapide pour vis BioComposite, 10 mm	AR-1996CT-10
Boite d'instrumentation pour vis BioComposite	AR-1996C

Consommables et accessoires

Kit usage unique pour LCA transtibial avec lames de type Hall, qté 5	AR-1897S
Kit usage unique pour LCA transtibial sans lames, qté 5	AR-1898S

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4. Weiler, et al, Biodegradable Implants in Sports Medicine: The Biologic Base, *Arthroscopy*, Vol 16, No 3, 2000: 305-321.
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Arthrex
BioComposite Interference Screws for ACL and PCL Reconstruction

Arthrex Research and Development

Introduction

Arthrex has developed a new absorbable composite interference screw for graft fixation in ACL and PCL reconstruction procedures, combining the resorbability of a biocompatible polymer with the bioactivity of a ceramic. The BioComposite Interference Screw is a combination of 70% poly(L-lactide-co-D, L-lactide) (PLDLA) and 30% biphasic calcium phosphate (BCP).

Material Composition

Biodegradable polymeric materials such as polylactide (PLA) and polyglycolide (PGA) have been used in orthopaedic applications since the 1970s, when sutures made from these materials were approved for use by the FDA. Both materials are easily degraded within the body - PLA into lactic acid and PGA into glycolic acid. PLA is a crystalline material with a slow resorption rate, while PGA is amorphous and resorbs much faster. PLA and PGA materials can be combined in different ratios to produce poly(lactide-co-glycolide) (PLGA) polymers with variable degradation rates. PLA exists in two isomeric forms, L-lactide and D-lactide. L-lactide is more commonly found and semi-crystalline, while D-lactide is much less common and amorphous. Even combining just these PLA isomers alone can also alter degradation time and mechanical strength. The 70:30 L:DL ratio in the PLDLA material in our BioComposite Interference Screw results in retention of ½ of its tensile strength after 32 weeks and ½ of its shear strength after 45 weeks *in vitro* [1]. Implanted pins made from 70:30 PLDLA, as in our product, were completely replaced by new bone at 36 months *in vivo* in an osteochondral fracture [2], while complete *in vitro* degradation occurred at about 18 months [3]. Spinal cages made from the same 70:30 PLDLA were completely degraded *in vivo* by 12 months [4]; this can be attributed to the location of the implant in the spine vs. in an osteochondral defect. The degradation of PLDLA falls between poly(L-lactide-co-D-lactide) (PLDA), with a degradation time of 12-16 months, and poly(L-lactide) (PLLA), with a degradation time of 36-60 months [5].

Ceramics such as hydroxyapatite (HA) and Beta-tricalcium phosphate (ß-TCP) are commonly used as bone void filler materials because of their excellent bone biocompatibility and similarity in mineral content to natural bone. However, as seen with polymers, these materials have resorbability issues. HA is crystalline and has a slow resorption rate on the order of years [6], ideal for maintaining structure, but can lead to ingestion of ceramic particulates by surrounding tissues. ß-TCP is amorphous and resorbs quickly, not leaving enough time for new bone to replace the material in the defect site. Combining the resorption rates of HA and ß-TCP would be ideal. A new class of ceramic materials, biphasic calcium phosphates (BCPs) [7], can be created by combining HA and TCP in different ratios, resulting in a range of controllable resorption profiles. Typical commercial BCP formulations can vary in HA:ß-TCP ratio from 60:40 to 20:80. The ratio of calcium to phosphorus (Ca/P) in bone and HA is 1.67, which is considered "optimal". Calcium-deficient BCP has a Ca/P ratio lower than 1.67, which is controlled by the amount of HA to ß-TCP in the base material, after being sintered at a high temperature to convert the ceramic to a mixture of the two ceramics. It has been demonstrated that using a homogeneous calcium-deficient HA powder to form BCP as opposed to physically combining separate HA and ß-TCP powders results in higher compressive strength and less degradation *in vivo* [8]. Physically combining the powders might create voids in the final material, leading to the decrease in strength and increase in degradation. BCP also has the ability to support new bone formation much better than HA or ß-TCP alone, since studies have shown new bone formation without a fibrous tissue layer at earlier timepoints with BCP as opposed to HA or ß-TCP separately [9]. The 60:40 biphasic ratio of HA: ß-TCP in our BioComposite Interference Screw shows good mechanical strength in a rabbit segmental defect model compared to pure HA [10] and shows excellent biocompatibility without a fibrous interface in a rat calvarial defect model both with and without platelet-rich plasma (PRP) [11].

An osteoconductive material supports bone formation, propagation, and growth, and provides suitable mechanical

strength when the right cells, growth factors, and other signals are in the vicinity. A study comparing PLDA and PLDA-ß-TCP interference screws to titanium interference screws found that the composite screws had higher pull-out strength and stiffness compared to the metallic screws [12]. Combining HA and BCP ceramics to PLA-urethane materials also results in higher dynamic modulus [13]. Another study found that as BCP content increases in PLDLA materials, ultimate tensile strength decreases, but is still within range for bone fixation materials [14]. A 70:30 PLDLA spinal cage, containing BCP particles in a 60:40 HA:ß-TCP ratio and combined with adipose-derived stem cells, showed new bone formation and osteoclast activity on the BCP after 4 weeks [15], similar to what studies using these materials separately have found. If the optimal properties of PLDLA and BCP can be combined in a spinal application, as shown above, similar results can be theorized in ACL and PCL reconstruction.

Arthrex vs. Our Competitors' Composite Screws

Table 1 shows the material composition of the Arthrex BioComposite Interference Screw vs. our competitors' composite screws. The ratio of polymer to ceramic in a composite material should be optimized for mechanical strength and material behavior. Either lowering or raising the amount of polymer and/or ceramic material can affect strength at the interface by making the screw brittle or pliable, or possibly increase resorption via acidosis. Polymer degradation that occurs too quickly can lead to a pH drop, therefore increasing the activity of osteoclasts [16] to resorb tissue and screw material and weaken the interface.

Manufacturer	Product Name	Material Composition
Arthrex	***BioComposite Interference Screw***	***70% PLDLA & 30% BCP***
DePuy Mitek	Milagro	70% PLGA & 30% ß-TCP
DePuy Mitek	BioCryl	70% PLLA & 30% ß-TCP
Smith & Nephew	BioRCI-HA	95% PLLA & 5% HA
ConMed Linvatec	Matryx	Self-reinforced (SR) 96/4 PLDA and ß-TCP
Stryker	BiOsteon	75% PLLA and 25% HA
ArthroCare	BiLok	75% PLLA and 25% ß-TCP

Table 1

Controlled Solubility

Studies of the material properties of the BioComposite Interference Screw show that molecular weight (MW, Figure 1a) and inherent viscosity (IV, Figure 1b) drop slowly and uniformly from time 0 up to 12 weeks; however, the mechanical strength at both timepoints is equivalent.

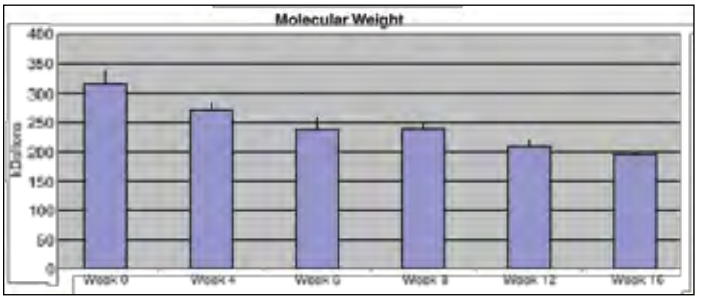

Figure 1a

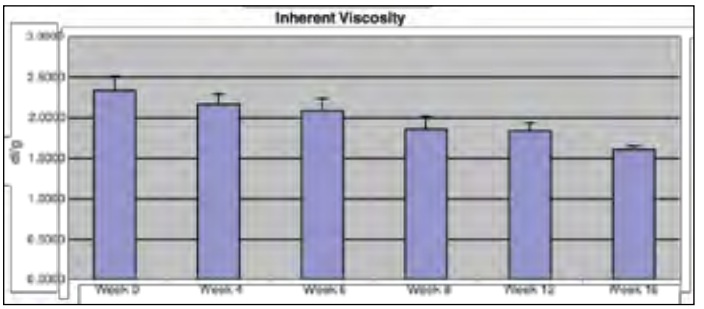

Figure 1b

Imaging characterization of the BioComposite Interference Screw shows uniform dispersion of the ceramic material within the screw structure (Figure 2). The green fluorescent stain represents the inorganic ceramic material within the screw, going from the center cannulated portion of the screw, all the way down to the threads (white arrows).

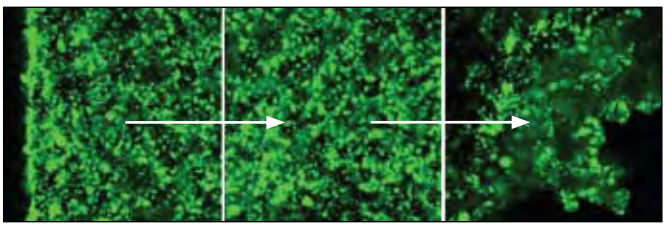

Figure 2

Testing found that 10 mm BioComposite Delta Screws, using a hexalobe driver, had a lower cyclic displacement and higher loads-to-failure compared to Milagro screws (Table 2), with similar insertion torques for both. It is important to note that these screws were not tested side-by-side in the same study. It is also important to note that the number of Milagro screws tested was low, but the initial trend indicates higher insertion torque for Milagro compared to the BioComposite Interference Screws.

	Milagro 10 mm (n=2)	BioComposite Delta 10 mm (n=6)
Insertion Torque (in-lbf)	**29 ± 11**	**28 ± 4**
Cyclic Displacement (mm)	**4.6 (n=1)**	**3.5 ± 1.5**
Yield Load-to-Failure (N)	**728 (n=1)**	**1053 ± 378**
Ultimate Load-to-Failure (N)	**877 ± 8**	**1206 ± 248**

Table 2

	9 mm Delta	10 mm Delta	11 mm Delta	12 mm Delta
Insertion Torque (in-lbf)	26 ± 7	28 ± 4	29 ± 5	35 ± 7
Cyclic Displacement (mm)	3.7 ± .7	3.5 ± 1.5	3.6 ± .5	3.6 ± .8
Yield Load-to-Failure (N)	783 ± 207	1053 ± 378	958 ± 189	837 ± 191
Ultimate Load-to-Failure (N)	955 ± 219	1206 ± 248	1071 ± 165	1029 ± 128

Table 3

In Vitro Testing

In vitro studies show similar amounts of human osteoblast adhesion after 24 hours (Figure 3a) and proliferation after 48 hours (Figure 3b) on the BioComposite Interference Screws vs. Milagro screws. Human osteoblasts were seeded onto all surfaces, including tissue culture polystyrene (TCP) as a control, at a density of 20,000 cells/cm^2. Adhesion after 24 hours was determined by counting in a Coulter counter, while proliferation at 48 hours was determined by measuring thymidine incorporation.

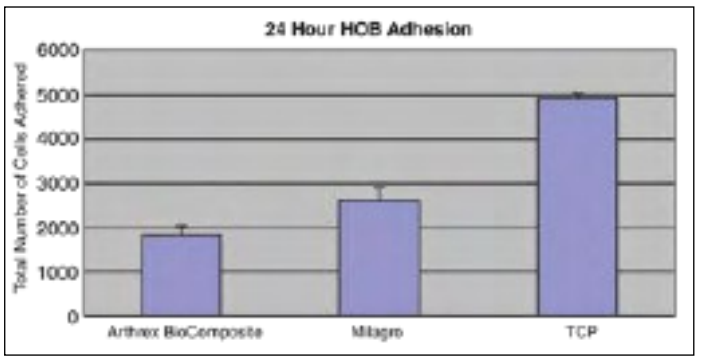

Figure 3a

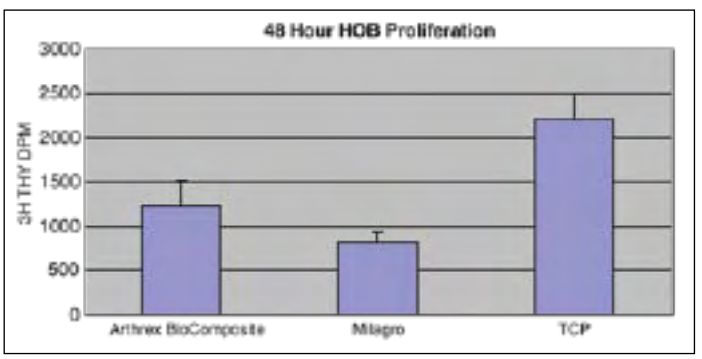

Figure 3b

Animal Testing - 12 Weeks

Computed tomography (CT) data indicate no substantial degradation *in vivo* in an ovine ACL reconstruction model at 12 weeks for either the BioComposite Interference Screw (Figure 4a) or the Milagro screw (Figure 4b) in a tibial insertion site. Hematoxylin and eosin (H&E) histology at 12 weeks shows a minimal inflammatory response for both the BioComposite Interference Screw (Figure 5a) and the Milagro screw (Figure 5b), also in a tibial insertion site.

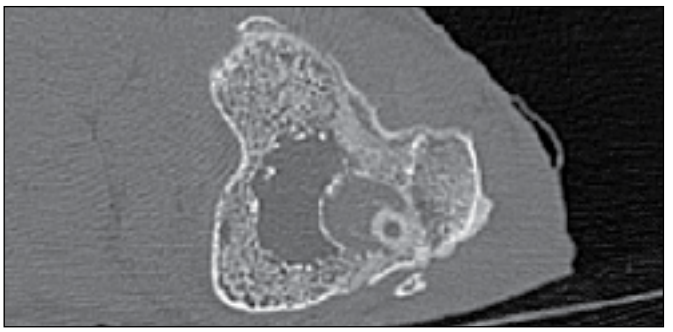

Figure 4a

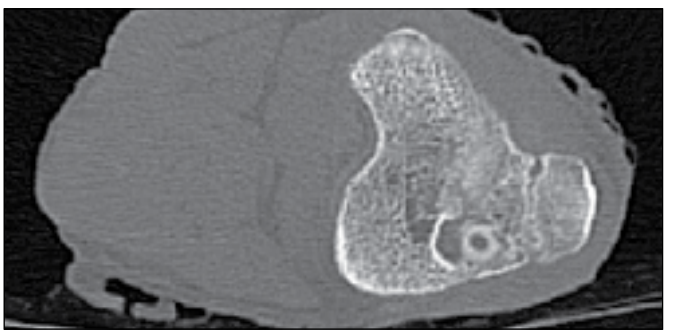

Figure 4b

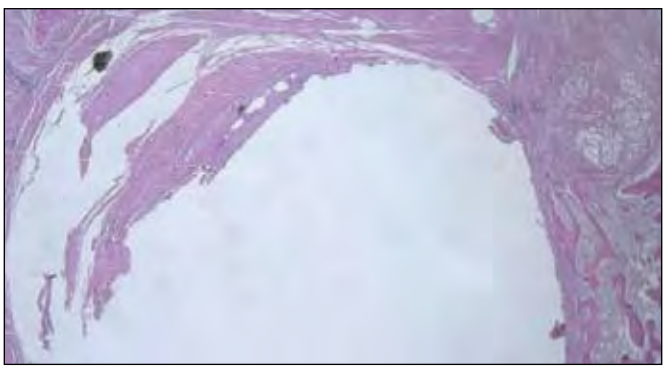

Figure 5a

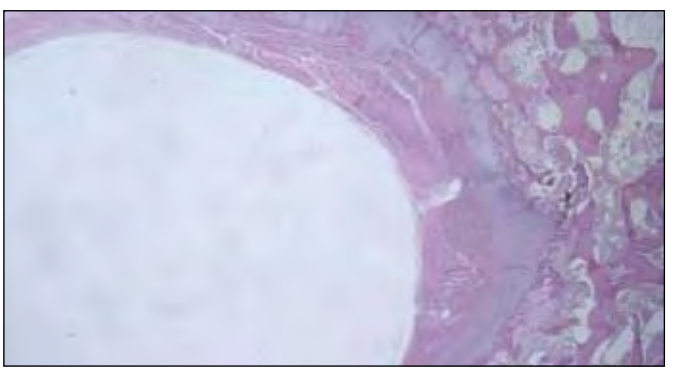

Figure 5b

Animal Testing - 26 Weeks

CT data at 26 weeks again shows no significant degradation for either screw type. However, initial bone integration at the tibial insertion site is seen with the BioComposite Interference Screws (Figure 6a), while minimal to no bone integration is seen with the Milagro screws (Figure 6b). Histology of the tendon-bone interface at the tibial insertion site shows Sharpey's fibers (black arrows) between tendon and bone using the BioComposite Interference Screws (Figure 7a), while there was close direct contact without Sharpey's fibers between the tendon and bone using the Milagro screws (Figure 7b). New bone (black arrows) was seen within the tibial screw site of the BioComposite Interference Screws (Figure 7c). The Milagro screws also have some minimal new bone within the tibial screw site (Figure 7d, black arrow). Both screw types also had a layer of fibrous tissue at the screw-tissue interface (not pictured).

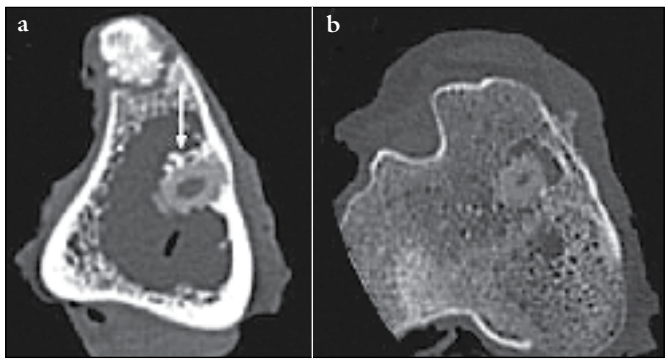

Figure 6

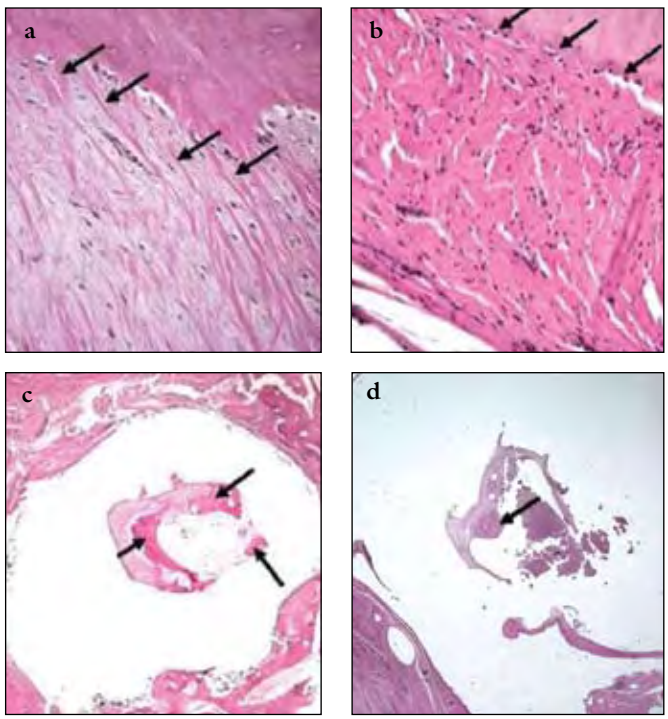

Figure 7

Animal Testing - 52 Weeks

CT data at 52 weeks at the tibial insertion site shows that the BioComposite Interference Screw keeps its shape and is well-integrated into cortical bone (Figure 8a), with some cancellous bone apposition. The Milagro screw (Figure 8B) is starting to lose its shape and does not integrate well with its surrounding bone. Histology at the tibial insertion site shows that the BioComposite Interference Screw has new bone (black arrow) within the screw site (Figure 9a), with some fibrous tissue. The Milagro screw (Figure 9b) also has a thin tract of new bone (black arrow), along with some fibrous tissue, in the screw site. In the femoral tunnel site, the BioComposite Interference Screw (Figure 9c) and the Milagro screw (Figure 9d) both show varying amounts of fibrous tissue at the screw-tissue interface.

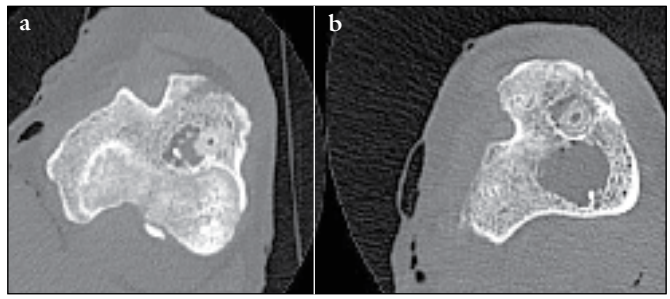

Figure 8

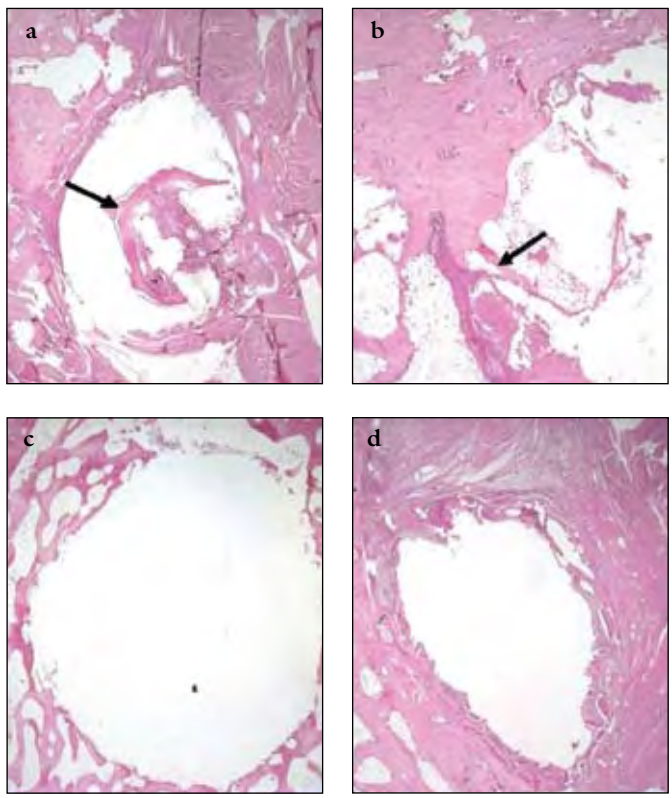

Figure 9

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Current state of the art of biphasic calcium phosphate bioceramics

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We have developed 15 years ago, with the collaboration of Lynch, Nery, and LeGeros in the USA, a bioactive concept based on biphasic calcium phosphate (BCP) ceramics. The concept is determined by an optimum balance of the more stable phase of HA and more soluble TCP. The material is soluble and gradually dissolves in the body, seeding new bone formation as it releases calcium and phosphate ions into the biological medium.

The bioactive concept based on the dissolution/transformation processes of HA and TCP has been applied to both Bulk, Coating and Injectable Biomaterials. The events at the calcium phosphate (CaP) biomaterial/bone interface represent a dynamic process, including physico-chemical processes, crystal/proteins interactions, cells and tissue colonization, bone remodeling, finally contributing to the unique strength of such interfaces. An important literature and numerous techniques have been used for the evaluation of the fundamental physico chemical and biological performance of BCP concept. This type of artificial bone used from a long time in preclinical and in clinical trial, revealed the efficiency for bone filling, performance for bone reconstruction and efficacy for bone ingrowth at the expense of the micro macroporous BCP bioceramics.

The development of calcium phosphate ceramics and other related biomaterials for bone graft involved a better control of the process of biomaterials resorption and bone substitution. Synthetic bone graft materials are available as alternatives to autogeneous bone for repair, substitution or augmentation. Synthetic biomaterials include essentially special glass ceramics described as bioactive glasses; calcium phosphates (calcium hydroxyapatite, HA; tricalcium phosphate, TCP; and biphasic calcium phosphate (BCP)). These materials differ in composition and physical properties from each other and from bone [1–4]; and must be take into consideration for more efficient bone ingrowth at the expense of the biomaterials and to adapt to new development of dedicated biomaterials.

We have developed 15 years ago, with the collaboration of Lynch, Nery, and LeGeros in USA, a bioactive concept based on BCP ceramics. The concept is determined by an optimum balance of the more stable phase of HA and more soluble TCP. The material is soluble and gradually dissolves in the body, seeding new bone formation as it releases calcium and phosphate ions into the biological medium [5–8]. BCP bioceramics consists of a mixture of hydroxyapatite (HA), $Ca_{10}(PO_4)_6(OH)_2$ and beta-tricalcium phosphate (β-TCP), $Ca_3(PO_4)_2$ of varying HA/β-TCP ratio. LeGeros initiated in USA basic studies on preparation of BCP and their *in vitro* properties in 1986 and Daculsi in France. At the present time, BCP is commercially available in Europe, Brazil, Japan, USA, Australia as a bone-graft or bone substitute materials for orthopaedic and dental applications under various trade mark (BCP®, MBCP®, Triosite®, Hatric®, Eurocer®, Biceram®, Bicalfoss® ...). It is now available in blocks, particulates, customized design (Fig. 1) and as an injectable material in a polymer carrier (Fig. 2).

BCP is obtained when a synthetic or biological calcium deficient apatite (CDA) is sintered at temperatures above 700 °C. The extent of calcium deficiency (Ca/P molar ratio < 1.67) depends on the method of preparation (by precipitation, hydrolysis or mechanical mixture), the reaction pH and temperature in the preparation of the unsintered apatite. The calcium deficiency determines the HA/β-TCP ratio in the BCP. The HA/β-TCP ratio in the BCP determines its reactivity [6, 8–10]: the lower the ratio, the higher the reactivity (expressed *in vitro* as the extent of dissolution in an acid buffer). Particle size, macro porosity and micro porosity (Figs. 3(a) and (b)) are also factors in the reactivity of BCP. Sintering temperature and conditions affect these properties.

The interest of BCP concept is the controlled dissolution and due to the structure, the bone ingrowth at the expense of the ceramic. Between 1920 and 1975, a very limited number of scientific articles reported that the use of calcium phosphate materials, described as ''tricalcium phosphate'', to repair bone defects successfully promoted bone formation [11, 12]; or periodontal

Figure 1 MBCP® block, granules, cylinders, wedges and customized design available for bone reconstruction.

Figure 2 Injectable Bone Substitute IBS™, MBCPgel® composite of BCP granules and hydrosoluble HPMC polymer.

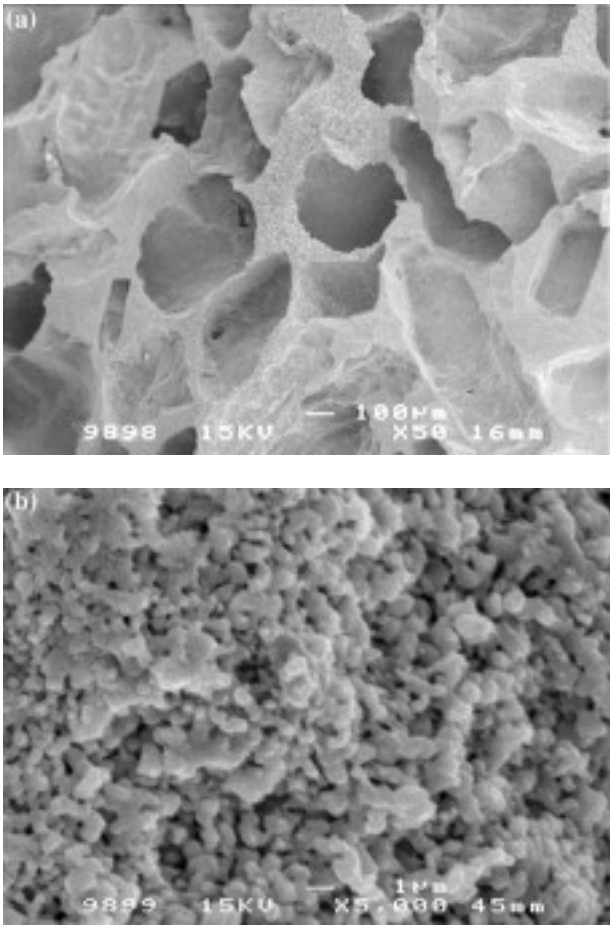

Figure 3 SEM of Triosite® blocs showing macroporous structure (a) and micropore (b).

defects [13]. The ''tricalcium phosphate'' material used by Nery was subsequently identified by LeGeros in 1988 as consisting of a mixture of 20% β-TCP and 80% HA [18]. This material and other mixtures of ß-TCP and HA were later described as a BCP.

The main attractive feature of bioactive bone graft materials such as BCP ceramic is their ability to form a strong direct bond with the host bone resulting in a strong interface compared to bio inert or bio tolerant materials which form a fibrous interface [1, 2, 14, 15].

The formation of this dynamic interface is believed to result from a sequence of events involving interaction with cells; formation of carbonate hydroxyapatite CHA (similar to bone mineral) by dissolution/precipitation processes.

Cellular events

The BCP materials elicit responses from bone cells and related cells *in vitro* and *in vivo* that are similar to those elicited by bone. These materials allow cell attachment, proliferation and expression. The first biological events after BCP ceramics implantation are biological fluid diffusion, followed by cells colonization. These cells are macrophages, in early steps, followed by mesenchymal stem cells, osteoblasts, osteoclasts, into the macropores of the implants (Fig. 4). The resorbing cells forming both at the surface of the newly formed bone and the bioceramic surface looks like osteoclast and are TRAP positive (Fig. 5). In human spine arthrodesis we have demonstrated what after a couple of months bone remodeling occurs, with secondary osteoclast resorption of the artificial bone and bone ingrowth at the expense of the implant (Fig. 6).

Generally when granules are used in osteo-articular surgery, some grains will be released in cartilage or non osseous site. Neither it was described foreign body reaction and rejected materials. Resorption or tissue incorporation was demonstrated. For example, in human spine arthrodesis after 3.5 months of implantation, granules of Triosite® appears surrounded by newly

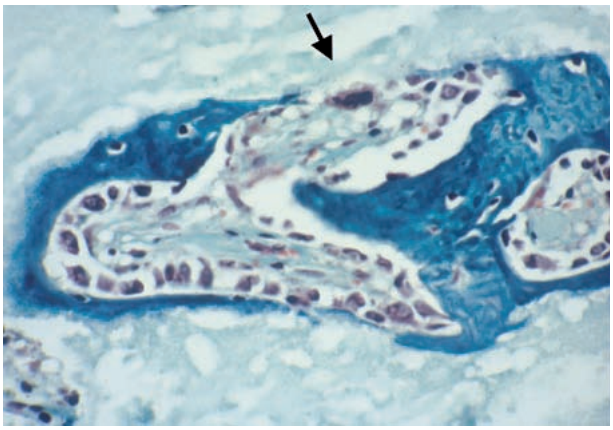

Figure 4 Newly formed bone into MBCP™ or Triosite® macropore in femoral epiphysis of rabbit after 14 days of implantation showing osteoclasts (arrow) and osteoblasts. Decalcified section stained with Masson's Trichromic staining.

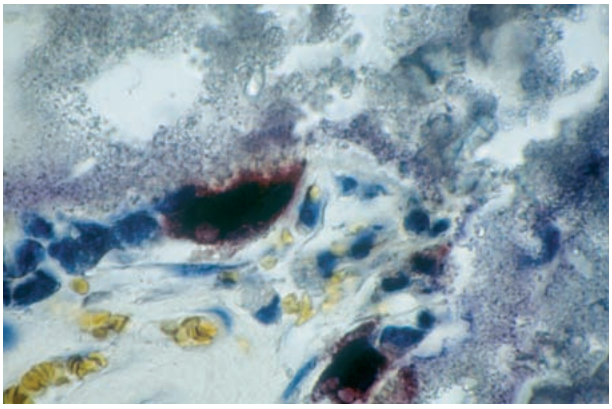

Figure 5 TRAP staining of osteoclast in femoral epiphysis of rabbit after 14 days of implantation.

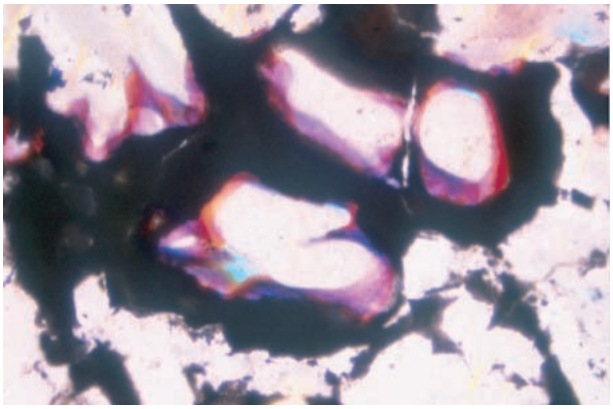

Figure 8 MBCP® granules implanted 2 weeks in muscular area of rabbit. Non-decalcified section with Movat's staining.

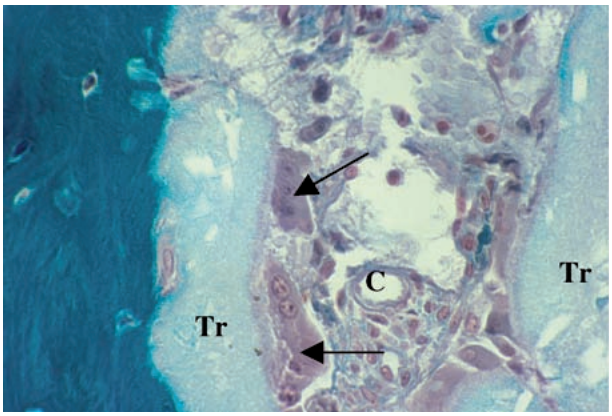

Figure 6 Human spine arthrodesis using Triosite® blocks after 3.5 months of implantation showing bone ingrowth at the expense of the Triosite® (Tr) with osteoclast (arrow) near vascular channel (C).

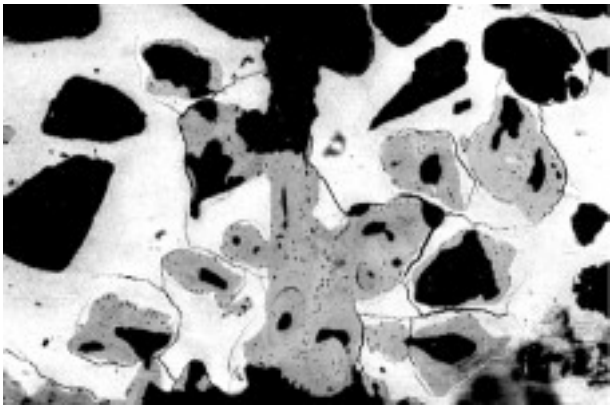

Figure 9 Bone reconstruction into MBCP® implant associated with autologous bone marrow and implanted in 65 grays irradiated femoral canine bone defects.

formed cartilage without fibrous encapsulation (Fig. 7). Moreover, in non osseous site after implantation in subcutaneous area, we have sometimes observed into some macropores of micro macroporous biphasic calcium phosphate (MBCP®) osteoid formation (Fig. 8). These observations suggest that BCP with macropores present suitable chemical environment associated to efficient architecture able to catch mesenchymal stem cells and to induce their phenotype to osteogenic cell lines. These observations have been also described by other groups in Netherlands [16]. This property can be used for artificial bone in irradiated implantation site. Irradiation produces irreversible effects on normal tissues, involving damages on their reparation properties. Nevertheless quality of life of patients who undergo radiotherapy could be improved by bone reconstructions. A preclinical study performed in irradiated dogs demonstrated bone ingrowth at the expense of structured implants of micro macroporous biphasic calcium phosphate filled by autologous bone marrow after implantation in irradiated soft and bone tissue [17] (Fig. 9).

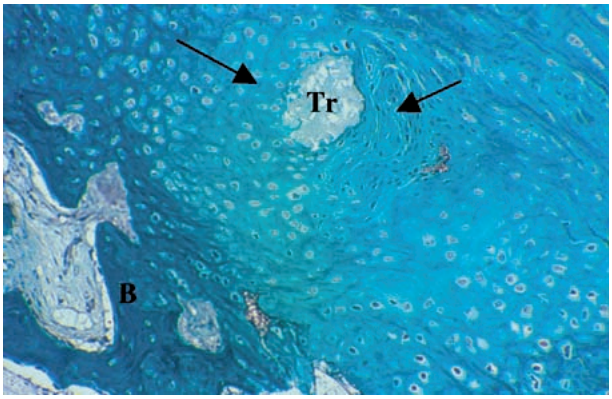

Figure 7 Human spine arthrodesis after 3.5 months of implantation showing hyaline and fibrous cartilage (arrows) growth all around a granule of Triosite® (Tr) and close to the newly formed bone at the expense of the implant (B).

Biodegradation, biodissolution and biological apatite precipitation significance

The biodegradation of BCP included the dissolution of the individual HA or β-TCP crystals [6, 9, 10]. The proportion of HA to β-TCP crystals in BCP appeared greater after implantation [18] and the known higher reactivity or solubility of β-TCP compared to HA.

The resorbability (reflecting *in vivo* dissolution) of BCP ceramics depends on their β-TCP/HA ratios, the higher the ratio, the greater the resorbability [6, 19]. Formation of microcrystals (which are able to diffract X-rays) with Ca/P ratios similar to those of bone apatite crystals was also observed after implantation. The abundance of these crystals was directly related to the

initial β-TCP/HA ratio in the BCP: the higher the ratio the greater the abundance of the microcrystals associated with the BCP crystals. According to these data it is possible to control the kinetic of dissolution and precipitation, and subsequently the bioactivity [20].

Using high resolution TEM Daculsi *et al*. [7] demonstrated for the first time that the formation of these microcrystals after implantation were non-specific, i.e., not related to implantation site, subjects of implantation, and types of CaP ceramics (Fig. 10).

The coalescing interfacial zone of biological apatite and residual crystals provides a scaffold for bone-cell adhesion and further bone ingrowth [18]. The resorbing process involves dissolution of calcium phosphate crystals and then a precipitation of CHA needle-like crystallites in micropores close to the dissolving crystals. The coalescing zone constitutes the new biomaterial/bone interface, which includes the participation of proteins and CHA crystals originating from the CaP materials, but does not include the biomaterial surface. The following events of bone ingrowth and the newly formed bone progressively replaces the initially formed CHA from the CaP biomaterials.

The process of cell colonization, adhesion, phagocytosis and osteoclastic resorption, Extra Cellular Matrix (ECM) elaboration and mineralization, bone in growth and bone remodeling associated with the biological apatite precipitation during CaP ceramics dissolution, are continuously in progress. Consequently the interface is not static but dynamic, in constant evolution, taking into account bone physiopathology, biomechanical factors and bone maturation. The processes involve a well organized and mineralized bone ingrowth at the expense of the artificial bone (Fig. 11). X-rays microtomography (micro scanner imaging) of the bone ingrowth at the expense macroporous BCP is able to demonstrate the three-dimensional bone organization into the macropores implant (Figs. 12(a) and (b)).

This concept of bioactivity could also be applied to implant coating and to Injectable Bone Substitute MBCPgel® [20]. CaP materials are also used as components or fillers in polymeric composites [21, 22] and in cements [23]. The hydraulic cement are not macroporous and numerous studies have demonstrated the necessity of macropores for bone osseous-conduction [4]. The bioactive concept of BCP have been applied to a new composite associating hydrosoluble polymer and BCP granules [24]. We have elaborated such injectable bone substitute ready to use and able to be largely invaded by osseous-conduction due to osteogenic cells [15]. These materials are perfectly biocompatible and potentially resorbable and, thanks to their initial plasticity, they can fit bone defects very easily, without

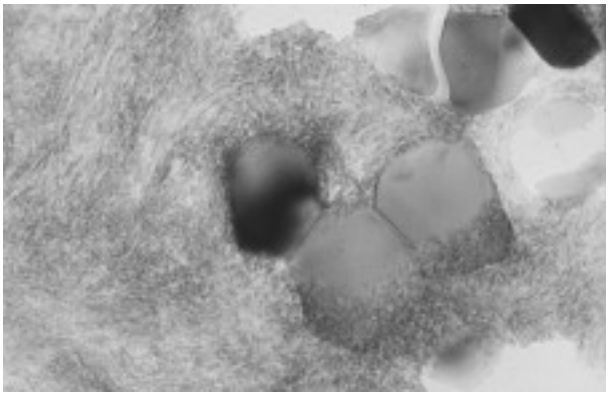

Figure 10 Biological apatite precipitation at the surface of residual crystals in BCP observed in high resolution TEM.

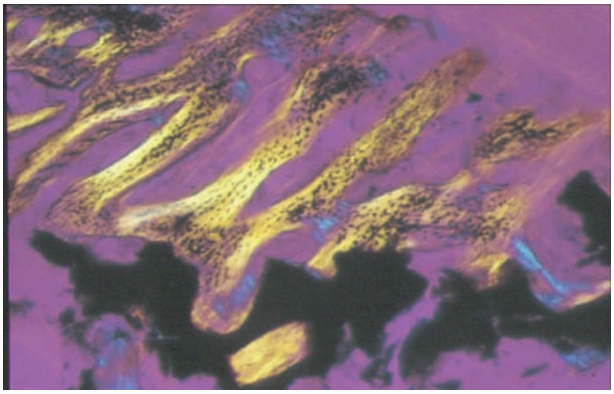

Figure 11 Spongious bone formed at the expense of Triosite® blocks in human spine arthrodesis.

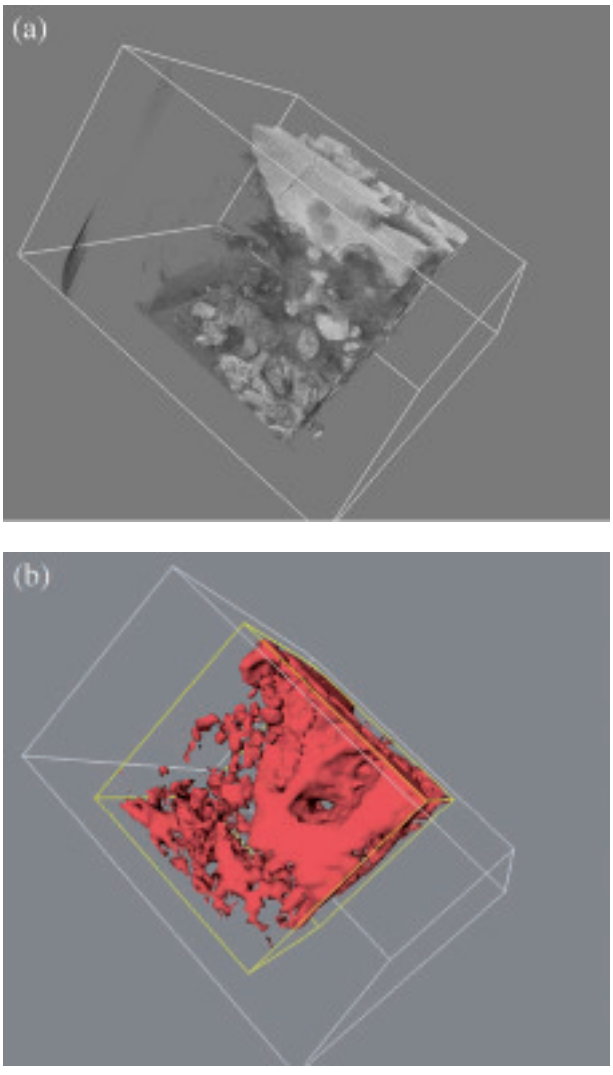

Figure 12 X-ray microtomography (Synchrotron facility, ESRF Grenoble France) of macroporous BCP implant in rabbit femoral epiphysis. (a) Total imaging with bone ingrowth (gray level) at the expense of bioceramics (white). (b) 3-D image reconstruction of bone ingrowth alone.

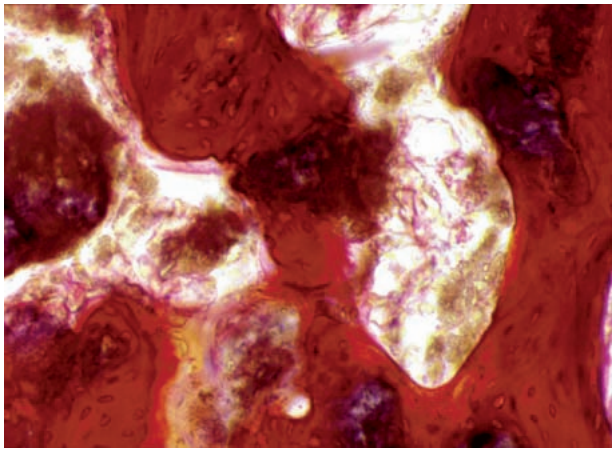

Figure 13 Cancellous bone formed into rabbit femoral epiphysis after 3 weeks of implantation of IBS® (Movat's staining).

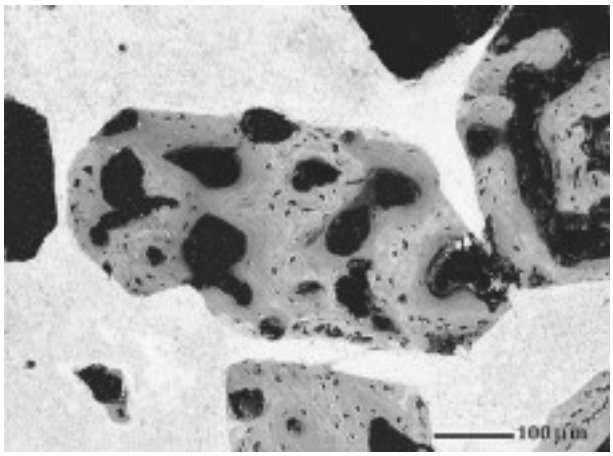

Figure 14 Scanning electron microscopy using Backscattered Electron imaging of polished section of MBCPgel® after 3 week of rabbit implantation showing bone growth closely associated to the residual grain of calcium phosphate.

necessity to elaborate shaping of implantation site [25, 26].

The IBS cannot have mechanical properties like hydraulic bone cement able to have a hardening process [23]. However bone cells are able to invade the spaces released by the disappearance of the polymer. Bone ingrowth take place all around and at the expense of the resorption of the BCP grains (Figs. 13 and 14). In time, mechanical property could be observed due to the presence of bone.

Conclusion

The bioactive concept based on the dissolution/transformation processes of HA and TCP can be applied to both Bulk, Coating and Injectable Biomaterials. The Biphasic Calcium Phosphate concept based on the mixture of HA and β-TCP in the three different forms have the same evolution and adaptation to the tissues: (1) partial dissolution of the CaP ceramic macrocrystals cause an increase in the calcium and phosphate concentrations in the local microenvironment; (2) formation of CHA (either by direct precipitation or by transformation from one CaP phase on an other or by seeded growth) incorporating ions (principally carbonate) from the biological fluid during its formation; (3) association of the carbonate-apatite crystals with an organic matrix; and (4) incorporation of these microcrystals with the collageneous matrix in the newly formed bone (in osseous sites). The events at the CaP biomaterial/bone interface represent a dynamic process, including physico-chemical processes, crystal/proteins interactions, cells and tissue colonization, bone remodeling, finally contributing to the unique strength of such interfaces. These type of artificial bone revealed from a long time in preclinical and in clinical trial the efficiency for bone filling, performance for bone reconstruction and efficacy for bone ingrowth at the expense of the micro macroporous biphasic calcium phosphate bioceramics.

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Properties of Calcium Phosphate Ceramics in Relation to Their In Vivo Behavior

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Bone replacement has been under investigation for many centuries. The first report on bone replacement comes from the bronze age, when a skull defect was treated by implantation of a bone autograft.[1] However, the first successful treatment of a bone defect with a bone graft was performed by the Dutch surgeon Job van Meek'ren in 1668.[2] After that, it took many centuries before the first large series of bone transplants was reported.[3] Since that time, the advantages and disadvantages of bone transplantation have become clearly understood. The need for bone replacement is evident in traumatology and orthopedics. Loss of bone caused by trauma, infection, or tumor resection poses great problems on both the treating surgeon and the patient. Treatment of these conditions often includes the implantation of autogenous bone transplant material, but this method leads to significant consequences for the patient.[4] Harvesting autogenous bone grafts causes comorbidity in 6 to 20% of patients, such as persistent pain, hypersensitivity, or anesthesia, and 3 to 9% have more serious problems.[5] Artificial bone replacement materials can avoid these consequences.

Since the first use of plaster of paris as an artificial bone replacement material in 1894,[6] different groups of artificial bone replacement materials have been developed over the years. Glass ceramics, metal ceramics, polymers, and calcium phosphate ceramics, such as hydroxyapatite (HA) and tricalciumphosphate (TCP) have been investigated extensively. These materials have different properties and, therefore, display different interactions with the host tissue. Factors such as porosity, osteoconductivity, and biocompatibility seem to become increasingly important in the development of new artificial bone replacement materials. This paper focuses on the relation between the properties of bone replacement materials, especially calcium phosphate ceramics, and the host tissue, to provide some clarity in the processes involved in the incorporation of these materials in bone tissue. Developments in the combination of osteogenic or osteoinductive substances and calcium phosphate ceramics will be discussed as well.

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POROSITY

Osteoconductive biomaterials provide a scaffold for the ingrowth of bone. One of the major factors influencing the osteoconductivity is the porosity of the ceramic material. Several different aspects of the porosity are important for the osteoconductive properties: the pore size, the total porous volume, which is the relationship between pore volume and specimen volume, and the interconnectivity of the pores.

Pore Size

Pore size can be divided in two different groups: microporous ($<$5-μm pores) and macroporous ($>$100-μm pores).[7,8] The microporosity is important for the bioresorbability of the material (see Bioresorption section).[9] The macroporosity plays an important role in the osteoconductivity. A large macroporosity (i.e., 400–600 μm) facilitates infiltration by fibrovascular tissue and revascularization, allowing bone reconstruction (Fig. 1). The optimal macroporosity for the ingrowth of bone tissue, as stated by several investigators,[10–12] is in the range between 150 and 500 μm.

Total Porous Volume

The invasion by host tissue is mostly facilitated by a larger porosity. Porous materials have the advantage of allowing circulation of body fluids and of increasing the potential for firm attachment of body tissue.[13] However, the disadvantage of a larger total porous volume is a decrease in mechanical strength. For example, an increase of the total porous volume from 10 to 20% results in a factor four decrease in mechanical strength.[10,14–16] Furthermore, bone is a tissue that proliferates and remodels according to the influence of mechanical forces acting on it. The porosity of a material provides the invading fibrovascular tissue an unnatural pathway, by which it is forced in the direction of the pores. This could influence the proliferation and remodeling of bone. Small particles of a dense biomaterial could avoid these problems. In dense particles, the invading tissues can grow over and around the particles according to their own dictates.[8,17,18] In other words, dense particles could provide the ingrowing tissue a large surface for scaffolding. They also have the ability to move within the implant site and, thereby, can obey the needs of the developing bone matrix, as determined by the mechanical forces.

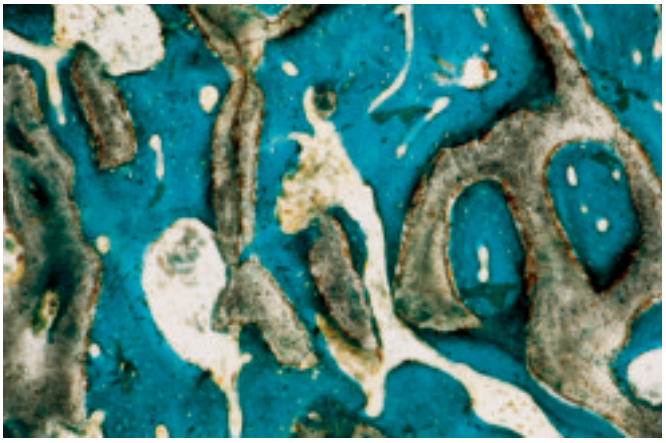

FIG 1. **HA incorporated in newly formed bone (Goldner's trichrome staining, original magnification, 10×). The porosity of the HA has facilitated the ingrowth of newly formed bone and direct contact between the bioactive surface of the HA and the newly formed bone, without interposition of fibrous tissue, can be observed.**

Interconnectivity

Another important factor that determines the effectiveness of porosity is the structure of the pores with respect to each other. The pores may either be interconnecting or they contain "dead-ends." Interconnecting pores can be achieved by producing so-called replamineform or coral ceramics. These ceramics are manufactured by replacing sea coral structure by, e.g., hydroxyapatite. The species of the coral involved determines the pore size. In general, biomaterials with interconnective pores are considered to be superior to biomaterials containing dead-end pores, because a spatial continuous connection of the pore system has a decisive meaning for the ingrowth of new bone,[16] especially in long-term tissue interface maintenance.[19] However, when used in combination with osteogenic cells, materials containing interconnective pores are less able to contain osteogenic cells, resulting in a longer period until the pore space has been filled with newly formed bone.[20]

CHEMISTRY

Bone is a specialized type of connective tissue, characterized by the presence of cells in a hard dense matrix. This matrix contains collagen, ground substances, and bone mineral. The bone mineral consists of complexes of calcium phosphates in amorphous and crystalline fractions. The mineral components compose approximately 30% amorphous calcium phosphate [$Ca_3(PO_4)_2$] and a little less than 70% fine crystalline varieties of hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$].[21] Hydroxyapatite has a hexagonal crystal structure. Besides plate-like crystallites, needle-like apatite crystallites have been demonstrated. Initially the crystals appear within the substances of the collagen fibers and then additional crystals form around the peripheries of these fibers through epitaxial growth. Epitaxial crystal growth is a thermodynamically controlled process, in which quest crystals use a host crystal surface as a nucleation site, or template, for the deposition and perpetuation ("growth") of their own phase. The final product of this growth process, bone, consists mainly of collagen fibers and hydroxyapatite crystals with a Ca/P ratio of 1.77.[21] Other calcium phosphates present in small quantities in bone are octacalcium phosphate, calcium pyrophosphate, and brushite.[22]

The chemical composition of several biomaterials has developed toward a composition that resembles the natural bone matrix as much as possible. The best known of these so-called chemical anisotropic biomaterials are calcium phosphate biomaterials such as hydroxyapatite and tricalcium phosphates. Other calcium phosphates include the calcium pyrophosphates [$Ca_2P_2O_7$] and other oxide compounds [$XCaO \cdot P_2O_5$].

The calcium phosphate biomaterials can virtually all be classified as polycrystalline ceramics. The calcium phosphates are formed by a process called sintering. This is a process in which high temperatures (1,100–1,300°C), pressure, and different apatites are being used to form the final product, calcium phosphates. The combination of a certain temperature, pressure. and different apatites determines several properties of the final product. For example, pure HA is formed by using an apatite with a Ca/P ratio of 1.7, whereas TCP is formed by using an apatite with a Ca/P ratio of 1.5. When apatites with varying Ca/P ratios are sintered, different amounts of HA and TCP are formed in the final ceramic, resulting in biphasic calcium phosphates (BCPs). Another factor that is determined by the sintering parameters is the residual microporosity.[21] The microporosity of the ceramics is due to gaps left between the sintered particles, and it is mainly influenced by the crystallization of the apatite used.

Dense and porous ceramics are produced by different sintering techniques. Dense ceramics are produced by compaction under high pressure, resulting in a frequently called "green" state, and are sintered after the compaction process. Porous ceramics are produced by using appropriate-sized naphthalene particles, incorporated in apatite. After compaction under high pressure, removal of naphthalene is accomplished by sublimation which leaves a macroporous green state. The integrity of this macroporous green state is maintained through the sintering step. Another method of producing porous ceramics relies on the decomposition of hydrogen peroxide to generate a pore-filled structure.[8] A novel hydrothermal exchange method producing calcium phosphate replicas of marine coral structures has also been developed. The calcium carbonate of the coral is replaced by calcium phosphate replicas with special production methods. Depending on the coral species used, HA and TCP can be produced with varying porosities. The interconnective macroporosity is preserved in this hydrothermal conversion.[13]

The crystalline structure of the calcium phosphate can be determined by using x-ray diffraction analysis. The crystalline structure can be classified as microcrystalline or macrocrystalline. Microcrystalline structures have a poor spatial organization, whereas macrocrystalline materials have a well-organized crystal structure. The diffraction pattern of the ceramics, as determined by x-ray diffraction analysis, can be compared to natural bone, which has a microcrystalline structure. The comparison of the diffraction patterns provides

insight into the resemblance of the crystalline structure of a calcium phosphate to natural bone.

Calcium phosphate ceramics can dissolve in basic, neutral, or acid solutions, depending on their chemical composition. Especially in acidic environments calcium phosphate ceramics dissolve rapidly. Important for the dissolution process is the Ca/P ratio of the ceramic used. TCP (Ca/P <1.67) dissolves 12.3 times faster than HA (Ca/P $= 1.7$) in acidic medium and 22.3 times faster than HA in basic medium.[23] Other properties of the biomaterial, i.e., porosity, crystallinity, and impurities of the biomaterial can influence this process.[21]

The dissolution process results in an increase of the extracellular concentrations of calcium ($[Ca^{2+}]_e$) and phosphorous ($[PO_4^{3-}]_e$). The high $[Ca^{2+}]_e$ and $[PO_4^{3-}]_e$ results in the precipitation of apatites on a substrate ceramic, forming a carbonate-apatite-crystal layer. The very strong interface between the material and bone is believed to be influenced by this crystal layer.[21] Besides this, the formation of apatite crystals on the surface of a ceramic stimulates the process of epitaxial crystal growth. HA, as stated before, has a low dissolution rate which results in almost direct bonding with bone and tissue components. When degradation is extensive, as in the case of β-TCP, the dissolution/recrystallization layer is correspondingly wide.[24]

The different stages in manufacturing, handling, sterilization, and implantation are important in the prevention of introduction of surface impurities along bioceramic interfaces. Standard specifications and recommendations for manufacturing HA and TCP ceramics list less than 50-ppm impurities as within the basic chemical analysis.[25] Products from HA and TCP contain elements that are normal to biologic environments (compounds of calcium and phosphorous) and, therefore, concerns about toxicity, hypersensitivity, or carcinogenicity are minimal for this class of biomaterials.[26] The stages within HA and TCP can be altered by steam autoclaving, leading to a decrease in fracture strength. Therefore, if the materials have not been presterilized, clean, dry-heat exposure in air has been advocated by some companies and investigators.[27]

BIOCOMPATIBILITY

Biocompatibility can be defined as the ability of a material to perform with an appropriate response in a specific application. This generally accepted definition was provided by Williams as an outcome of a consensus conference.[28] With regard to the specific interactions between biomaterials and the local and systemic tissues, three different levels of biocompatibility can be distinguished: inert, bioactive, or biodegradable.[15,19,29]

Bioinertness

Bioinertness means that no chemical interaction takes place between the implant material and host tissue. Bioinert materials were developed because of the concern about the degradation products of previously used materials such as metal implants, glass ceramics, alloys, and polymers.[28–30] The degradation products of these materials are often toxic, causing an allergenic or carcinogenic response.[22] Although biocompatibility was improved by the development of bioinert materials, the absence of a chemical interaction between materials and host tissue is a disadvantage of these materials. The incorporation and integration is disturbed and a fibrous tissue layer surrounding the implant is formed, especially in weight bearing applications.

Bioactivity

The integration of biomaterials was significantly improved by the introduction of bioactive substances. Bioactivity can be described as the occurrence of an interaction between a biomaterial and the surrounding tissue. In the 1970s, several studies led to the idea that local biodegradation products would favorably influence the interfacial tissue responses and stimulate biointegration, resulting in bioactive properties of the biomaterial.[11,31,32] This same general idea of limited interactions over time between ceramics and bone tissue (bioactivity) was also proposed by Jarcho and coworkers.[18,32] More recently, it has been shown that this interaction consists mainly of the formation of a layer of hydroxyapatite on the surface, whereas the bulk of the material remains unchanged.[33] This layer of hydroxyapatite increases integration and incorporation of biomaterials (Fig. 1). A possible explanation for this increase in integration and incorporation could be that hydroxyapatite may have many areas on its surface that meet the electrical and spatial requirements for primary bone bonding as described by Jarcho et al.,[18] resulting in a chemical bonding by which even dense materials can become strongly attached to bone despite of that there is no ingrowth of bone into a dense material.

A more cellular approach of bioactivity comes from several in vitro studies that have demonstrated good attachment, migration, growth, and differentiation of osteogenic cells on ceramic surfaces.[20,34–36] This finding can be explained by the presence of certain biomolecules, such as fibronectin, laminin, and other adhesion glycoproteins, that modify the interaction between cell and implant surfaces. These extracellular matrix molecules are deposited onto a mineralized surface, by both osteogenic cells and osteoclasts.[37] They affect the rate and efficiency of bone formation in the calcium phosphate system.[20,36] Because these molecules are also involved in the adhesion of osteoclasts, they presumably affect the process of remodeling. Apart from the adhesion molecules, the release of Ca^{2+} ions has also been shown to enhance adhesion of osteogenic cells[38,39] and of osteoclasts.[37] Because several molecules and Ca^{2+}-ions are important for the adhesion and activity of both osteogenic cells and osteoclasts, the concept of bioactivity is strongly related to biodegradation, or bioresorption, of ceramic materials.

Bioresorption

Bioresorption is a biological mechanism by which certain ceramic materials resorb partially or completely and thereby disappear partially or completely over a period of time. Ideally, the rate of resorption, resulting in a sequentially changing bone-biomaterial interface, is similar to the rate of for-

mation of new bone. The advantages of a resorbing material are obvious. First of all, no foreign body remains in place during the rest of the lifetime. Second, remodeling of the newly formed bone is not influenced by the presence of the (porous or dense) ceramic. Third, after resorption of the ceramic material the remodeled bone is stronger than the combination of a ceramic and newly formed bone. By implanting resorbable bioceramics for the purpose of bone replacement, a completely biological and physiologic situation of bone healing can be achieved. However, the rate of resorption and the mechanisms by which resorption takes place are still subject of discussion.

The studies of Klawitter and Hulbert and Hulbert et al.[11,40] on porous calcium aluminates demonstrated an interactive nonmineralized surface zone between the ingrown bone and ceramics. This was explained by an abnormal pH in the region immediately adjacent to these particular ceramic surfaces, indicating biodegradation of the calcium aluminate ceramics. Graves and coworkers supported the concept of partially biodegradable calcium aluminate ceramic used as biomaterial.[41] Biodegradable tricalcium phosphates were introduced by Driskell and coworkers for the use of bone graft applications in the late 1970s.[9] In the 1980s, concern arose about mechanical integrity, uncontrolled biodegradation, and the possibility of generating long-term debris. The emphasis, therefore, shifted toward controlled bioresorption and biointegration. Investigators[42] proposed using biodegradable calcium phosphate ceramics that would resorb within months after implantation, resulting in a sequentially changing bone-biomaterial interface by bioresorption of the material.

Several features of the host tissue and the implanted biomaterial play a role in controlled bioresorption of calcium phosphate ceramics. The activity of phagocytosing cells of the host tissue and microporosity and chemical composition of the material are characteristics that determine the extent and rate of resorption. The resorption activity of the osteoclast is linked to the osteoblastic activity, and these two activities determine the remodeling process. Therefore, the remodeling process of the host bone and the resorption of a ceramic material are interlinked. If the composition of a certain ceramic material can balance the osteoclastic and the associated osteoblastic activity, it can take part in the physiologic remodeling process.[43]

The population of phagocytosing cells consists mainly of multinuclear cells and osteoclasts (Figs. 2 and 3). There is no consensus on which cells play the key role in the resorption process. Lane has stated that the cell that is involved in the partial resorption of hydroxyapatite seems to be the foreign body giant cell and not the osteoclast.[10] But strong evidence exists that the osteoclast is responsible for the resorption process in calcium phosphate ceramics. Osteoclastic resorption has been demonstrated in biphasic calcium phosphates with different HA/TCP ratios.[20,21,37] Others have shown that macrophages are involved in the phagocytosis of calcium phosphate ceramics as well.[44,45] In a recent study by Frankenburg et al.,[46] a combination of macrophages and osteoclasts has been demonstrated to be involved in the phagocytosis of an injectable carbonate apatite (Dahllite).

After attachment of osteoclasts to the calcium phosphate ceramic, the osteoclasts create a sealed extracellular compartment at the osteoclast-ceramic interface into which they secrete acid. The dissolution of calcium phosphate is increased by an acidic environment as mentioned before.[24] The released calcium in this sealed extracellular microenvironment ($[Ca^{2+}]_i$) is an important factor in the regulation of ongoing resorption. The $[Ca^{2+}]_i$ influences osteoclast activity directly. As the resorption proceeds, the increase of $[Ca^{2+}]_i$ causes cessation of the resorptive phase, which is followed by a migratory phase of the osteoclast. Therefore, the solubility of a particular calcium phosphate ceramic determines the osteoclastic activity and, thus, the rate of bioresorption. Yamada et al. investigated the osteoclastic resorption of calcium phosphate ceramics with different HA/β-TCP ratios.[37] β-TCP dissolves rapidly resulting in a high $[Ca^{2+}]_i$, and, therefore, an ineffective resorption by the osteoclasts was seen, with discontinuous lacunae, appearing like a chain of small islands. In contrast, β-TCP in combination with HA in a 75/25 ratio dissolves more slowly. When subjected to osteoclastic resorption, this material showed more continuous large lacunae, indicating an effective osteoclastic activity. These lacunae resembled the lacunae formed on natural mineralized organic tissues. This finding means that a particular ceramic may present a solubility more appropriate for osteoclastic activity. As osteoblastic bone formation is related to oste-

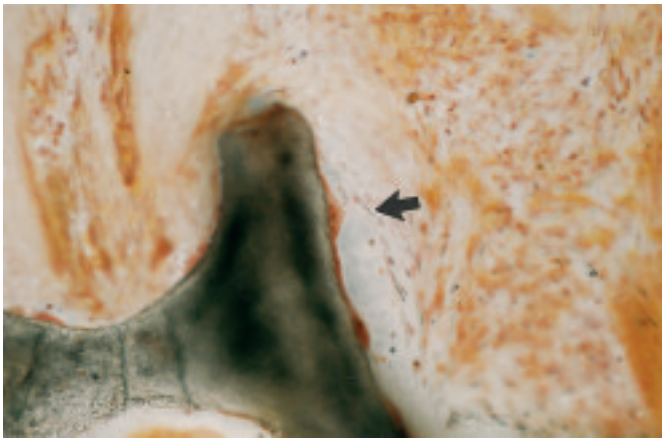

FIG 2. **Multinuclear giant cell (*arrow*) adjacent to HA. Goldner's trichrome staining; original magnification, 20×.**

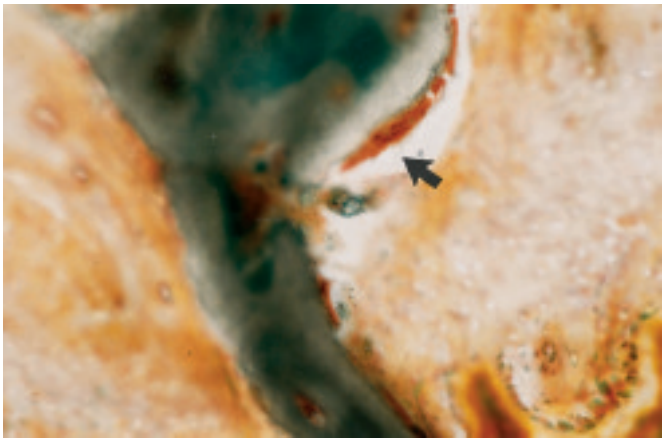

FIG 3. **Another multinuclear giant cell (*arrow*) adjacent to HA. Goldner's trichrome staining; original magnification, 20×.**

oclastic resorption activity,[47] appropriate resorbable BCP presumably offers the advantage of forming and maintaining dynamical biologic union to living bone through resorption/bone substitution processes and providing chemical bonding between bone apatite and similar apatite formed on the ceramic surface by dissolution/precipitation reactions.[37]

COMBINATIONS WITH OSTEOGENIC AND OSTEOINDUCTIVE MATERIALS

Although ceramic biomaterials have developed toward materials with a composition that resembles natural bone matrix, and the materials can be porous, dense, resorbable, bioactive, or bioinert, according to the desired properties for a specific application, ceramic bone substitute materials are osteoconductive only. They only provide a scaffold for the newly formed bone and are not osteoinductive. The clinical application of osteoconductive biomaterials, therefore, is merely restricted to relatively small bone defects.[48] The combination of bone substitute materials with osteogenic or osteoinductive materials seems a logical step forward in the development of bone replacement.

Osteogenic Substances

The osteogenic properties of bone marrow, as first described by Goujon in 1869,[49] are well known. The mechanisms by which bone marrow induces new bone formation have been elicited over the past decades. When marrow is transplanted into a bone defect, primary bone formation is induced by this marrow. The initial bone is then remodeled by invading host tissue.[50] This is a similar mechanism as observed in cancellous bone grafts[51] and fresh bone autografts.[52,53] The cellular events responsible for this osteogenic capacity of bone marrow are various. Danis was the first to demonstrate a marrow-cell origin of osteoblasts by in vivo implantation of marrow cells placed in diffusion chambers,[54,55] soon followed by others.[56,57] When transplanted, hematopoietic cells disappear and proliferation of the stromal cell population occurs in the bone marrow.[58] Osteoblasts are formed out of osteoprogenitor cells that are derived from mesenchymal stem cells (MSCs) present in the bone marrow stroma.[59] The MSCs play a major role in bone regeneration, because they can differentiate along multiple cell lineages that form mesenchymal tissues and, thus, the application of a pool of MSCs is the main objective of transplantation of bone marrow. The MSCs can be directed into the osteogenic lineage, depending on the site of implantation, cell density, and vascularization.[60] Various bioactive molecules such as bone morphogenetic proteins (BMPs) seem to play an important role in this process of differentiation.[61] However, despite the osteogenic capacity of bone marrow, it is not osteoconductive and it cannot be used as a spatial filler. Therefore, when used in combination with bone replacement materials such as calcium phosphate ceramics the ceramics supply a matrix, osteoconductivity, and a bioactive surface for the osteogenic bone marrow.

The osteogenic properties of marrow cells in combination with porous ceramic composites have been well demonstrated.[20,50,62–65] The ceramics act as a delivery vehicle for bone marrow. The bioactive properties of calcium phosphate ceramics provide a good substratum for the attachment of the osteogenic bone marrow cells.[63] The porosity of the ceramic material influences the process of bone formation by supplying an appropriate vascular ingrowth, which prevents cartilage formation. Furthermore, the porosity determines the ability of the material to retain preloaded marrow cells.[20,60,62]

When marrow cells are combined with porous ceramics, cell viability and total cell count in the ceramic are two important factors that contribute to the effectiveness of inducing osteogenesis.[66] Cell viability depends mostly on the age of the donor.[67] The critical initial cell density required for bone formation (density of cell suspension in which porous ceramics are soaked before implantation) has been determined by several investigators. A suspension of less than 5×10^5 cells/mL showed insufficient osteogenesis, whereas a cell density of more than 5×10^6 cells/mL showed consistent osteogenesis.[20,57,63,65] This number of cells can be achieved either by performing a punction of the iliac crest to obtain red marrow, or by culturing marrow cells in vitro.

OSTEOINDUCTIVE SUBSTANCES

Bone induction is defined as the mechanism by which a mesenchymal tissue is induced to change its cellular structure to become osteogenic.[68] Urist was the first to describe BMPs as the active proteins responsible for ectopic bone formation after subcutaneous of intramuscular implantation of demineralized bone matrix.[69] Since the isolation of single BMPs and the identification of their structure in 1988,[70] extensive knowledge has been gathered about structure, working mechanism, and effectiveness of several individual BMPs. The BMPs belong to an expanding TGF-β super family, and they are the only growth factors that can stimulate differentiation of the MSCs into a chondroblastic and osteoblastic direction.[71–74] After injury to the bone matrix, BMPs are released. They are responsible for various mechanisms that contribute to bone formation such as angiogenesis and chemotaxis and differentiation of mesenchymal cells. BMPs have pleomorphic functions that range from nonskeletal and skeletal organogenesis to bone generation and regeneration.[75] BMPs-induced bone in postfetal life recapitulates the process of embryonic and enchondral ossification.[10]

Two BMPs possessing good osteoinductive capacities are BMP-2 and BMP-7 (OP-1). These BMPs and their receptors have been demonstrated in fractures and in callus.[76–80] Their efficacy in the stimulation of bone defect healing has been described by several investigators.[81–88] Different matrix materials have been used as a delivery system, although there is no absolute biologic requirement for one.[89] The combination of bioactive and osteoconductive calcium phosphate ceramics, or similar materials, and the osteoinductive BMPs seems to be synergistic on the healing of bone defects.[90–98] Because of the bioactive properties of calcium phosphate ceramics, they provide a substratum for cell growth and differentiation, and their osteoconductive properties stimulate bone healing as well.

The results of an experimental study, in which the combination of porous hydroxyapatite (HA) and osteogenic pro-

tein-1 (OP-1) was tested in a segmental defect in sheep, have been described previously.[99] In short, a 3-cm segmental defect was created in the tibia in 30 adult female sheep. The defect was left empty in six sheep, filled with 10 mL of HA granules in eight sheep, filled with 10 mL of HA granules in combination with OP-1 in eight sheep, and filled with an autologous bone graft (ABG) in eight sheep. After 12 weeks, the animals were killed and bone healing was evaluated. Bone healing was significantly improved by the addition of OP-1 to the HA granules. Because the effect of this combination was comparable to the effect of ABG on bone healing, the combination of OP-1 and HA granules provides a useful alternative in the treatment of large bone defects.

FUTURE DIRECTIONS

At this moment, calcium phosphate ceramics have developed toward materials that are bioinert and bioactive. The chemical composition of these materials approximates the composition of natural bone matrix. Currently, bioresorbable materials are being introduced for clinical applications. The advantages of having resorbable materials are numerous. Long-term foreign-body effects can be avoided, and presumably these materials are replaced by newly formed bone through a process that resembles physiologic bone remodeling. Influencing chemical and mechanical properties by different manufacturing techniques offers the possibility to adjust specific materials to the application site by changing rate of bioresorption, mechanical strength, and porosity. However, although some evidence exists that hydroxyapatite under certain circumstances can act as an osteoinductor,[100] calcium phosphate ceramics are generally regarded as osteoconductive materials. In preclinical studies, the combination of calcium phosphate ceramics with osteogenic or osteoinductive substances shows better results in the treatment of larger bone defects, where osteoconductivity alone is insufficient to achieve solid union. This new development seems to be very promising but has not yet been validated for clinical applications.

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Synthetic biodegradable polymers as orthopedic devices

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Abstract

Polymer scientists, working closely with those in the device and medical fields, have made tremendous advances over the past 30 years in the use of synthetic materials in the body. In this article we will focus on properties of biodegradable polymers which make them ideally suited for orthopedic applications where a permanent implant is not desired. The materials with the greatest history of use are the poly(lactides) and poly(glycolides), and these will be covered in specific detail. The chemistry of the polymers, including synthesis and degradation, the tailoring of properties by proper synthetic controls such as copolymer composition, special requirements for processing and handling, and mechanisms of biodegradation will be covered. An overview of biocompatibility and approved devices of particular interest in orthopedics are also covered.

Keywords: Biodegradable; Bioabsorbable; Polylactide (PLA); Polyglycolide (PLG)

1. Introduction

Research in the first half of the 20th century with polymers synthesized from glycolic acid and other α-hydroxy acids was abandoned for further development because the resulting polymers were too unstable for long-term industrial uses. However, this very instability — leading to biodegradation — has proven to be immensely important in medical uses in the last three decades. Polymers prepared from glycolic acid and lactic acid have found a multitude of uses in the medical industry, beginning with biodegradable sutures first approved in the 1960 s [1]. Since that time other medical devices, based on lactic and glycolic acid, as well as other materials, including poly(dioxanone), poly(trimethylene carbonate) copolymers, and poly(ε-caprolactone) homopolymers and copolymers, have been accepted for use as medical devices [2]. In addition to these approved devices, a great deal of research continues on polyanhydrides [3], polyorthoesters [4], and other materials [5,6].

Why would a medical practitioner want a material to degrade? There may be a variety of reasons, but the most basic begins with the physician's simple desire: to have a device, which can be used as an implant and will not necessitate a second surgical event for removal. In addition to not requiring a second surgery, the biodegradation may offer other advantages. For example, a fractured bone, fixated with a rigid, non-biodegradable stainless steel implant, has a tendency for re-fracture upon removal of the implant. The bone does not carry sufficient load during the healing process, because the load is carried by the rigid stainless steel. However an implant prepared from biodegradable polymer can be engineered to degrade at a rate that will slowly transfer load to the healing bone [7]. Another exciting application for which biodegradable polymers offer tremendous potential is the basis for drug delivery, either as a drug delivery system alone or in conjunction to functioning as a medical device. In orthopedic applications, the delivery of a bone morphogenic protein may be used to speed the healing process after a fracture [8], or the delivery of an antibiotic may help prevent osteomyelitis following surgery [9].

Polymer scientists, working closely with those in the device and medical fields, have made tremendous advances over the past 30 years. In this article we will focus on a number of these devices. We will also cover the chemistry of the polymers, including synthesis and degradation, how properties can be controlled by proper synthetic controls such as copolymer composition, special requirements for processing and handling, and discuss some of the commercial devices.

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Nomenclature

Abbreviations

LPLA	poly(L-lactide)
PGA	poly(glycolide)
DLPLA	poly(DL-lactide)
PDO	poly(dioxanone)
LDLPLA	poly(DL-lactide-*co*-L-lactide)
SR	self-reinforced
DLPLG	poly(DL-lactide-*co*-glycolide)
PGA-TMC	poly(glycolide-*co*-trimethylene carbonate)
LPLG	poly(L-lactide-*co*-glycolide)
PCL	poly(ε-caprolactone)

The general criteria for selecting a polymer for use as a biomaterial is to match the mechanical properties and the time of degradation to the needs of the application. The ideal polymer for an application would have the following properties:

- does not evoke an inflammatory/toxic response, disproportionate to its beneficial effect,
- is metabolized in the body after fulfilling its purpose leaving no trace,
- is easily processed into the final product form,
- has acceptable shelf life,
- is easily sterilized.

The mechanical properties match the application so that sufficient strength remains until the surrounding tissue has healed

2. Synthesis

As expected, biodegradable polymers can be either natural or synthetic. Here we will cover uses and properties of synthetic biodegradable polymers. These synthetic polymers in general offer greater advantages over natural materials in that they can be tailored to give a wider range of properties and have more predictable lot-to-lot uniformity than materials from natural sources. Also a more reliable source of raw materials is obtained with synthetic polymers that are free of concerns of immunogenicity [2].

The factors that affect the mechanical performance of biodegradable polymers are those that are well known to the polymer scientist. These factors are monomer selection, initiator selection, process conditions, and the presence of additives. These factors in turn influence the polymer's hydrophilicity, crystallinity, melt and glass transition temperatures, molecular weight, molecular weight distribution, end groups, sequence distribution (random versus blocky), and the presence of residual monomer or additives [10]. In addition, the polymer scientist working with biodegradable polymers must also evaluate each of these variables for its effect on biodegradation. Examples will be given throughout the text illustrating how some of these variables affect performance.

Biodegradation has been accomplished by synthesizing polymers that have hydrolytically unstable linkages in the backbone. These most common chemical functional groups are esters, anhydrides, orthoesters, and amides.

The following is an overview of the synthetic-biodegradable polymers that are currently being used or investigated for use as wound closure (sutures, staples), and orthopedic fixation devices (pins, rods, screws, tacks, ligaments). Most of the commercially available biodegradable devices are polyesters composed of homopolymers or copolymers of glycolide and lactide. There are also products made from copolymers of trimethylene carbonate, ε-caprolactone, and polydioxanone.

2.1. Notation

A polymer is generally named based on the monomer it is synthesized from. For example, ethylene is used to produce poly(ethylene). For both glycolic acid and lactic acid, an intermediate cyclic dimer is prepared and purified, prior to polymerization. These dimers are called glycolide and lactide, respectively. Although most references in the literature refer to poly(glycolide) or poly(lactide), you will also find references to poly(glycolic acid) and poly(lactic acid). Poly(lactide) exists in two stereo forms, signified by a D or L for dexorotary or levorotary, or by DL for the racemic mix.

Poly(glycolide) (PGA) Poly(glycolide) is the simplest linear aliphatic polyester. PGA was used to develop the first totally synthetic absorbable suture that has been marketed as DEXON® since the 1960s by Davis and Geck [5,6]. Glycolide monomer is synthesized from the dimerization of glycolic acid. The ring opening polymerization of glycolide yields high-molecular-weight materials with about 1–3% residual monomer present (Fig. 1). PGA is highly crystalline (45–55%) with a high melting point (220–225°C) and a glass transition temperature of 35–40°C [6]. Because of its high degree of crystallization, it is not soluble in most organic solvents; the

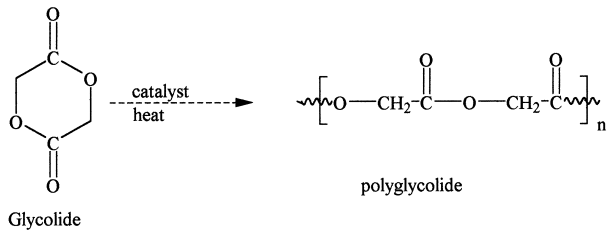

Fig. 1. Synthesis of poly(glycolide) (PGA).

Table 1
List of commercial biodegradable devices [13]

Application	Trade name	Composition	Manufacturer
Fracture fixation	SmartPins	SR-LPLA	Bionx Implants
Fracture fixation	SmartPins	SR-PGA	Bionx Implants
Fracture fixation	SmartScrew	SR-LPLA	Bionx Implants
Fracture fixation	SmartTack	SR-LPLA	Bionx Implants
Fracture fixation	Phantom SofThread Soft Tissue Fixation Screw	LPLA	DePuy
Fracture fixation	Orthosorb Pin	PDO	J & J Orthopedics
Interference screws	Full Thread Bio–Interference Screw	LPLA	Arthrex
Interference screws	Sheathed Bio–Interference Screw	LPLA	Arthrex
Interference screws	Phantom Interference Screw	LPLA	DuPuy
Interference screws	Biologically Quiet Interference Screw	85/15 DLPLG	Instrument Makar
Interference screws	BioScrew	LPLA	Linvatec
Interference screws	Sysorb	LLPLA	Sulzer Orthopedics
Interference screws	Endo–Fix Screw	PGA–TMC	Smith and Nephew
Suture anchors	Bankart Tack	SR-LPLA	Bionx Implants
Suture anchors	SmartAnchor-D	SR-LPLA	Bionx Implants
Suture anchors	SmartAnchor-L	SR-LPLA	Bionx Implants
Suture anchors	Phantom Suture Anchor	LPLA	DuPuy
Suture anchors	BioROC EZ 2.8 mm	LPLA	Innovasive Devices
Suture anchors	BioROC EZ 3.5 mm	LPLA	Innovasive Devices
Suture anchors	Biologically Quiet Biosphere	85/15 DLPLG	Instrument Makar
Suture anchors	Biologically Quiet Mini-Screw	85/15 DLPLG	Instrument Makar
Suture anchors	Bio-Anchor	LPLA	Linvatec
Suture anchors	GLS	LPLA	Mitek Products
Suture anchors	Panalok	LPLA	Mitek Products
Suture anchors	Panalok RC	LPLA	Mitek Products
Suture anchors	Suretak 6.0	PGA–TMC	Smith and Nephew
Suture anchors	Suretak 8.0	PGA–TMC	Smith and Nephew
Suture anchors	Suretak II w spikes	PGA–TMC	Smith and Nephew
Suture anchors	TAG 3.7 mm Wedge	PGA–TMC	Smith and Nephew
Suture anchors	TAG Rod II	PGA–TMC	Smith and Nephew
Suture anchors	SD sorb 2 mm	82/18 LPLG	Surgical Dynamics
Suture anchors	SD sorb 3mm	82/18 LPLG	Surgical Dynamics
Suture anchors	SD sorb E–Z TAC	82/18 LPLG	Surgical Dynamics
Suture anchors	Bio–Statak	LPLA	Zimmer
Craniomaxillofacial fixation	LactoSorb Screws and Plates	82/18 LPLG	Biomet
Meniscus repair	Menicus Arrow	SR–LPLA	Bionx Implants
Meniscus repair	Clearfix Meniscal Dart	LPLA	Innovasive Devices
Meniscus repair	Clearfix Meniscal Screw	LPLA	Innovasive Devices
ACL reconstruction	Biologically Quiet Staple	85/15 DLPLG	Instrument Makar
Meniscus repair	Meniscal Stinger	LPLA	Linvatec
Meniscus repair	SD sorb Meniscal Staple	82/18 LPLG	Surgical Dynamics

exceptions are highly fluorinated organic solvents such as hexafluoroisopropanol. Fibers from PGA exhibit high strength and modulus and are too stiff to be used as sutures except as braided material. Sutures of PGA lose about 50% of their strength after two weeks and 100% at four weeks and are completely absorbed in 4–6 months [6]. Glycolide has been copolymerized with other monomers to reduce the stiffness of the resulting fibers [11,12]. Barber [13] has reviewed the commercially available orthopedic devices and only one device was made of PGA (Table 1).

Poly(lactide) (PLA) Lactide is the cyclic dimer of lactic acid, which exists as two optical isomers, D and L. L-lactide, is the naturally occurring isomer, and DL-lactide is the synthetic blend of D-lactide and L-lactide. The polymerization of lactide is similar to that of glycolide (Fig. 2). The homopolymer of L-lactide (LPLA) is a semi-crystalline polymer. PGA and LPLA exhibit high tensile strength and low elongation and consequently have

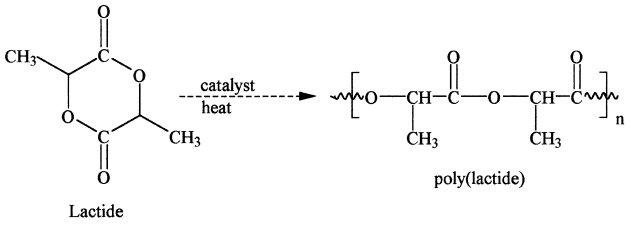

Fig. 2. Synthesis of poly(lactide) (PLA).

a high modulus that makes them more applicable than the amorphous polymers for load-bearing applications such as in orthopedic fixation and sutures. Poly(DL-lactide) (DLPLA) is an amorphous polymer having a random distribution of both isomeric forms of lactic acid and accordingly is unable to arrange into a crystalline organized structure. This material has lower tensile strength and higher elongation and much more rapid degradation time making it more attractive as a drug delivery system. Poly(L-lactide) is about 37% crystalline with a melting point of 175–178°C and a glass transition temperature of 60–65°C [14,15]. The degradation time of LPLA is much slower than that of DLPLA requiring greater than 2 years to be completely absorbed [16]. Copolymers of L-lactide with glycolide or DL-lactide have been prepared to disrupt the L-lactide crystallinity accelerating the degradation process [1,6]. Barber's review of 40 commercial orthopedic devices listed 22 of the devices as being composed of LPLA [13] (Table 1).

Poly(ε-caprolactone) (PCL): The ring opening polymerization of ε-caprolactone (Fig. 3) yields a semicrystalline polymer with a melting point of 59–64°C and a glass-transition temperature of −60°C. The homopolymer has a degradation time of the order of two years. Copolymers of ε-caprolactone with DL-lactide have been synthesized to yield materials with more rapid degradation rates [17]. A block copolymer of ε-caprolactone with glycolide that has reduced stiffness compared to pure PGA is being sold as a monofilament suture under the trade name MONOCRYL® by Ethicon [5,11,12], but no commercial medical devices are listed by Barber as made of PCL [13].

Poly(dioxanone) (a polyether-ester): The ring opening polymerization of *p*-dioxanone resulted in the first clinically tested monofilament synthetic suture that is known as PDS® marketed by Ethicon (Fig. 4). This material has about 55% crystallinity with a glass-transition temperature of −10 to 0°C. Poly(dioxanone) demonstrated no acute or toxic effects on implantation [6]. Johnson and Johnson Orthopedics has an absorbable pin for fracture fixation composed of poly(dioxanone) on the market [13].

Poly(lactide-co-glycolide) (PLG): Using the polyglycolide and poly(L-lactide) properties as base materials, it is possible to copolymerize the two monomers to extend the range of homopolymer properties (Fig. 5). Copolymers of glycolide with both L-lactide and DL-lactide have been developed for both device and drug-delivery applications. It is important to note that there is not a linear relationship between the copolymer composition and the mechanical and degradation properties of the materials. For example, a copolymer of 50% glycolide and 50% DL-lactide degrades faster than either homopolymer (Fig. 6) [18]. Copolymers of L-lactide with

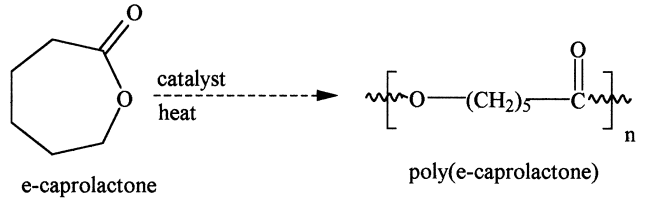

Fig. 3. Synthesis of poly(ε-caprolactone) (PCL).

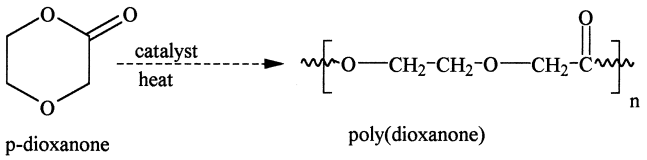

Fig. 4. Synthesis of poly(dioxanone) (PDS).

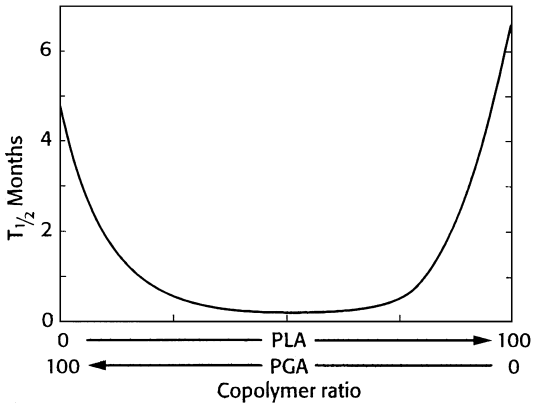

Fig. 6. Half-life of PLA and PGA homopolymers and copolymers implanted in rat tissue [11].

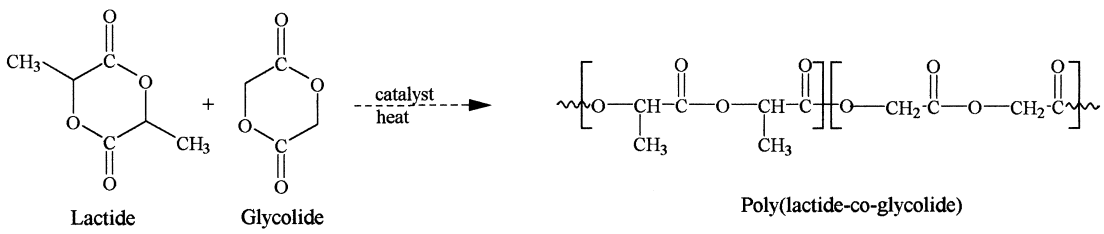

Fig. 5. Synthesis of poly(lactide-*co*-glycolide) (PLG).

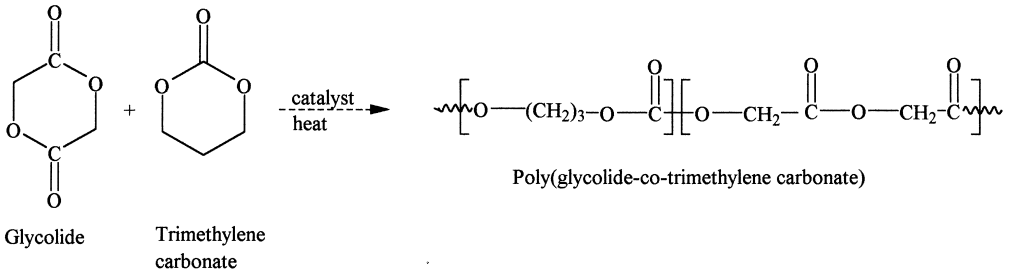

Fig. 7. Synthesis of poly(glycolide-co-trimethylene carbonate) (PGA–TMC).

25–70% glycolide are amorphous due to the disruption of the regularity of the polymer chain by the other monomer [1]. The Biologically Quiet™ line of products by Instrument Makar are composed of an 85/15 poly(DL-lactide-co-glycolide). Surgical Dynamics and Biomet have chosen an 82/18 poly(L-lactide-co-glycolide) copolymer for use as suture anchors and as screws and plates for craniomaxillofacial repair respectively [13, 19].

Copolymers of glycolide with trimethylene carbonate (TMC) called polyglyconate have been prepared as both sutures (MAXON®, Davis and Geck) [12] and as tacks and screws (Smith and Nephew Endoscopy) [13]. Typically these are prepared as A–B–A block copolymers in a 2:1 glycolide:TMC ratio with a glycolide-TMC center block (B) and pure glycolide end blocks (A) (Fig. 7). These materials have better flexibility than pure PGA and are absorbed in about seven months [6]. Glycolide has also been polymerized with TMC and *p*-dioxanone (BIOSYN® by US Surgical) to form a terpolymer suture with reduced stiffness compared to pure PGA fibers, with absorption within 3–4 months [13].

Currently, only resorbable fixation devices made from homopolymers or copolymers of glycolide, lactide, caprolactone, *p*-dioxanone and trimethylene carbonate have been commercialized [13]. There are other polymers, however, that are being investigated for use as materials for biodegradable devices that merit mentioning.

Poly(amino acids): The use of synthetic poly(amino acids) as polymers for biomedical devices would seem a logical choice because of their wide occurrence in nature. However, in practice, pure insoluble poly(amino acids) have found little utility due to their high crystallinity which makes them diffcult to process and gives relatively slow degradation. Also, the antigenicity of polymers with more than three amino acids in the chain also makes them inappropriate for use in vivo [20]. To circumvent these problems, modified "pseudo" poly(amino acids) have been synthesized using a tyrosine derivative. Tyrosine-derived polycarbonates are high strength materials that may be useful as orthopedic implants [5,20].

The search for new candidate polymers for drug delivery may offer potential for medical device applications as well. In drug delivery the formulation scientist is concerned not only with shelf life stability of the drug but also with stability after implantation, where the drug may reside in the implant for 1–6 months or more. For drugs that are hydrolytically unstable, a polymer that absorbs water may be counter-indicated, so researchers began evaluating more hydrophobic polymers that degrade by surface erosion rather than bulk hydrolytic degradation. Two classes of these polymers are the polyanhydrides and the polyorthoesters.

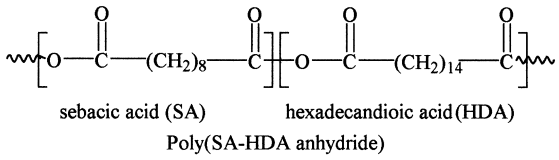

Fig. 8. Molecular structure of a polyanhydride.

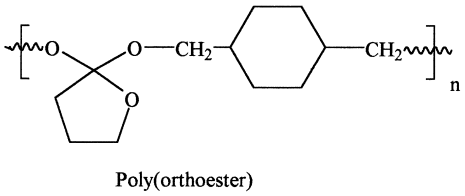

Fig. 9. Molecular structure of a polyorthoester.

Polyanhydrides: Polyanhydrides have been synthesized by the dehydration of diacid molecules by melt polycondensation (Fig. 8). Degradation times may be adjusted from days to years by degree of hydrophobicity of monomer selection. They degrade primarily by surface erosion and possess excellent in vivo compatibility. So far they have been only approved as a drug delivery system. The Gliadel® product designed for delivery of BCNU in the brain was approved by the FDA in 1996 and is being produced by Guilford [3,5].

Polyorthoesters: Polyorthoesters were first investigated in the 1970s by the Alza Corporation and SRI International in search of a new synthetic biodegradable polymer for drug-delivery applications (Fig. 9). These

materials have gone through several generations of synthetic improvements to yield materials that can be polymerized at room temperature without production of condensation by-products. These materials are hydrophobic with hydrolytic linkages that are acid-sensitive, but stable to base. They degrade by surface erosion and degradation rates may be controlled by incorporation of acidic or basic excipients [2,4,5].

3. Physical properties

The selection of a material for an orthopedic implant depends on the mechanical properties needed for the application and the degradation time desired. Polymers may be either semicrystalline or amorphous. Semicrystalline polymers have regular repeating units that allow the chains to fold into dense regions called crystallites. These act as crosslinks giving the polymer higher tensile strengths and higher modulus (stiffness) as compared to an amorphous analog. No polymer can completely organize into a fully crystalline material so there are still amorphous areas in semicrystalline polymers. When a semicrystalline polymer is raised above its melting point (T_m) it may be shaped into rods or molded parts. Amorphous polymers and the amorphous regions of semicrystalline polymers exhibit a glass transition temperature or T_g. At temperatures above T_g, a polymer acts more like a rubber and at temperatures below T_g, a polymer acts more like a glass. A polymer that has a T_g around body temperature may be much more ductile when implanted than it appears to be at room temperature. These properties can affect both the mechanical properties as well as the degradation time of the implant [10,21]. For the polyesters, the presence of water can act as a plasticizer and lower the T_g and affect degradation and mechanical properties. Koelling et al. [22] evaluated the mechanical properties of 90/10 poly(L-lactide-co-DL-lactide) under both wet and dry conditions. They saw the mechanical properties were lower for the polymers tested in the wet condition.

A good example of the differences between a semicrystalline and amorphous polymer is illustrated by the differences between poly(L-lactide) and poly(DL-lactide) discussed earlier under the synthesis section. The semicrystalline poly(L-lactide) has a modulus about 25% higher than poly(DL-lactide) and a degradation time on the order of 3 to 5 years. The amorphous poly(DL-lactide) has a degradation time of 12 to 16 months [21,23,24].

A common way of affecting crystallinity is by the use of comonomers in the synthesis. Unlike monomers do not typically co-crystallize and crystallinity can be disrupted by copolymerization, with the effect being more pronounced at higher comonomer levels. For example, both glycolide and L-lactide homopolymers are semicrystalline, and copolymers of L-lactide and glycolide exhibit some crystallinity when either monomer is present over 70 mol% [1]. Copolymers of DL-lactide and glycolide are amorphous when DL-lactide is the major component [23]. For applications where an implant will be under substantial load the family of semicrystalline biodegradable polymers would typically be chosen. Daniels et al. [14] have reviewed the mechanical properties for both reinforced and unreinforced biodegradable polymers. Table 2 shows some of the physical properties and degradation times for selected biodegradable polymers.

4. Processing

Biodegradable polymers may be processed similar to any engineering thermoplastic in that they can be melted

Table 2
Physical, mechanical, and degradation properties of selected biodegradable polymers; bone and steel included as reference materials [20,21,23]

Polymer	Melting point (°C)	Glass transition temperature (°C)	Modulus[a] (Gpa)	Elongation (%)	Degradation time[b] (months)
PGA	225–230	35–40	7.0	15–20	6 to 12
LPLA	173–178	60–65	2.7	5–10	> 24
DLPLA	Amorphous	55–60	1.9	3–10	12 to 16
PCl	58–63	− 65– − 60	0.4	300–500	> 24
PDO	N/A	− 10–0	1.5	N/A	6 to 12
PGA–TMC	N/A	N/A	2.4	N/A	6 to 12
85/15 DLPLG	Amorphous	50–55	2.0	3–10	5 to 6
75/25 DLPLG	Amorphous	50–55	2.0	3–10	4 to 5
65/35 DLPLG	Amorphous	45–50	2.0	3–10	3 to 4
50/50 DLPLG	Amorphous	45–50	2.0	3–10	1 to 2
Bone			10–20		
Steel			210		

[a] Tensile or flexural modulus.
[b] Time to complete resorption.

and formed into fibers, rods and molded parts. Final parts can be extruded, injection molded, compression molded, or solvent spun or cast. In some circumstances the primary processing may be followed by subsequent machining into final parts.

The additional complication during processing is the potential for molecular weight decrease due to the hydrolytic sensitivity of the polymer bonds. The presence of moisture during processing can reduce the molecular weight and alter the final polymer properties. To avoid hydrolytic degradation during processing, extra precautions need to be taken to dry the polymer before thermally processing and preventing moisture from contacting the polymer during processing. Michaeli and von Oepen [25,26] have studied the influence of several processing factors on degradation during processing. Drying a polymer 24 h at 80°C prior to processing reduced degradation by approximately 30% when processing above 200°C. Drying may be accomplished by vacuum drying or drying in a resorption circulating air dryer. Von Oepen reported drying semicrystalline polymers at 140°C resulted in moisture contents of less than 0.02% without incurring degradation during drying. They recommend moisture content not to exceed 0.02% to avoid excessive degradation during processing [25]. Michaeli and von Oepen reported that most of the moisture is removed after 4 h drying [26]. Middleton et al. [27] reported the effects of drying on the melt viscosity of PGA when processed at 250°C. Here the polymer was vacuum dried 24 h at room temperature followed by vacuum drying 24 h at 100°C. This drying cycle reduced the moisture from 0.02 to 0.003%. PGA processed at 250°C with 0.02% moisture resulted in over 50% degradation as indicated by a decrease in melt viscosity, whereas drying to 0.003% did not. Care must be exercised when drying polymers above room temperature. For example, amorphous polymer pellets may fuse when the drying temperature exceeds the glass transition temperature. Most of the amorphous polymers should only be dried at room temperature.

Other techniques may also be used to prevent moisture from entering the fabrication process. Packaging the polymers in small quantities is recommended so that the material is used up quickly during processing once the package is opened to prevent moisture absorption over time. Blanketing the material hopper or material inlet with nitrogen or dried air will also prevent moisture from entering the system.

Most synthetic, resorbable polymers have been synthesized by ring-opening polymerization and there exists a thermodynamic equilibrium between the polymerization reaction and the reverse reaction that will result in monomer formation. Excessively high processing temperatures can push the equilibrium to depolymerization resulting in monomer formation during the molding or extrusion process. The presence of excess monomer may act as a plasticizer changing the mechanical properties and may catalyze the hydrolysis of the device resulting in altered degradation kinetics [6].

There are also strong interactions among temperature, moisture content, shear rate, and residence time in the machine. Residence time is defined as time at temperature the material is in the barrel of a molding machine. Michaeli and von Oepen [25,26] have studied the effect of these interactions on polymer degradation for LPLA. When the temperature was raised from 190 to 230°C all the other effects were inconsequential. Higher shear rates and longer residence times resulted in increasing polymer degradation even at lower temperatures. In general, processing at the mildest conditions possible and the rigorous exclusion of moisture are the recommended. In many cases this is difficult as the devices being extruded or molded are small fibers or parts from very high-molecular-weight polymer. High temperatures are often needed to reduce the melt viscosity or high pressures needed to enable the polymer to flow through small orifices to create fiber or fill a mold. Several iterations of molding or extrusion may be needed to get the final part properties necessary for the application.

5. Packaging and sterilization

Because these polymers are hydrolytically unstable, the presence of moisture can degrade them in storage, during processing (as already discussed), and after device fabrication. The solution for hydrolysis instability is simple in theory: eliminate the moisture and eliminate the degradation. Because the materials are naturally hygroscopic, eliminating water and keeping the polymer free of water are difficult. The as-synthesized polymers have relatively low water contents, as any residual water in the monomer is consumed in the polymerization reaction. The polymers are quickly packaged after manufacture and generally double bagged under an inert atmosphere or vacuum. The bag material may be polymeric or foil, but it must be very resistant to water permeability [23]. The polymers are typically stored in a freezer to minimize the effects of moisture present. The packaged polymer should always be at room temperature when opened to minimize condensation and should be handled as little as possible at ambient atmospheric conditions [5]. As expected, there is a relation between biodegradation rate, shelf stability and polymer properties. For example, the more hydrophilic glycolide polymers are much more sensitive to hydrolytic degradation than those prepared from the more hydrophobic lactide. Williams et al. [28] have studied six different storage conditions for biodegradable polymers and found that the polymers remain stable even at room temperature for over two years as indicated by molecular weight retention when packaged in desiccated moisture proof bags.

Final packaging consists of placing the suture or device in an airtight moisture-proof container. A desiccant can be added to reduce the effect of moisture. For example, sutures are wrapped around a specially dried paper holder that acts as a desiccant. In some cases the final device may be stored at sub-ambient temperature as an added precaution against degradation.

The final devices should not be sterilized by autoclaving or dry heat because this will degrade the device. Typically the device is sterilized by γ-radiation, ethylene oxide (EtO), or other less-known techniques such as plasma etching [5,7,25] or electron beam irradiation. Both γ radiation and EtO have disadvantages. Radiation, particularly at doses above 2 Mrad, can result in significant degradation of the polymer chain, resulting in reduced molecular weight and influencing final mechanical properties and degradation times [6,8,15]. Poly(glycolide), poly(lactide) and poly(dioxanone) are especially sensitive to γ-radiation, and these are usually sterilized for device applications by exposure to ethylene oxide. The use of highly toxic EtO presents a safety hazard, so great care is used to ensure that all the gas is removed from the device before final packaging [5]. This may result in extremely long vacuum aeration times. One researcher has recommended a period of over 2 weeks [29] to fully remove the residual EtO gas. The temperature and humidity conditions should also be considered when submitting devices for sterilization. Temperatures must be kept below the glass transition temperature of the polymer to prevent the part geometry from changing during sterilization. If necessary, parts can be kept at 0°C or lower during the irradiation process. Of the 40 commercial orthopedic devices listed in Barber's review 25 were sterilized by EtO and 15 by γ irradiation [13]. No other techniques were listed.

6. Degradation

Once implanted in the body, the biodegradable device should maintain mechanical properties until it is no longer needed and then be degraded, absorbed, and excreted by the body, leaving no trace. Simple chemical hydrolysis of the hydrolytically unstable backbone is the prevailing mechanism for the polymer degradation. For semicrystalline polymers this occurs in two phases. In the first phase, water penetrates the bulk of the device, preferentially attacking the chemical bonds in the amorphous phase and converting long polymer chains into shorter, ultimately water-soluble fragments. Because this occurs in the amorphous phase initially there is a reduction in molecular weight without a loss in physical properties as the device matrix is still held together by the crystalline regions. The reduction in molecular weight is soon followed by a reduction in physical properties as water begins to fragment the device. In the second phase, enzymatic attack of the fragments occurs. The metabolizing of the fragments results in a rapid loss of polymer mass (Fig. 10) [21].

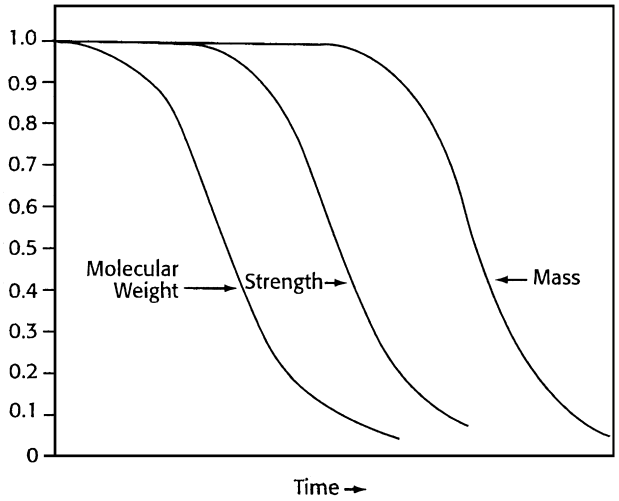

Fig. 10. Generic curves showing the sequence of polymer-molecular weight, strength, and mass-reduction over time [19].

Bulk erosion occurs when the rate at which water penetrates the device exceeds that at which the polymer is converted into water-soluble materials (resulting in erosion throughout the device). The lactide and glycolide commercially available devices and sutures degrade by bulk erosion [5]. This two-stage degradation mechanism has led one researcher to report that the degradation rate at the surface of large lactide–glycolide implants is slower that the degradation in the interior [30]. Initially, degradation does occur more rapidly at the surface due to the greater availability of water. The degradation products at the surface are rapidly dissolved in the surrounding fluid and removed from the bulk polymer. In the interior of the device the inability of large polymeric degradation products to diffuse away from the bulk device results in a local acidic environment in the interior of the implant. The increased acidic environment catalyses further degradation resulting in accelerated hydrolysis of the ester linkages in the interior. Athanasiou [31] has shown that low-porosity implants from 50/50 DLPLG degrade faster than high-porosity implants. He attributes this to the quick diffusion of low pH degradants from the interior of the high-porosity devices.

Polymer scientists have used this knowledge to tailor the degradation rates of biodegradable polymers. Tracy [32] reported the effects of replacing ester end groups with carboxylic acid end groups on DLPLG polymers (Figs. 11 and 12) accelerated both water uptake and degradation rate in vitro. The acid-end groups both add to the hydrophilicity of the polymer and catalyze degradation. Middleton et al. [33] conducted an in vitro degradation study in phosphate-buffered saline comparing

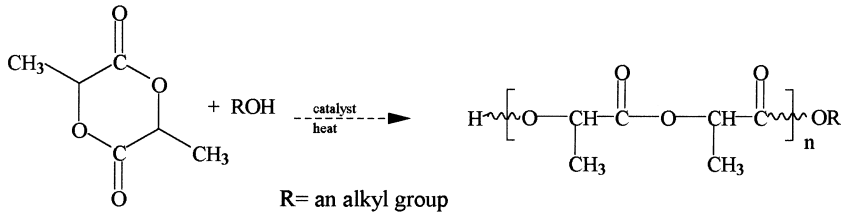

Fig. 11. Initiation of DL-lactide with an alcohol resulting in a polymer with one ester end group and one alcohol end group.

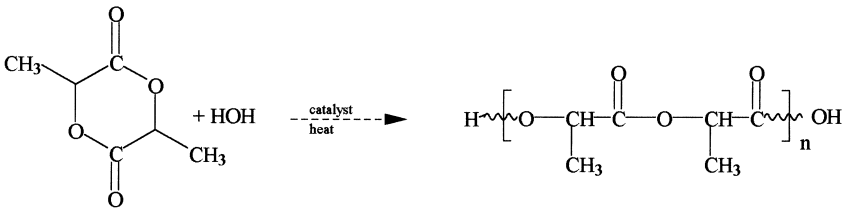

Fig. 12. Initiation of DL-lactide with water resulting in a polymer with one carboxylic-acid end group and one alcohol-end group.

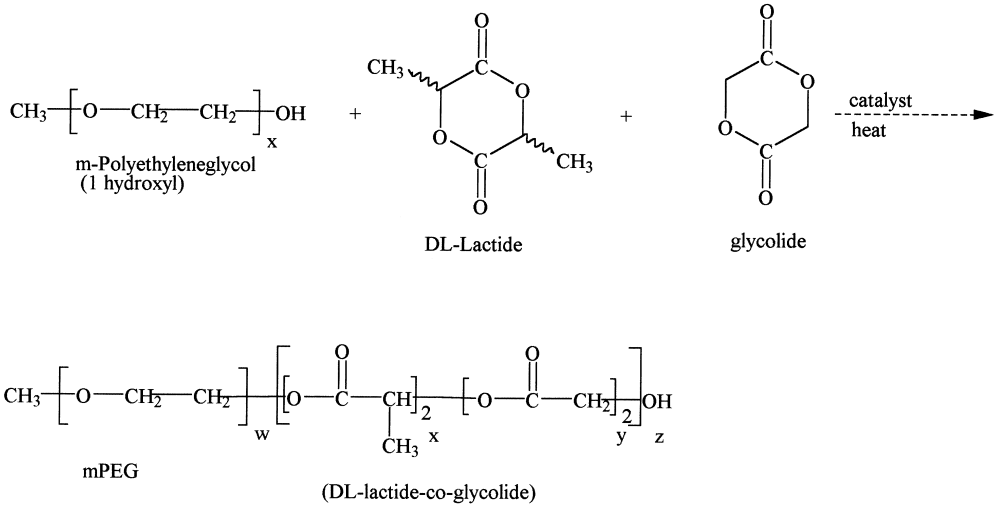

Fig. 13. Initiation of DL-lactide and glycolide with a monofunctional poly(ethyleneglycol) resulting a block copolymer consisting of a PEG block and a poly(DL-lactide-co-glycolide) block.

DLPLG rods where the ester end groups were replaced with covalently bound monofunctional poly(ethylene glycol) (mPEG) (Fig. 13). The mPEG-DLPLG demonstrated enhanced water uptake without accelerated degradation. It is believed the presence of the ethylene glycol units enhanced polymer hydrophilicity without lowering the pH of the local environment. By increasing the water uptake it may also have allowed the acidic degradants to more readily diffuse away from the interior of the rod.

There is a second type of biodegradation called surface erosion when the rate at which the polymer penetrates the device is slower than the rate of conversion of the polymer into water-soluble materials [5]. Surface erosion results in the device thinning over time while maintaining its bulk integrity. Polyanhydrides and polyorthoesters are examples of this type of erosion when the polymer is hydrophobic, but the chemical bonds are highly susceptible to hydrolysis. In general, this process is referred to in the literature as bioerosion rather than biodegradation.

The degradation-absorption mechanism is the result of many interrelated factors, including:

- the chemical stability of the polymer backbone,
- the presence of catalysts,
- additives,

- impurities or plasticizers,
- the geometry of the device,
- the location of the device.

The balancing of these factors to tailor an implant to slowly degrade and transfer stress to the surrounding tissue as it heals at the appropriate rate is one of the major challenges facing the researchers today.

The factors which accelerate polymer degradation are the following

- More hydrophilic monomer.
- More hydrophilic, acidic endgroups.
- More reactive hydrolytic group in the backbone.
- Less crystallinity.
- Smaller device size.

The location of the device can play an important role in the degradation rate of lactide–glycolide implants. Large devices implanted in areas with poor vascularization may degrade and overwhelm the body's ability to flush away degradants. This leads to a build up of acidic by-products. An acidic environment will catalyze the further degradation and cause further reduction in pH [7]. The local reduction in pH may also be responsible for adverse tissue reactions [34]. It has also been reported [35] that implants under stress degrade faster. It was proposed that the stressed implant may form microcracks increasing the surface area exposed to water [7].

7. Biocompatibility

Some of the requirements listed in the earlier section of this article stated that the ideal implant would not invoke an inflammatory or toxic response and that the degradants must be metabolized in the body after fulfilling its purpose leaving no trace. For example, poly(lactide) hydrolyzes to lactic acid that is a normal product of muscular contraction in animals. The lactic acid is then further metabolized through the tricarboxylic acid cycle and then excreted as carbon dioxide and water. Poly(glycolide) is degraded by hydrolysis and esterases to glycolic acid. Glycolic acid monomer may be excreted directly in urine or may react to form glycine. Glycine can be used to synthesize serine and subsequently transformed into pyruvic acid where it enters the tricarboxylic acid cycle [7].

There have been numerous studies on the biocompatibility of implants since the early 1960s mostly focusing on polymers of lactide and glycolide. The majority of results indicate that these polymers are sufficiently biocompatible, with a minority suggesting otherwise. The literature before 1993 has been summarized by Agrawal et al. [15].

Bergsma et al. [16] conducted a study on patients that have received PLLA implants for zygomatic fractures. They removed and analyzed the remaining LPLA material after 3.3 to 5.7 years. Some highly crystalline LPLA particles remained after 5.7 years. The particles were not irritable and did not cause injury to the cell, but did induce a reaction in the form of detectable swelling. Barber [36] evaluated 85 patients in two groups that received either a metal or LPLA interference screw. No statistical differences were found between the two groups after two years.

As with the other areas we have explored, there are many factors that may influence the reaction of the body to the presence of a biodegradable implant. The response may be related to the size and composition of the implant as well as the implant site. The degradation rate of the polymer and the implant site's ability to eliminate the acidic degradants play an important role in the local tissue's reaction to the implant. If the surrounding tissue cannot eliminate the acid by-products of a rapidly degrading implant then an inflammatory or toxic response may result [34].

In summary, the results from studies in humans are mostly favorable with some negative reports. The complications arising from biodegradable orthopedic implants of polymers of lactide and glycolide typically occur at a rate of less than 10% [7]. Although initially significant, these problems resolve with time making the future of biodegradable implants bright.

8. Commercial biodegradable devices

The total US revenues from commercial products developed from absorbable polymers in 1995 was estimated to be over $300 million with over 95% of revenues generated from the sale of bioabsorbable sutures. The other 5% is attributed to orthopedic fixation devices in the forms of pins, rods and tacks, staples for wound closure, and dental applications [37]. In addition, research into biodegradable systems continues to increase, with 60 to 70 papers published each year in the late 1970s to over 400 each year in the early 1990s. The rate at which bioabsorbable fixation devices are cleared through the 510(k) process by the US Food and Drug Administration (FDA) is also increasing, with seven approved in 1995 [19].

The two routes for getting FDA approval to market and sell medical devices in the US are the 510(k) process and the premarket approval (PMA) process. The 510(k) process requires that the new device be shown to be equivalent to a device currently on the US market in terms of safety and efficacy. Clinical data may or may not be required for these devices. The PMA process always requires clinical data and is as stringent as the requirements for a new drug application.

Orthopedic fixation devices of synthetic biodegradable polymers have advantages over metal implants in that

they transfer stress over time to the damaged area, allowing healing of the tissues, and eliminate the need for a subsequent operation for implant removal. The current approved materials have not been commercialized as bone plates for long bone support such as the femur. They have found applications where lower-strength materials are sufficient, such as in the ankle, knee, and hand areas as interference screws, tacks and pins for ligament attachment and meniscal repair, suture anchors, and rods and pins for fracture fixation. Barber has recently compiled a review of the commercially available orthopedic devices [13]. He grouped the devices into four categories with the number of devices listed in each category in parentheses: fracture fixation (6), interference-fixation screws (6), suture anchors (21) and other devices (7). Other devices include screws and plates for maxillofacial repair, tacks for meniscal repair and an implant for ACL reconstruction. The list appears in Table 1.

In this article we have attempted to provide an overview of the orthopedic uses of biodegradable polymers. While sutures were the first commercial product and still account for 95% of all sales, a number of products are now approved for a wide range of applications. And it is expected that a number of additional products will be approved in the next decade.

What is it about these materials that makes them so attractive to the device industry? First, in this conservative field, where devices serve critical, perhaps life and death functions, the industry is slow to accept new materials or new designs. But polymers prepared from these materials, particularly lactide and glycolide, have a long history of safety including the approval of several products. Building on this solid history, researchers continue to evaluate these materials for other uses. The wide range of properties that can be obtained in polymers built with these few monomer units has allowed for a variety of products. We expect that in the future, even more than today, surgeons will have available a number of products using biodegradable products that will speed patient recovery and eliminate follow-up surgeries.

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Current Concepts

Biodegradable Implants in Sports Medicine: The Biological Base

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Summary: Biodegradable implants are increasingly used in the field of operative sports medicine. Today, a tremendous variety of implants such as interference screws, staples, sutures, tacks, suture anchors, and devices for meniscal repair are available. These implants consist of different biodegradable polymers that have substantially different raw material characteristics such as in vivo degradation, host-tissue response, and osseous replacement. Because these devices have become the standard implant for several operative procedures, it is essential to understand their biological base. The purpose of this report is to provide a comprehensive insight into biodegradable implant biology for a better understanding of the advantages and risks associated with using these implants in the field of operative sports medicine. In particular, in vivo degradation, biocompatibility, and the osseous replacement of the implants are discussed. A standardized classification system to document and treat possible adverse tissue reactions is given, with special regard to extra-articular and intra-articular soft-tissue response and to osteolytic lesions. **Key Words:** Biodegradable implants—Clinical application—Sports medicine—Biocompatibility—In vivo degradation.

Materials that disintegrate in the body have been emerging over the past 3 decades, and there are now numerous implants available in the fields of orthopaedic surgery, general surgery, maxillofacial surgery, cardiology, gynecology, and urology. Terms such as absorbable, resorbable, and degradable, with or without the prefix 'bio' are inconsistently used in the literature. We use the term biodegradable to characterize materials that show disintegration after implantation and subsequent complete excretion.

For many years, biodegradable implants have been thought to offer advantages over metal analogs. In orthopaedic practice, metal implants can distort magnetic resonance imaging (MRI),[1,2] and they release metal ions into the surrounding tissue. Further disadvantages include the need for a second surgical procedure for implant removal and complicated revision surgery resulting from the presence of the implant. The intent of biodegradable implants is to provide secure initial fixation strength while allowing degradation and replacement by the host tissue. Therefore, there is no need for implant removal, revision surgery is not compromised, and radiological imaging is not distorted. In addition, functional loads can be assumed earlier by the healing bone while the material is degrading.[3,4]

In sports medicine, the development and use of biodegradable implants has emerged late compared with other fields, such as general orthopaedics, orthopaedic trauma surgery, and maxillofacial surgery. However, the strong interest of joint surgeons in these materials has led to the development of numerous implants becoming available and, as a result, the market has shown a dramatic change within the last few years. Today, we can choose from a large variety

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of biodegradable implants, such as sutures, staples, tacks, anchors, interference screws, and devices for meniscal repair. High mechanical properties of a biodegradable implant may be of primary importance in fracture fixation or other orthopaedic procedures where the implant is exposed to high loads. This may explain the slow progress of biodegradable implant technology in this field. In contrast, as several clinical and biomechanical studies have shown, certain operative procedures in sports medicine do not require implants of high mechanical strength. For interference screw fixation in cruciate ligament reconstruction, the cancellous bone may be the weak link and not the interference screw.[5-7] The fixation strength of a suture anchor construct may be limited by the suture or the bone stock quality.[8,9]

Biodegradable implants consist of different polymeric raw materials that have substantially different material characteristics and tissue response. We believe that it is inappropriate to apply the term biodegradable to all these different materials. Furthermore, it is important to know the basic biology of these materials, such as in vivo degradation, osseous replacement, and biocompatibility, in order to evaluate their appropriateness for the use in operative sports medicine. The purpose of this review is to focus on current developments and to provide the clinician with an insight in biodegradable implant biology.

IN VIVO DEGRADATION

Today, approximately 40 different biodegradable polymers are known.[10,11] Of these, the following materials have been studied to be used in orthopaedic implants:

1. Polyglycolide (PGA) and copolymers such as polyglycolide-co-trimethylene carbonate (PGA-co-TMC), poly-(D,L-lactide-co-glycolide) (PDLLA-co-PGA), and poly-(L-lactide-co-glycolide) (PLLA-co-PGA).
2. Poly-(L-lactide) (PLLA), poly-(D,L-lactide) (PDLLA), and their stereocopolymers with varying ratios of the L and D,L parts.
3. Polydioxanone (PDS).
4. Trimethylene carbonate (TMC).
5. Polyorthoester (POE).
6. Poly-c-capralacton (PCL).

Additionally, composite materials consisting of PLLA/tricalcium phosphate or PLLA/hydroxyapatite have been introduced.[12-15] Of major interest in implant technology in the field of operative sports medicine are the poly-α-hydroxy acids such as PLLA and PGA including their copolymers and stereocopolymers.[16]

In principal, synthetic biodegradable polymers consisting of poly-α-hydroxy acids undergo an unspecific hydrolytic chain scission due to water uptake.[17] Degradation starts at the amorphous phase of the implant leading to fragmentation of the material to smaller parts, which are phagocytosed primarily by macrophages and polymorphonuclear leukocytes.[18-20] Polymeric lactic acid oligomers degrade to monomers which enter the Krebs cycle and get dissimilated to carbon dioxide and water.[17] Beside the hydrolytic chain scission, glycolic acid monomers can be released by unspecific esterases and carboxypeptidases.[21]

Degradation kinetics of different raw materials differ substantially, which may be attributable to the hydrophilic or hydrophobic nature of the different polymers. Furthermore, although the degradation kinetics of biodegradable implants depend primarily on polymer choice, a large variety of additional factors also appear to contribute to this process, including molecular weight, sterilization, implant size, self-reinforcement, and processing techniques.[11,22-30]

We know that in vitro hydrolysis testing could differ markedly from in vivo testing because of the additional influence of environmental conditions. Due to a possible interaction between degrading polymers and the healing tissue, the in vivo degradation characteristics of biodegradable implants should be known. Unfortunately, only a few studies have investigated the in vivo degradation of the different polymers used in biodegradable implants, and these have reported vastly different results because of inconsistent test conditions and different implant processing techniques.[11] Vert et al.[31] tested the tensile strength of different polylactides implanted in sheep tibiae. They reported that PLLA maintains its tensile strength for over 150 weeks. In contrast, Gerlach et al.[24] found that PLLA rods lose approximately 50% of their bending strength within 4 weeks if implanted in rat dorsal muscles. Fischer et al.[14] reported that 2-mm rods made of PDLLA implanted in rat dorsal muscles maintained 90% of their initial bending strength for over 6 weeks with subsequent rapid degradation. In contrast, Mainil-Varlet et al.[32] reported that pushout forces of PDLLA rods implanted in sheep tibiae increased continuously over a period of 6 months and were significantly higher than those of PLLA rods. This may be the result of the implant swelling caused by water uptake of the stereocopolymer. In principal, it is reasonable to assume that slow or intermediate degrading materials such as PLLA, PLLA-co-PDLLA, or PDLLA maintain their mechanical strength at least for the time required

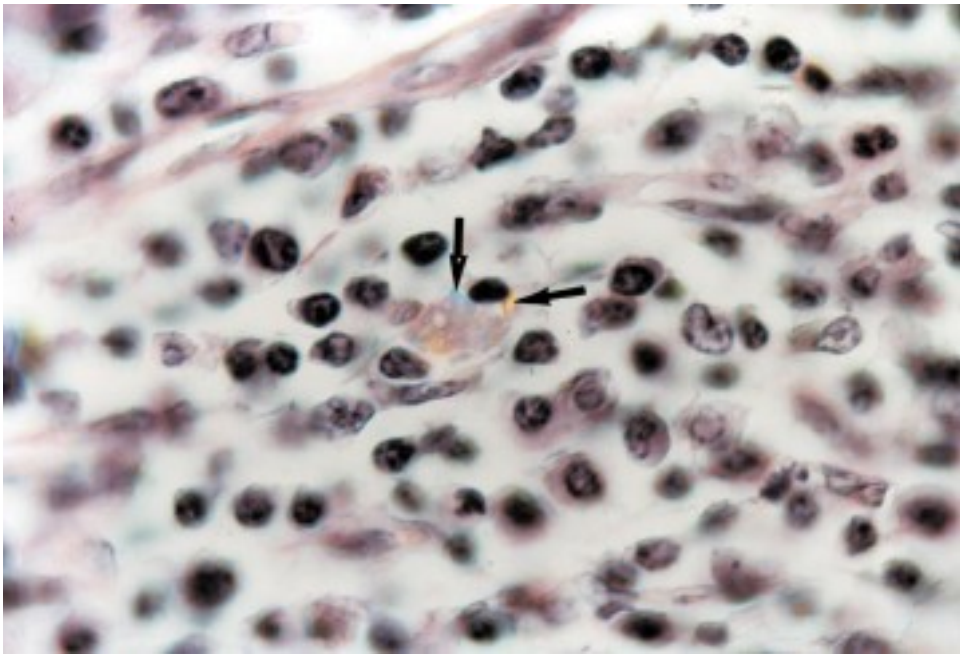

FIGURE 1. Inguinal lymph node of a sheep 6 months after implantation of crystalline self-reinforced PGA pins. Macrophage with intracellularly deposited polymeric particles (black arrows). (Reprinted with permission.[46])

for proper tissue healing. Other materials, such as PDS, PGA, PGA-co-TMC, or PDLLA-co-PGA, which are expected to degrade more quickly, could suffer a significant loss of mechanical strength in vivo within the period of tissue healing. However, clinical studies have not yet reported any healing failure resulting from the use of these materials.[33-39] For long-, intermediate-, and slow-degrading interference screws, different animal studies have proven that these screws withstand the forces until the graft is incorporated.[40-43]

While most reports studied the degradation kinetics of biodegradable implants by measuring strength retention biomechanically, less is known about the long-term fate of implant remnants in the body. Pistner et al.[30] found a large amount of particles of block-polymerized and injection-molded PLLA implants in dorsal rat muscle tissue 112 weeks after implantation, although the material had lost 80% of its bending strength 32 weeks after implantation. Clinical reports have shown that remnants of high molecular-weight PLLA implants could still be found several years after implantation. Bergsma et el.[44] found implant remnants up to 5.7 years after stabilization of midface fractures with PLLA plates and screws.[44] Böstman et al.[45] described the necessity of partial implant removal up to 45 months after stabilization of ankle fractures with highly crystalline self-reinforced PLLA screws. The occurrence of late hydrolytic degradation may depend on the degree of the material's crystallinity. Twelve months after implantation of self-reinforced PGA rods, Weiler et al.[46] found an absence of birefringent material at the implant site, but crystalline PGA remnants were detected in lymph nodes for up to 24 months after implantation (Fig 1). At rearthroscopy, Stähelin et al.[36] found bulky remnants of a highly crystalline PLLA interference screw 20 months after implantation (Fig 2). These reports suggest that a complete degradation of highly crystalline, so-called biodegradable, implants does not occur within an appropriate time. To monitor the complete degradation process of synthetic biodegradable implants in bone tissue, Pistner et al.[47] introduced a scheme of 5 phases of degradation (Table 1).

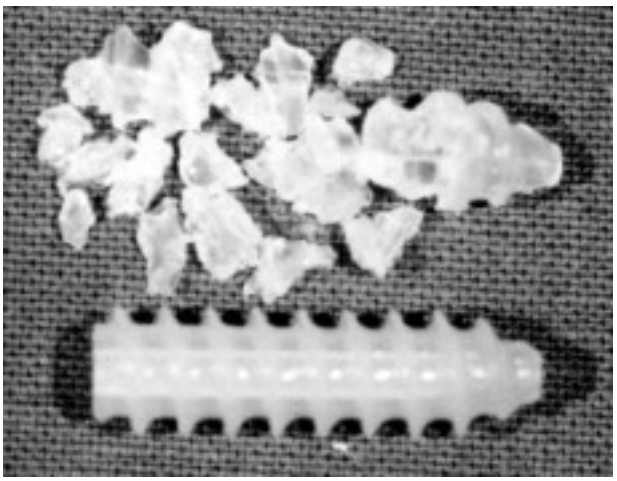

FIGURE 2. Bulky fragments of a highly crystalline PLLA interference screw 20 months after implantation compared with a nonused specimen. (Reprinted with permission.[36])

TABLE 1. *Phases of Degradation of Amorphous Biodegradable Implants and Tissue Reactions According to Pistner et al.*[47]

Phase	Tissue Reaction
1. Healing phase	Unchanged implant, development of a fibrous capsule with a high amount of fibroblasts
2. Latency phase	Unchanged implant, fibrous capsule gets thinner with less cells and more fibers or direct implant contact to bone
3. Protracted resorptive phase	Mainly central degradation of the implant, development of cracks, mild to moderate cellular response with invasion of macrophages and foreign-body giant cells
4. Progressive resorptive phase	Progressive disintegration of the implant with a severe tissue response (macrophages, foreign-body giant cells)
5. Recovery phase	No polymer remnants detectable, development of scar tissue or osseous replacement of the former implant site

OSSEOUS REPLACEMENT

A major intent of biodegradable implants is complete tissue replacement at the former implant site. Although an early replacement with fibrous granulation tissue takes place during degradation,[46,48-53] less is known about the long-term fate of the former implant site and its osseous replacement. Although a complete osseous replacement has been anticipated for all biodegradable implants, it has not yet been shown either experimentally or clinically in most cases. To facilitate uncompromised revision surgery, a complete osseous replacement should occur within a 2- to 3-year time frame to allow for a second interference fit or tack fixation as, for example, in cruciate ligament and shoulder revision surgery.

The osteogenic reaction of the host tissue starts early after implantation of the polymeric material and shows an osseous enclosure within the first few weeks[51,53] (Fig 3). During or following implant degradation, osseous replacement may follow 3 different patterns:

1. There is osseous ingrowth while the implant is degrading (Fig 4). This phenomenon is most desirable but has rarely been found. To our knowledge, it has only been reported to occur during the degradation of PLLA-co-PDLLA (70:30) or self-reinforced PLLA/PDLLA composite rods.[50,51]
2. There is osseous ingrowth in the center of the former implant site after the implant is degraded (Figs 5 and 6).[46]
3. There is an osseous scaring of the former implant site with a slow marginal ingrowth of new bone (Fig 7). This kind of replacement has been found in cases after an osteolytic lesion has occurred and may progress over several months or years.[46]

In general, it is reasonable to assume that the faster a material degrades, the earlier the osseous replacement

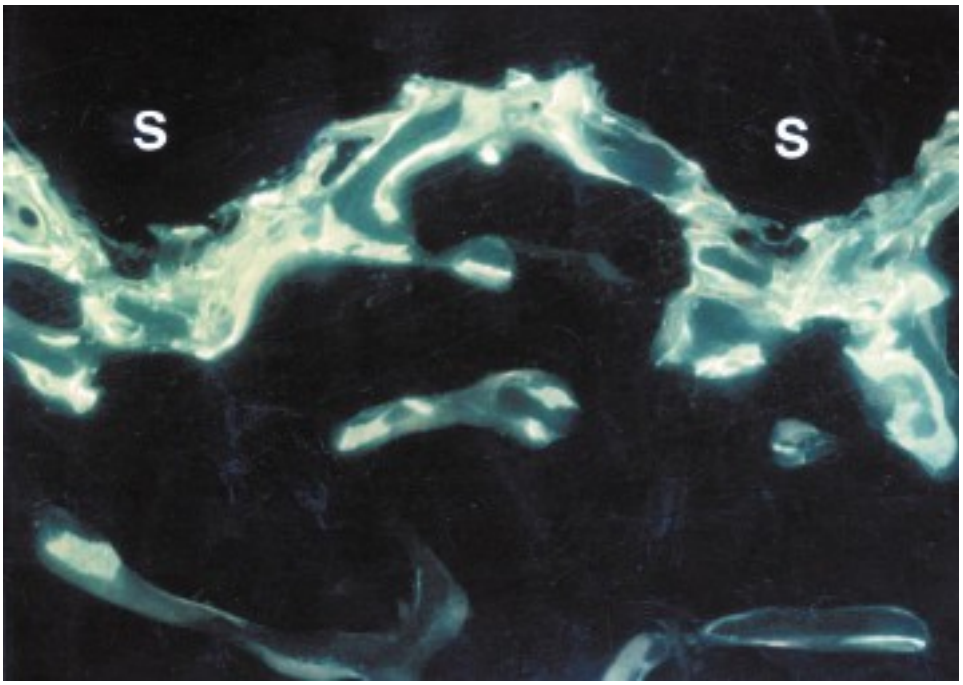

FIGURE 3. Tissue-implant interface 6 weeks after implantation of a PDLLA interference screw in a sheep femur. Polychrome sequential labeling shows activity of the early given fluorochromes (calcein green given at 4 weeks and xylenol orange at 6 weeks) indicating the early osseous enclosure of the implant (S, screw threading).

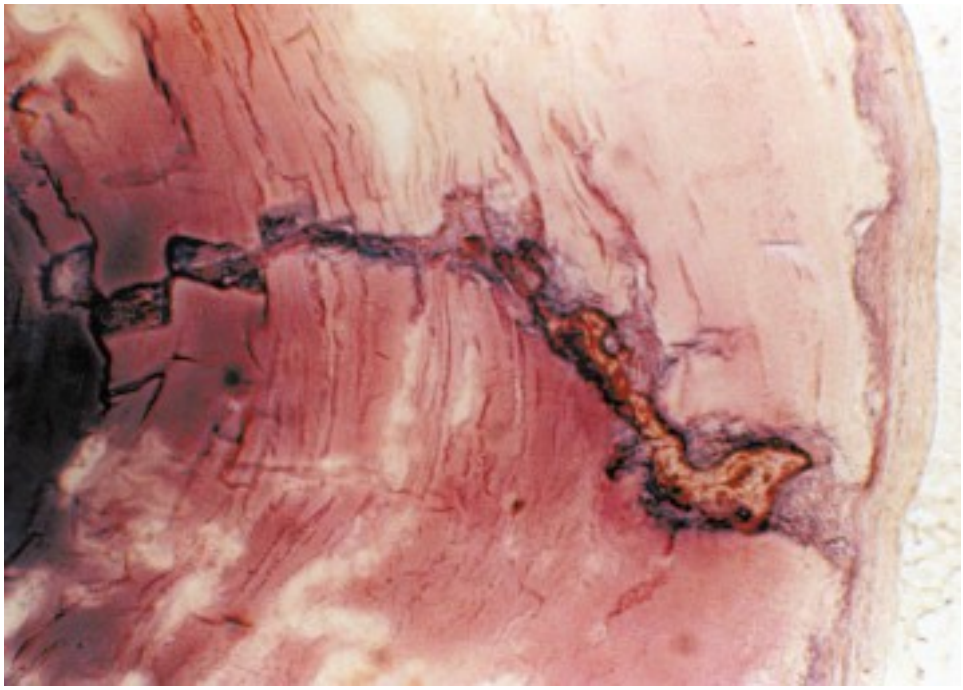

FIGURE 4. Bone trabeculae growing into a PLLA-co-PDLLA pin 15 months after intramedullary implantation in a sheep tibia.

takes place (Figs 8 and 9).[36,54] Materials such as PDLLA-co-PGA, PLLA-co-PDLLA, or PDLLA are considered to degrade faster compared with PLLA implants, for which the degradation process has been described to last for several years.[44,55,56] To our knowledge, no single report has shown complete osseous replacement of a PLLA implant in a clinical or experimental setup (Figs 10 and 11). Several experimental studies have been performed to investigate tissue response and tissue replacement after implantation of PLLA material into bone.[27,49,52,53,57] Unfortunately, their follow-up of 48 to 52 weeks was inappropriate to evaluate either tissue response or tissue replacement, because little or no signs of material degradation had taken place. Gatzka et al.[56] followed a series of patients after stabilization of ankle fractures

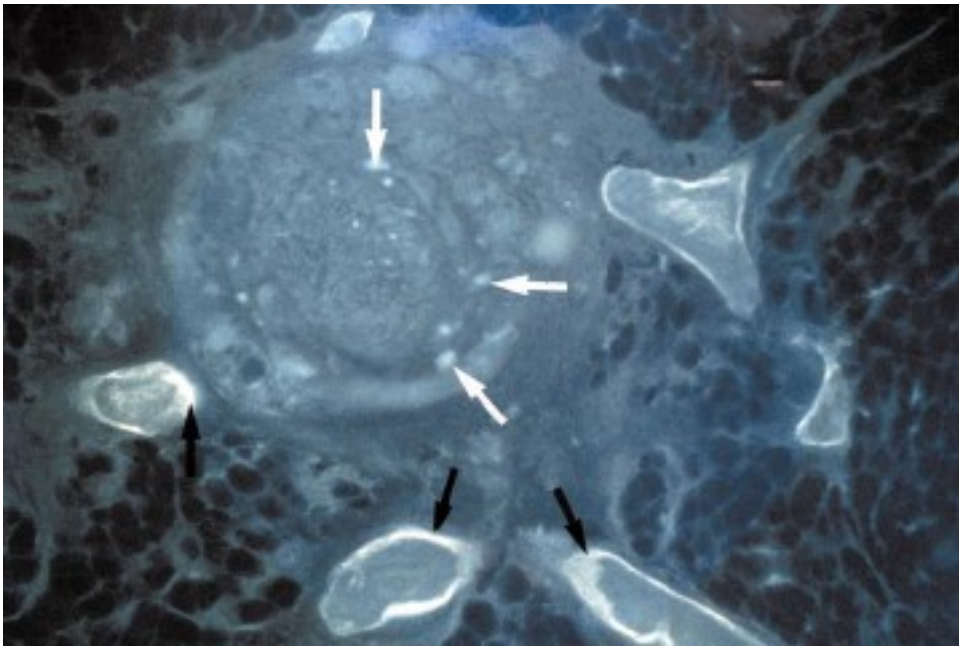

FIGURE 5. New bone trabeculae growing in the center of the former implant site 6 months after implantation of self-reinforced PGA pins in a sheep distal femur. The tetracycline fluorescence (black arrows) indicates the osseous activity. There are implant remnants left (white arrows). (Reprinted with permission.[46])

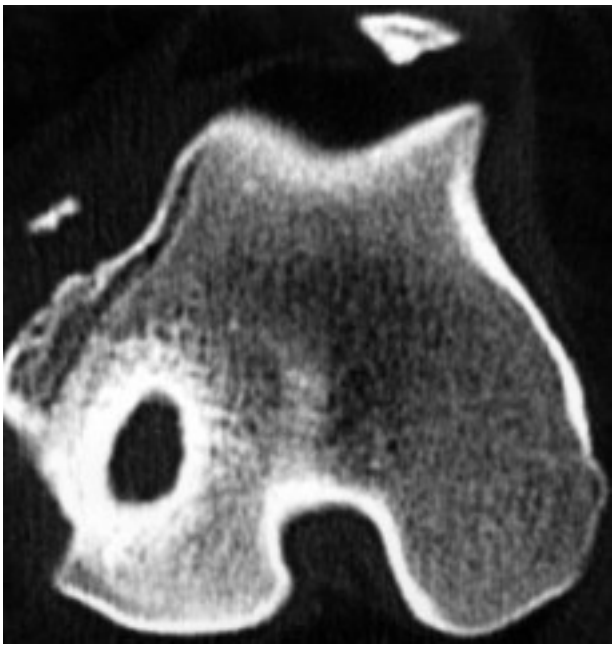

FIGURE 6. CT scan showing severe osseous sclerosis of an implant site 18 months after metaphyseal implantation of PLLA-co-PDLLA pins in a sheep.

with high molecular-weight PLLA screws.[56] In a study of MRI scans, they found that no osseous replacement of the implant had occurred up to 6 years after implantation (Fig 10). Pistner et al.[47] studied the intraosseous long-term fate of injection-molded PLLA and PLLA-co-PDLLA screws inserted in the femur of guinea pigs. After implantation of 150 weeks, they found that osseous replacement of the former implant site had occurred and, therefore, stated that amorphous polylactides are fully biodegradable materials. However, even for faster-degrading implants, the process of osseous replacement may require several years if there has been evidence of an osteolytic lesion during the final stage of degradation (Fig 12).

BIOCOMPATIBILITY AND CLINICAL CLASSIFICATION OF TISSUE RESPONSE

Since the mid 1960s, many studies have been performed to evaluate the suitability of various synthetic biodegradable polymers. Prompted by the results arising out of these investigations, biodegradable implants for various orthopaedic procedures have been introduced. However, the biocompatibility of these materials is still controversial.

The degradation process and tissue response have been documented by many authors. These studies show that biodegradable poly-α-hydroxy acids cause mild, nonspecific tissue response with fibroblast activation and the invasion of macrophages, multinucleated foreign-body giant cells, and neutrophilic polymorphonuclear leukocytes during their final stage of degradation.[47,48,51-53,57-62] The initial euphoria arising out of excellent clinical results was abated by the first reports of foreign-body reactions with biodegradable implants in fracture treatment. In 1987, Böstman et al.[63] re-

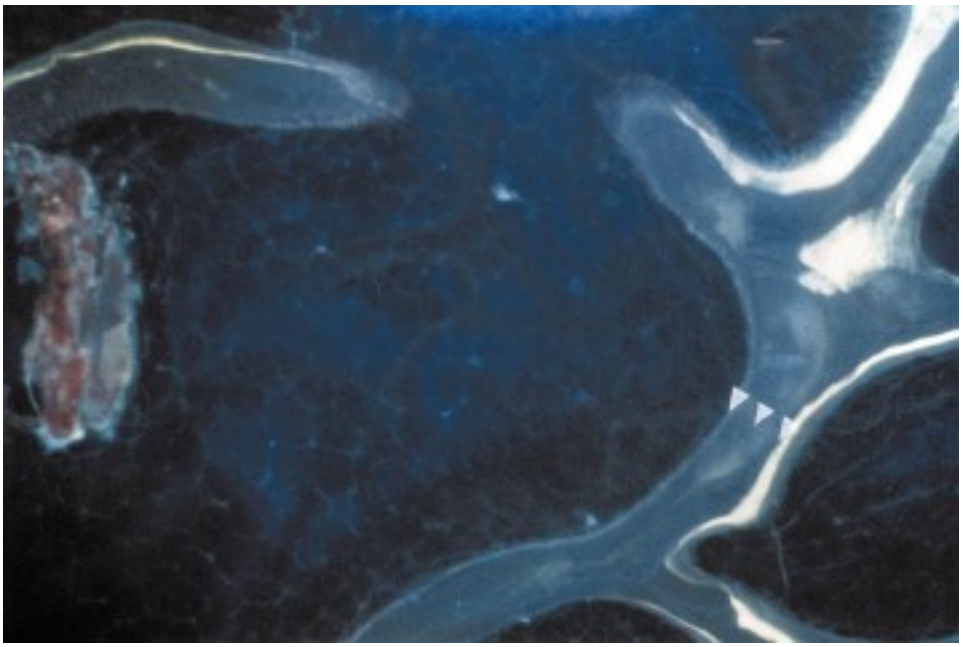

FIGURE 7. Implant site after 18 months of implantation of a self-reinforced PGA rod. Slow bony formation at the margin of the implant site; tetracycline labeling (arrows) 12 months before harvesting the knee (fluorescence microscopy with an almost selective tetracycline presentation).

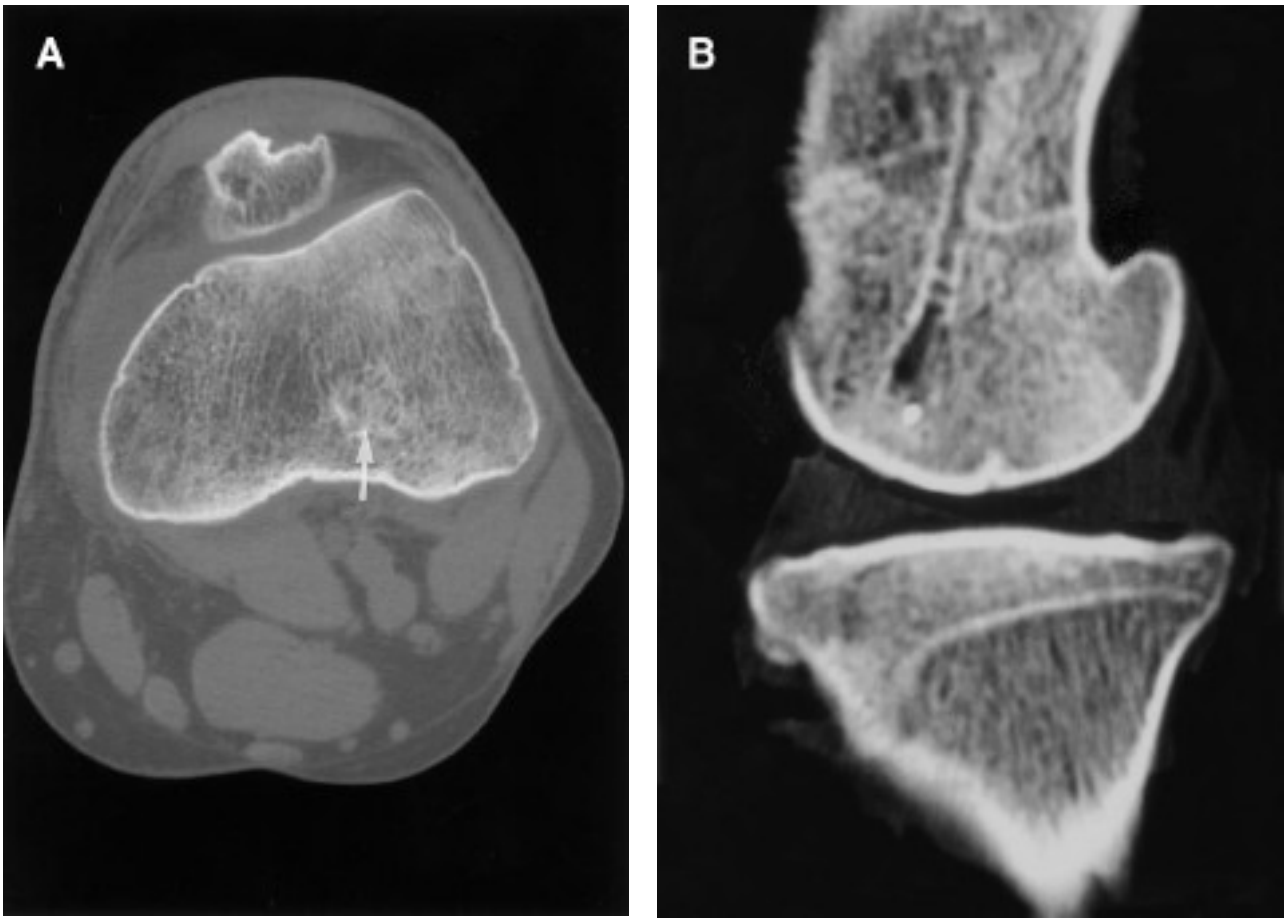

FIGURE 8. (A) CT scan 12 months after anterior cruciate ligament reconstruction with a patellar tendon graft fixed with a PDLLA-co-PGA interference screw. There is a complete osseous replacement of the former implant site (arrow). (B) CT scan 30 months after implantation of a PLLA-co-PDLLA pin in a sheep femur. There is almost a complete osseous restitution of the former implant site.

ported a sterile sinus formation after the use of PGA rods in ankle fractures. Since then, other reports have shown that foreign-body reactions to PGA implants occurred in varying degrees of severity ranging from mild osteolytic changes to intense granulomatous inflammatory soft-tissue lesions necessitating surgical intervention.[46,64-68] This reported intensive inflammatory tissue response was associated with the use of highly crystalline self-reinforced PGA implants, which consequently led to a decrease in their clinical use. However, these experiences led to deep concerns about the suitability of biodegradable implants in orthopaedic surgery.

Many different biodegradable polymers are currently available with better biocompatibility, such as PDS, PLLA including its stereocopolymers and copolymers, and some PGA copolymers. Because many factors contribute to biocompatibility and many different polymers are increasingly implanted, it is essential to have standards to compare the tissue response in experimental or clinical studies and to discuss these reactions strictly individualized for the different materials. Literature reviews on tissue reactions to PGA implants have highlighted the problem of the inability to compare results because of the lack of a well-defined classification system.[16,46] Therefore, we suggest a standardized classification system based on our previous investigations and clinical experiences.[46,51,66,69,70] Such a tool may enable us to gain more standardized information on the incidence and severity of tissue reactions in relation to the choice of polymer, implant design, or anatomic location.

Foreign-body reactions to biodegradable implants should be divided into osseous, extra-articular, and intra-articular synovial inflammatory soft-tissue responses. In each group, tissue responses are differentiated into 4 groups according to the severity of radiological and clinical findings.

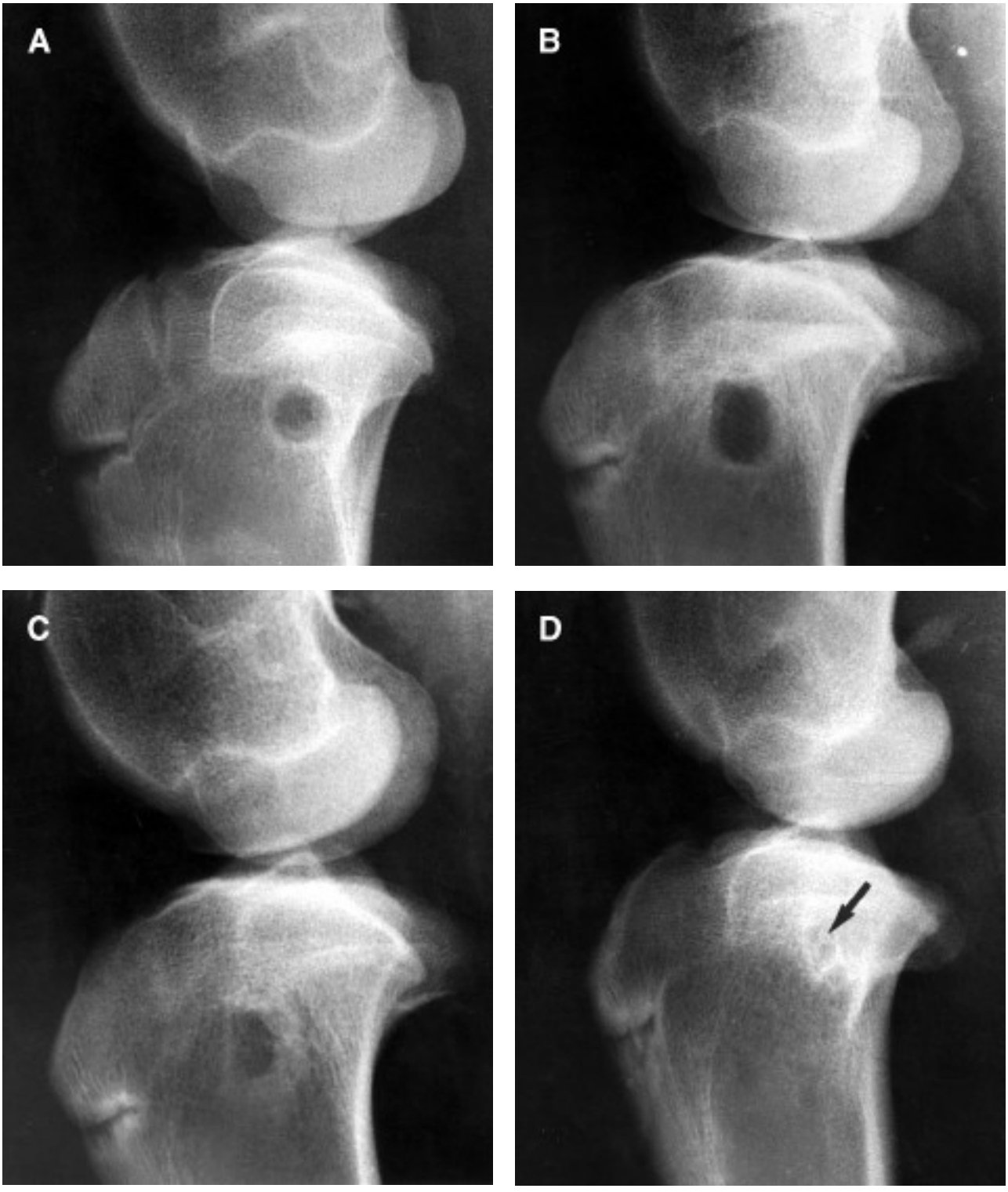

FIGURE 9. Radiographs after metaphyseal implantation of a PDLLA interference screw in a sheep tibia. After 72 weeks, the former implant site appears with an almost complete osseous replacement (arrow) after a transient mild osteolytic change (O-1) at 24 weeks. (A) Postoperative view, (B) after 24 weeks, (C) after 56 weeks, and (D) after 72 weeks.

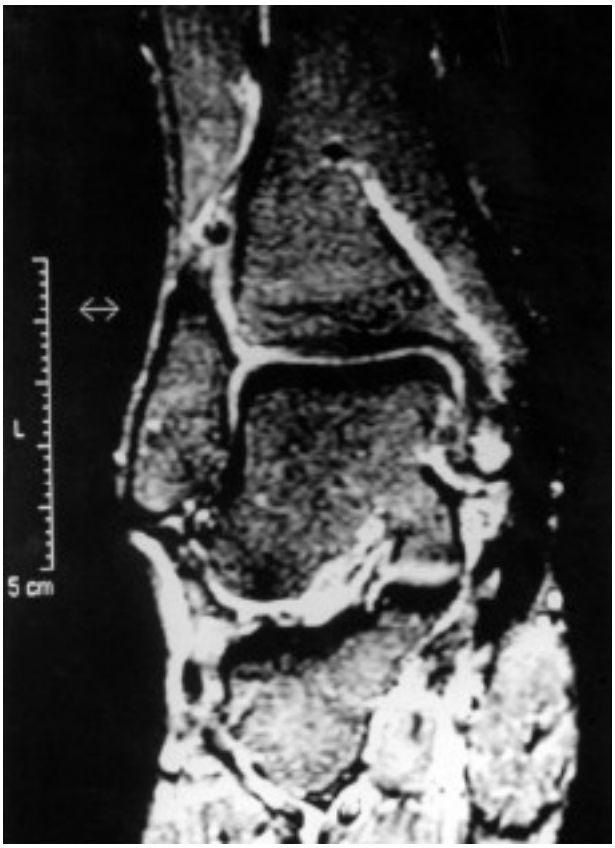

FIGURE 10. MRI 6.5 years after stabilization of a fracture of the medial malleolus with PLLA screws. There are no signs of an osseous replacement, but the hypointense signal indicates the degradation.

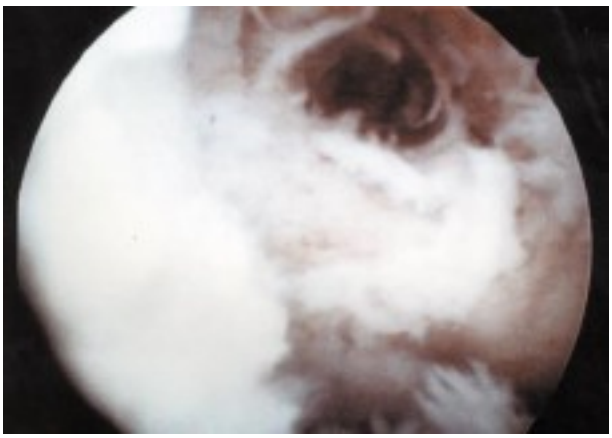

FIGURE 11. Arthroscopic view of the femoral fixation site of a patellar tendon graft 30 months after the use of a PLLA interference screw. Grossly, there are no signs of osseous ingrowth and the threading imprint is still visible.

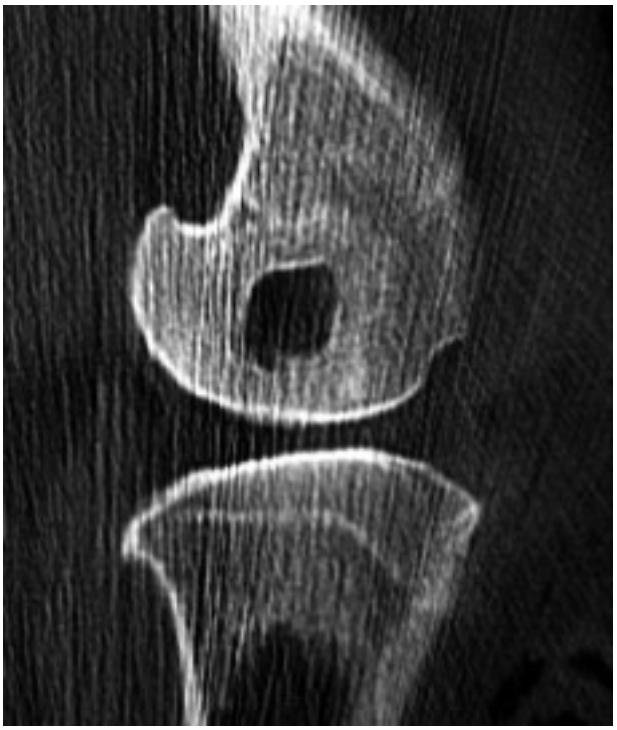

FIGURE 12. CT scan 24 months after implantation of a PGA pin in a distal sheep femur. There is still a moderate osteolytic lesion with no signs of new bone formation, although the implant site contained no PGA material after 6 months. (Reprinted with permission.[46])

Osteolysis

The first reaction at the implant site consists of bone resorption stimulated by the byproducts released during the degradation, and this is visible as radiolucencies on plain radiographs and computed tomography (CT) scans (Table 2). MRI scans are often appropriate to measure these lesions, but interpretation of findings may be difficult because of the reactive surrounding zone accompanying the final implant degradation.[71] Radiolucencies vary from mild osteolytic changes at the implant site to cystic-like extended resorption cavities (Fig 13A). Mild osteolytic changes probably have no effect on fracture healing, soft-tissue fixation, or the static properties of the bone.[71,72] However, if these changes exceed a certain level, they are likely to interfere with fracture healing (Fig 13B)[73] or graft fixation. The predictable osteolytic reaction described for PGA implants[46,65,68,74-77] has also been observed to be associated with the use of PLLA, PDLLA-co-PGA, PGA-co-TMC, and PLLA stereocopolymers, although with a lower incidence and intensity.[51,78-80]

Extra-articular Soft-Tissue Reactions

If the material is applied extra-articularly in soft tissue or in cancellous bone of the metaphysis, such as wrist or

TABLE 2. *Classification of Osteolysis (O) According to Hoffmann et al. and Weiler et al.*[46,69]

Osteolysis		Radiological Findings
O-0	None	No osteolytic changes visible
O-1	Mild	Osteolytic changes at the implant site (osteolysis 1 mm or larger than implant diameter)
O-2	Moderate	Cystic-like extended osteolysis (osteolysis 3 mm or larger than implant diameter, Fig 13A)
O-3	Severe	Confluence of osteolysis into a resorption cavity (if more than 1 implant is used)
O-4	Disturbed healing	Fracture displacement, fragment sequestration, or healing failure of soft tissue due to osteolysis (Fig 13B)

ankle fractures or the tibial interference screw in anterior cruciate ligament reconstruction, the debris accumulated at the implant site during degradation could be expelled into the surrounding soft tissue (Table 3, Fig 14). This can be followed by a progressive inflammatory response, manifesting as a subcutaneous soft-tissue induration or a fluctuant swelling that may perforate the skin and form a sinus (Fig 15). The incidence depends on the anatomic location and ranges from 4% to 14.6% in ankle fractures and from 22.5% to 40% in wrist fractures if self-reinforced PGA implants are used.[66,68,74,81] These reactions have also been observed with a much lower incidence and intensity for PDS or PLLA implants.[45,82-85]

Intra-articular Synovial Reactions

The intra-articular biocompatibility is of special interest in the field of operative sports medicine

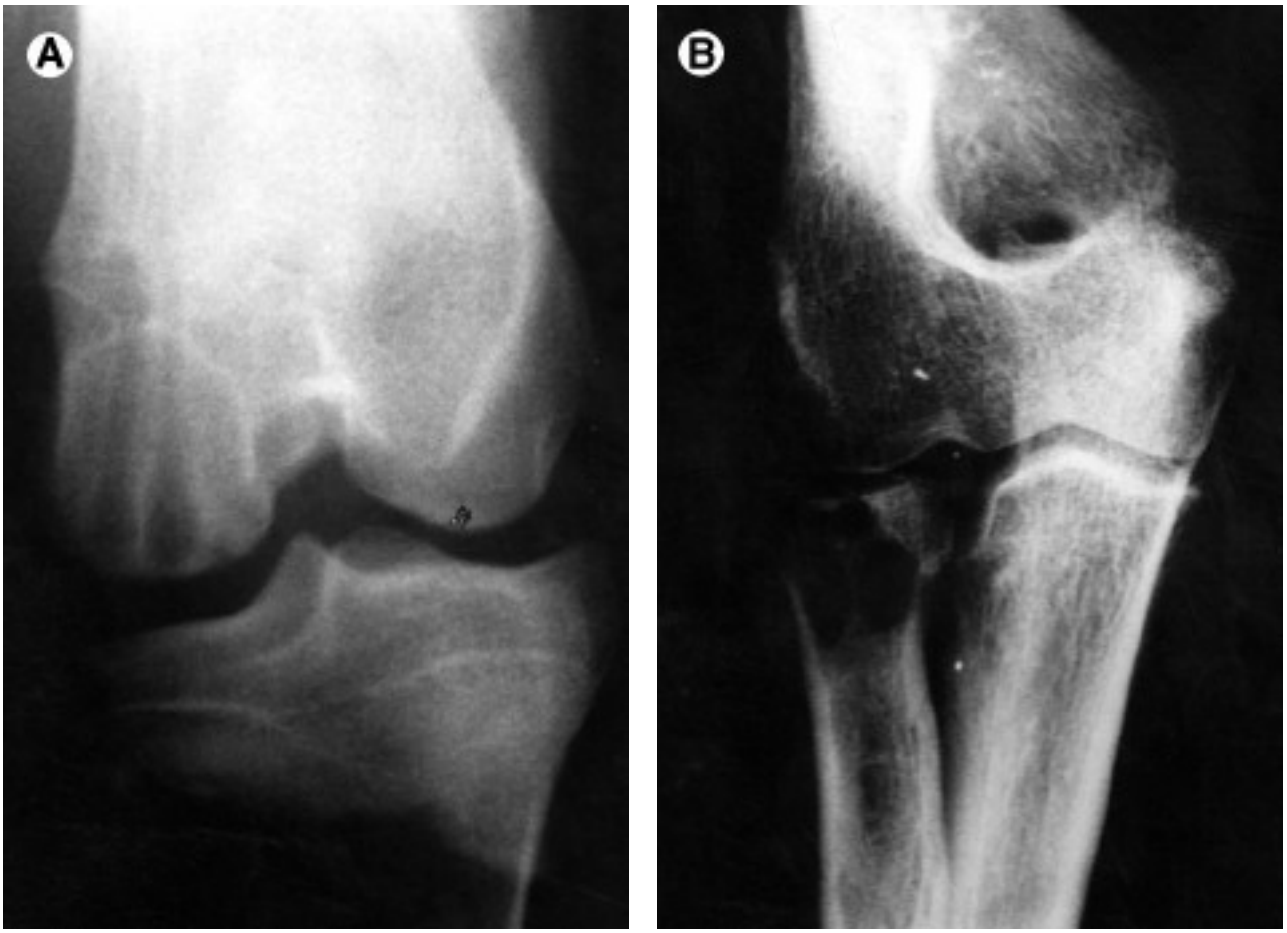

FIGURE 13. (A) Cystically extended resorption cavities (O-2) 12 weeks after osteochondral fragment fixation in a sheep with self-reinforced PGA pins. (Reprinted with permission.[46]) (B) Fracture sequestration (O-4) after stabilization of a multifragmentary radial head fracture with PLLA pins. The fracture situation has been considered to be unstable, and osteolyses occurred 6 months after surgery, although final material degradation is expected to occur later.

TABLE 3. *Classification and Treatment of Extra-articular Soft-Tissue Reactions (EA) According to Hoffmann et al.*[69]

Extra-articular Soft-Tissue Reactions		Symptoms/Findings/Treatment
EA-0	None	No or subclinical reaction
EA-1	Mild	Local, mild soft-tissue induration; no treatment
EA-2	Moderate	Fluctuant swelling, fluid accumulation (ultrasound), local warmth, reddening, swelling, pain; single or repetitive puncture necessary (Fig 15A)
EA-3	Severe	Spontaneous discharge of sinus, primary sterile, secondary possible bacterial contamination; debridement and open wound treatment (Fig 15B)
EA-4	Bacterial superinfection	Deep soft-tissue/bone infection following EA-2 or EA-3; extensive and repetitive debridement

because most implants are applied intra-articularly, such as sutures or tacks for meniscus or labrum repair, or the implant site may be connected with the joint space as in the case of interference screws or suture anchors (Table 4). Whereas osteolysis and extra-articular reactions are associated with the final stage of implant degradation, an inflammatory intra-articular response may also be associated with loosened fragments or wear debris released before implant degradation. This has been shown for the knee and shoulder joint[86,87] and may occur principally with tacks for labrum or meniscus repair. As soon as a connection between the implant site and the joint space exists, the synovial membrane can come into contact with the polymeric debris at the time of final degradation (Fig 16). Barfod and Svendsen[88] and Friden and Rydholm[89] reported cases of severe synovitis following intra-articular use of crystalline self-reinforced PGA rods. In these cases, crystalline polymeric debris surrounded by foreign-body giant cells could be identified as the cause. Recent reports describe a high incidence of loss of motion with synovial adhesions attributable to the inflammatory response after the use of PGA-co-TMC tacks in the shoulder joint.[39,90-92] Intra-articular synovial reactions vary from mild joint effusions to severe synovitis with the necessity of surgical intervention (Table 4).

As compromised biocompatibility is most commonly detected in the latter stages of implant decomposition, it is well accepted that the degradation byproducts are responsible for tissue reactions. Consequently, this implies that a large amount of byproducts being released per time unit from the implant cannot be adequately handled by the clearing capacity of the surrounding tissue. This mainly depends on the degradation kinetics of the implant. This process can last up to several years and influences the time schedule for experimental or clinical follow-up studies. Maximum extent of foreign-body reactions associated with PGA implants should occur approximately 12 weeks after

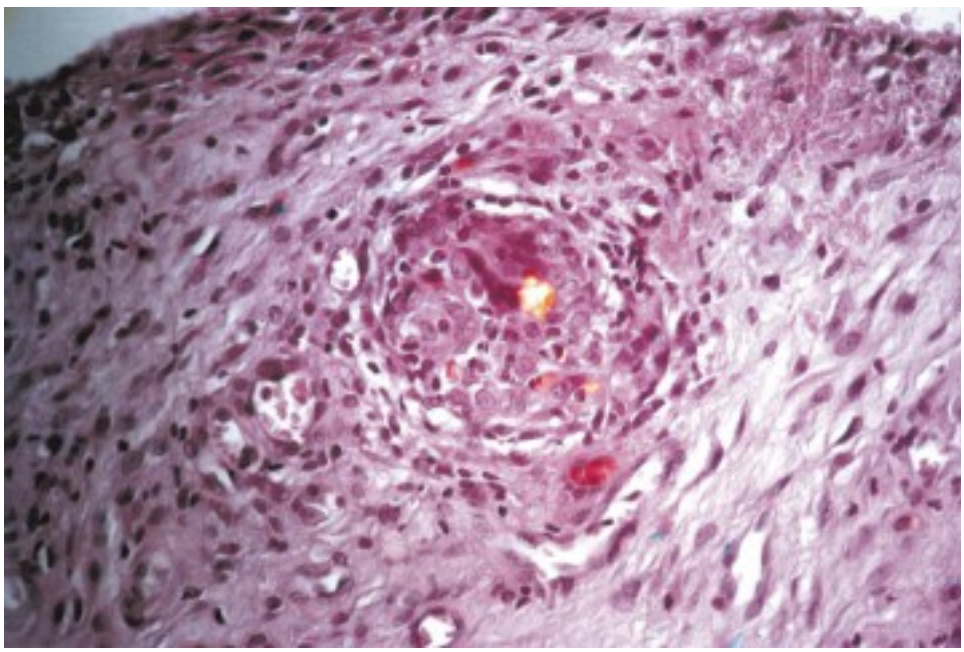

FIGURE 14. Histology of the discharge after a sterile sinus formation shows leukocytes and foreign-body giant cells surrounding the birefringent PGA particles (polarized light).

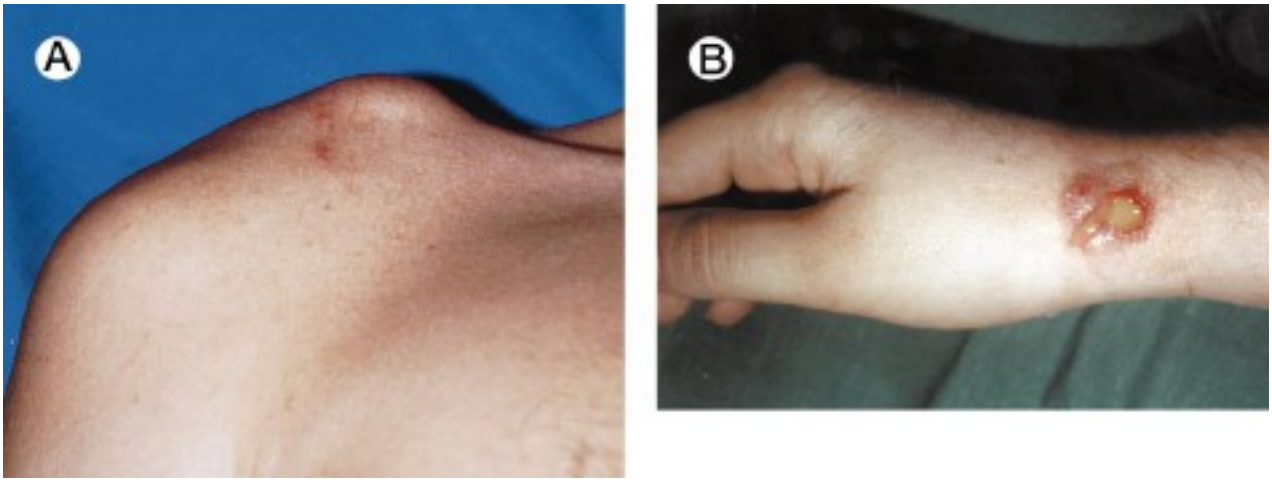

FIGURE 15. (A) Subcutaneous fluctuant swelling (EA-2) after reduction of a Rockwood type V acromioclavicular joint separation with a PDS band. (B) Spontaneous discharge of debris (EA-3) after stabilization of a wrist fracture with self-reinforced PGA rods. (Reprinted with permission.[69] Copyright 1997 by Springer-Verlag.)

surgery.[46,57] Those accompanied with PDS, PGA-co-TMC, or PDLLA-co-PGA may occur between 8 and 24 weeks after implantation. With the few reported cases of foreign-body reactions associated with PLLA or PLLA-co-PDLLA implants, they may occur between 1 and 2 years at the earliest but normally occur later, depending on implant processing techniques, stereocopolymer composition, implant design, and molecular weight.[51,82,85,93]

As for soft-tissue reactions, it is reasonable to assume that fast accumulation of implant fragments or low molecular-weight byproducts cannot be handled adequately by the clearing capacity of the tissue, represented by macrophages and polymorphonuclear leukocytes. Therefore, soft-tissue reactions are mostly associated with fast-degrading implants, such as those composed of PGA. However, they may also be observed for PLLA if the implant volume exceeds a certain level and the local clearing capacity of the tissue is overloaded.[82]

It is known that debris of degradable or nondegradable materials, such as polyethylene or polymethylmethacrylate, leads to an inflammatory tissue response if the particles get phagocytosed by macrophages.[18,62,94,95] In addition, macrophage activation leads to bone resorption via mediator release, which results in osteoclast activation.[96-98] This may account for the appearance of osteolytic changes with the use of biodegradable implants, because maximum macrophage accumulation at the tissue-implant interface correlates with the maximum expansion of osteolysis, as it has been described for PGA implants.[46,57]

As an important factor, there are several reports that the local decrease in pH at the implant site during the degradation is 1 of the main reasons for the inflammatory tissue response.[99-101] On the contrary, in a recent

TABLE 4. *Classification and Treatment of Intra-articular Synovial Reactions (IA) According to Hoffmann et al.*[69]

Intra-articular Synovial Reactions		Symptoms/Findings/Treatment
IA-0	None	No or subclinical reaction
IA-1	Mild	Mild (sterile) joint effusion, no additional local or systemic signs of inflammation, single need for puncture, foreign-body giant cells, round cells, or implant remnants in puncture fluid or synovial membrane
IA-2	Moderate	Significant (sterile) joint effusion, no other additional local or systemic signs of inflammation, need for recurrent puncture, foreign-body giant cells, round cells, or implant remnants in puncture fluid or synovial membrane; administration of nonsteroidal anti-inflammatory drugs, partial weight-bearing until disappearance of symptoms
IA-3	Severe	Significant (sterile) joint effusion with local signs of inflammation (pain, reddening, warmth), need for recurrent punction or surgical revision (e.g., arthroscopic synovectomy), foreign-body giant cells, round cells, or implant remnants in puncture fluid or synovial membrane
IA-4	Bacterial superinfection	IA-1 to IA-3 and positive microbiological examination, arthroscopic or open debridement with lavage and synovectomy

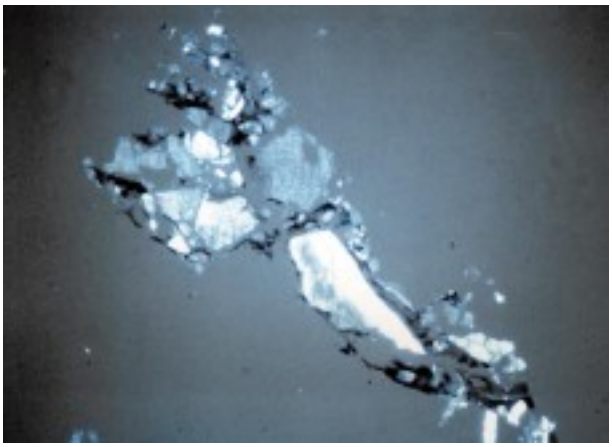

FIGURE 16. Synovium of a patient at rearthroscopy 30 months after implantation of a highly crystalline PLLA interference screw. There are birefringent implant remnants, although the implant site grossly showed no material remaining (see Fig 11).

study, Ignatius and Claes[102] were able to show that the accumulation of PLLA-co-PDLLA or PLLA-co-PGA degradation products itself may reduce growth in cell culture. The toxic influence was dependent on a high concentration of degradation products after pH adjustment.

It is reasonable to assume that a protracted degradation is of primary importance in increasing the biocompatibility of a biodegradable implant, especially with regard to the soft-tissue response. But even slow-degrading and amorphous polymers may provoke osteolytic changes if there is insufficient drainage of byproducts in the surrounding tissues or when the cellular clearing capacity may be overloaded.

However, other factors appear to contribute to biocompatibility. Matlaga et al.[103] and Lam et al.[104] showed that even the implant shape affects the intensity of an inflammatory response using degradable and nondegradable polymers. This has largely been discussed for the self-reinforcement of PGA implants but has not yet been proved. Additionally, mechanical instability at the implant site may accelerate degradation and may consequently lead to a higher amount of degradation products being released per unit of time, thus possibly increasing the host-tissue response. Furthermore, the crystallinity of a biodegradable implant, which prevents late hydrolytic degradation, can result in a foreign-body reaction.[44,104-106] Thus, use of materials with low crystallinity has been advocated for medical purposes.[107]

Synovial reactions are associated with the release of implant fragments into the joint space. This rare but severe complication was observed with the use of PGA, PGA-co-TMC, or PLLA implants in the knee and shoulder joints.[39,46,86,88-92,108,109] This specific synovial reaction to polymeric particles also occurred with a high incidence using artificial nondegradable ligaments for cruciate ligament reconstruction.[110-114] Ligament wear particles were identified as the cause,[115-117] and recent clinical observations and an experimental study have shown that these wear particles are deposited in the draining lymph nodes.[118,119] This phenomenon has also been described for crystalline PGA and PLLA implants, which suggests that only incomplete degradation of highly crystalline materials occurs[46,120] (Fig 1). Future studies should take into consideration the fact that crystalline implant remnants may provoke late synovial reactions; for example, if highly crystalline PGA, PLLA, or PGA-co-TMC implants, such as tacks and pins for labrum and meniscus repair, are used intra-articularly. The fatal long-term results of these reactions after stabilization of ankle fractures with PGA rods has recently been described.[108] Böstman[108] reported the development of a moderate to severe osteoarthritis of the ankle that occurred 36 to 109 months after surgery in 10 of 74 patients who had previous inflammatory soft-tissue reactions. He concluded that the joint damage seemed to be caused by polymeric debris entering the articular cavity through an osteolytic lesion.

CONCLUSION

The use of biodegradable implants offers distinct advantages in the field of operative sports medicine. Thus, research and development of biodegradable implants should be given high priority. The research on these devices should be encouraged by the will to define and solve problems and to find technical solutions, rather than driven by the desire for quick results.

Concerns about the poor biocompatibility of self-reinforced PGA implants do not necessarily apply to other materials with an appropriate tissue response. Biocompatibility depends on a large variety of factors. Therefore, each biodegradable implant should be tested regarding its intraosseous, soft-tissue, and intra-articular biocompatibility, and discussion of the results should be strictly individualized for each of the different polymers, copolymers, and stereocopolymers. Furthermore, in vivo long-term studies are necessary, with follow-up until implant remnants have disappeared and an osseous replacement has taken place. To gain more information on biocompatibility according to the specific choice on polymer and

implantation site, the clinical use of biodegradable implants is recommended to be performed under study conditions, and all results concerning tissue response should be evaluated with a standardized classification system.

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