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REVIEW ARTICLE

Bioabsorbable materials in orthopaedics

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The applications of bioabsorbable implants in Orthopaedic Surgery have mainly been mandated from the need to eliminate implant removal operations. Although they have not gained widespread popularity among orthopaedic surgeons, they still represent an area of evolution. Considerable effort has been put into developing new bioabsorbable materials with fewer adverse effects. In this article an extensive review of the literature is presented emphasising on basic science and clinical applications of these materials. A review of the types of implants, the materials used, their biochemical properties, their adverse effects and some of the potential future applications is presented.

Keywords : bioabsorbable materials ; bioabsorbable implants ; biodegradable.

INTRODUCTION

The advent of synthetic materials for bone fixation is of paramount importance in Orthopaedic Surgery (*14*). Adverse effects such as migration, growth disturbance, rigidity, radio-opacity, infection, effects on cellular level and implant removal operations, often accompany the use of these materials (*8*). Patients are mostly concerned about implant removal operations. Mittal *et al* (*49*) asked 100 adult patients who suffered a fracture, to fill a questionnaire regarding the way they would like to have their fracture fixed. Detailed information was provided to the patients regarding the metallic and bioabsorbable materials. Ninety five percent answered that they would prefer to have their fracture fixed with bioabsorbable devices while 80% would like to participate in a clinical trial to compare metallic to bioabsorbable devices. The first study concerning biodegradable materials used for implantation was presented in 1966 by Kukri *et al* (*39*), who studied the biocompatibility of poly-L-lactic acid (PLLA) in animals. The material proved to be non-toxic and gradually degraded, and the use of PLLA plates and screws to fix mandibular fractures in dogs was presented by Kulkarni *et al* (*38*). During the same year (1971) another study was published presenting the results of PLLA sutures in mandibular fractures (*20*), reporting no serious tissue reactions. A variety of biodegradable implants has been used ever since. Most of the clinical trials

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concerning the use of polyglycolic acid (PGA) and polylactic acid (PLA) were published in the early 90's (*17*). A number of innovations in material science, such as the self-reinforcement technique that was presented by Tormala *et al* (*65*) in 1998, and the introduction of co-polymers, led to implants with better biodegradation and mechanical properties.

Types of implants

Many companies are currently involved in the bioabsorbable material industry and a variety of devices and implants constructed from different materials are commercially available. Pins and screws made of PGA have been widely used, while a variety of PLA implants including pins, rods, tacks, screws and plates are available. Many other implants such as membranes, arthroscopic and spine surgery implants, are currently in use. Their composition and the mode of reinforcement vary according to the operation for which they are intended.

Materials

Many studies have been conducted regarding the biocompatibility and biodegradation of different materials that are used as surgical implants. Orthopaedic surgery mandates the use of materials with biocompatibility and unique mechanical properties. PLA and PGA have both enjoyed widespread popularity among orthopaedic surgeons. Nowadays, materials such as poly[ortho esters], poly[glycolide-co-trimethylene carbonate], poly[p-dioxanone] (PDS), poly[ε-caprolactone] (PCL), poly[β-hydroxybutyrate] (PHB) and poly[PHB-hydroxyvaleric acid] are available. Furthermore, pseudo-poly[aminoacids] or polyaminocarbonates show promising properties (*3*). However, most of the commercially available implants are still made of PGA and PLA or their co-polymers. Therefore implants made of these materials are included in this review.

PGA is hydrophilic and highly crystallic. Degradation and strength loss, occur early and lead to post-operative complications. PGA glass transition temperature is 36° C and it becomes malleable only if this temperature is exceeded. Intraoperatively, the material must be heated to a temperature that exceeds its glass transition temperature, in order to adapt to the implantation surface, and cooled thereafter in order to be implanted. This is a major drawback, in terms of intraoperative time consumption.

PLA has an extra methyl-group in its monomer (lactic acid) that makes it more hydrophobic. Two enantiomeric isomers of PLA, the L-isomer and the D-isomer, have different properties. The L-isomer (poly-L-lactic acid or PLLA) is rather hydrophobic and crystallic, with prolonged degradation time (up to several years) a fact that makes it similar to non-degradable materials (in vivo behaviour) and leads to late adverse reactions at the final stages of polymer degradation. The D-isomer is rather amorphous and less stable, properties proven to be advantageous in building co-polymers (*3, 73*). The glass transition temperature of PLLA is 57°C.

Although commonly used in surgery, PDS is not widely accepted as an osteofixation device material, mainly due to its rapid degradation (about 2 months) and unfavourable mechanical properties (*36*).

The problem of degradation has led to the development of the copolymers. Bostman *et al* (*17*) presented a great number of patients treated with such implants, and reported many material-related complications.

P(L/D)LA : PLLA is hydrophobic and crystallic and thus resistant to hydrolysis and degradation. By adding D-isomers into an L-isomer based polymerisation system, polymer chains widen and cannot be packed as tightly as PLLA polymer chains. This results in a less crystallic and more rapidly degraded material (*6*). Optimisation of the copolymers properties has been achieved by changing the enantiomeric polymer's rate. For example, adding more than 10% of D-isomers results in an amorphous stereocopolymer (*73*). One of the most popular copolymers currently in use particularly in oral and maxillofacial surgery is P(L/D)LA 70/30 both in simple (*1, 9, 11, 40*) and self-reinforced (SR) (*6, 22, 48, 60, 67, 73, 77, 78*) form.

PLGA : Copolymers are also manufactured from PLA and PGA, combining properties of both materials and a rather low crystallinity (*6*). They are

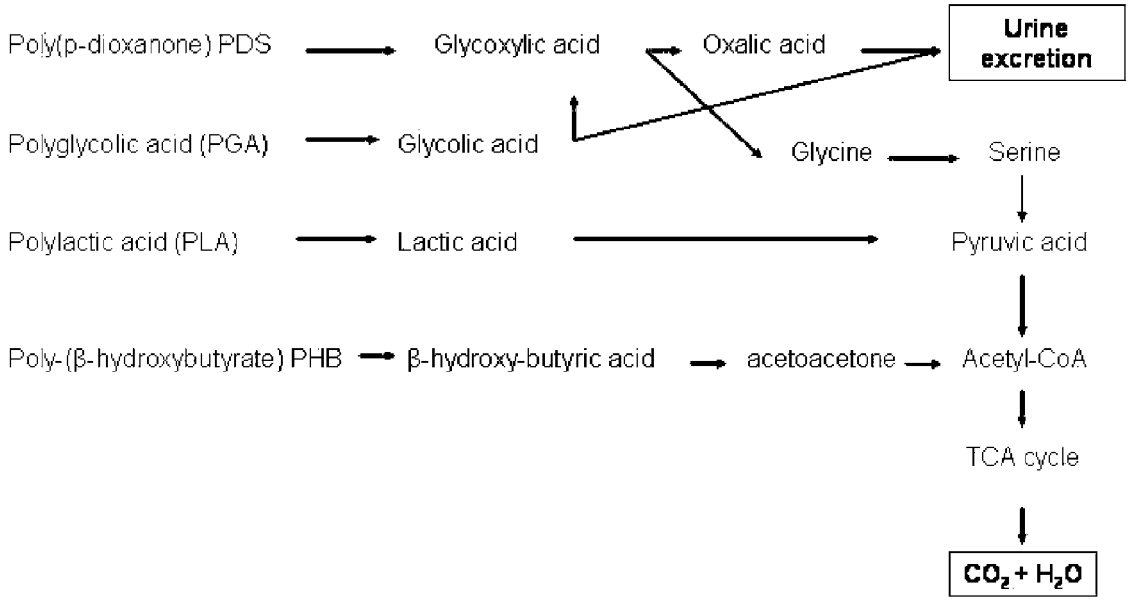

Fig. 1. — Schematic representation of *in vivo* degradation routes of commonly used polyhydroxyacids (*3, 13*)

used in oral and maxillofacial surgery in both adults and children since the mid 1990's (*6*) in both simple (*23, 40, 44*) and SR (*7*) forms.

Self-reinforcing

Considerable effort has been made to overcome the disadvantages of the aforementioned polymers by manufacturing copolymers, but the range of their clinical application still remains narrow. In the self-reinforcing technique, a composite structure is produced by a partially crystalline or amorphous polymeric material made of orientated fibres, fibrils or chain crystals and binding matrix (*64, 65*). Initially, two different materials were used as matrix and reinforcing material (reinforcement), but the adheson promoters required for fabrication proved to be toxic (*8*). The self-reinforcing technique led to better mechanical properties (higher reinforcement degree) and eliminated the problem of toxic adhesion promoters. The high degree of molecular orientation makes implants rigid and strong along their longitudinal axis (*6*), and comparable to bone and metallic implants. Implants made of these materials have been used in anatomic areas exposed to high stress such as the femoral neck (*28, 29*) and situations like Pipkin fractures (*55*). The microstructure of these materials involves orientation in two perpendicular directions. Consequently, the implants become strong and malleable at room temperature and the need for time-consuming heating and cooling procedures is eliminated. Furthermore these implants can withstand four-times bending before their mechanical properties are attenuated. In addition, they exhibit only slight "memory" (tendency to return to previous shape after bending) (*6*). Finally self-reinforced materials can be sterilised by gamma-irradiation, thus eliminating toxic residues that remain after other methods of sterilisation. This method cannot be used with non-reinforced materials because it will decrease the material's molecular weight and consequently affect the mechanical properties of implants (*73*).

Bioabsorption – Biodegradation (fig 1)

Poly-hydroxy-acid degradation starts with random hydrolysis of polymer ester bonds that leads to gradual molecular weight reduction and

mechanical properties attenuation. Afterwards polymer degradation leads to oligomers and monomers that follow the routes presented in the schematic presentation above. The final products (CO_2 and H_2O products of the TCA cycle) are excreted or used by the body. PGA and PDS degradation products can also be excreted by the kidneys (*13*). It is also known that PGA degradation is partially performed by enzymes such as esterase (*75*). Enzymes also seem to take part in PLA degradation (*46*). Polymer breakage produces products that lower the regional PH and thus accelerate the procedure. Macrophages and giant cells are considered responsible for the final degradation of polymer debris (*51*). These cells contribute to the mild local tissue reaction that takes place around absorbable implants. This reaction is demonstrated by the production of a thin macrophage layer with incidentally multinucleated giant cells surrounded by a mild connective tissue capsule (*21*). This procedure is responsible for many adverse effects, and is affected by many other factors which are discussed later. The polymer's crystallicity specifies its hydrophobicity and thus affects the degradation speed, as amorphous and hydrophilic materials allow a grater contact of water molecules with the material, increasing the hydrolysis speed.

Table I shows the factors that affect implant biodegradation. These factors affect the speed of absorption and loss of mechanical properties. Table II demonstrates the time of full absorption and mechanical properties loss.

Table I. — Factors affecting implant biodegradation (*3, 73*)

Implant factors	Environmental factors
1. Chemical composition	Implantation site
2. Molecular weight	Tissue type
3. Fiber orientation (SR)	Stress on the implant
4. Monomer concentration (for copolymers)	Vascularity
5. Stereoisomerism	
6. Material phase	
7. Conformation	
8. Volume/surface rate	
9. Pores	
10. Presence of additives or impurities	
11. Sterilisation method	
12. Degradation mechanism (enzymatic vs. hydrolysis)	

Tissue reactions

Throughout the literature, tissue reactions are considered a main disadvantage in clinical application of bioabsorbable materials.

Histopathology

Laine *et al* (*41*) reported that tissue biopsy of the reaction (after mandibular osteotomy fixed with SR-P(L/DL)LA 70/30 plates and screws) revealed granulomatous inflammation consisting of lymphocytes, plasma cells, endothelial cells and a few giant cells in only one of three specimens. Other reports demonstrated inflammatory foreign body reactions with polymer debris (birefringent under polarised light), surrounded by mononuclear phagocytes and multinucleated giant cells. Particles sized about 25 μm usually lied extracellularly, while immunohistochemically, T lymphocytes were found to be present (*17*).

Most of histopathological evidence is available from animal studies. After implantation, the material is surrounded by a capsule consisting of a thin internal cell layer (2-3 cells thick) and an external fibrous capsule with a few spindle shaped cells (*21, 36*). A type III collagen predominance was evident immunohistochemically in the internal zone while type I collagen predominance was observed in the outer zone. No difference was observed in T cell concentration between the two zones (*36*). Apart from inner zone macrophages that contribute to the phagocytosis of the material, lymphocytes and polymorphonuclear (PMN) granulocytes are present in the infiltration that surrounds the material. At the first stages of the reaction, PMN's are found in high numbers, probably due to tissue response to trauma. A point that is still not clear according to De Jong *et al* (*21*), is the role of lymphocytes (mostly CD4+ but CD8+ too), which are thought to ensue macrophage reaction.

Table II. — Time of full absorption and mechanic properties loss

Material	*Complete absorption time*	*Mechanical properties loss time*
PGA	4-7 weeks (*69*)	36 weeks (*51*)
SR-PGA	3 months (*3*) 6-12 months (*59*)	1 month (*3*)
PLLA	> 5 years (*12, 62, 73*)	
SR-PLLA	5-6 years (*3*) > 5 years (*73*)	Reduction to cortical bone levels in 36 weeks (*47*)
P(D/L)LA 70/30	2-3 years (*3, 8*)	18-36 weeks (*8*)
PLA/PGA (PLGA) 80/20	1-2 years (*8*) 1-1.5 years (*6*)	6-8 weeks (*8*)
P(D/L)LA 96/4	2 years (*54*)	
PDS	2 months (*36*)	

Symptoms and signs

Adverse tissue reactions present themselves with a wide range of symptoms and signs from mild fluid accumulation to serious reactions that require active and/or immediate treatment. Bostman *et al* (*17*) presented serious reactions in patients in which PGA implants were used. These reactions had an acute onset with a painful erythematous fluctuating papule over the implant track. The papule, if left untreated, bursts within a few days and revealed a sinus draining liquid remnants of the implant. Fluid cultures were sterile unless infected after bursting. In the same study, radiographic examination of the patients who presented with tissue reaction revealed osteolysis around the implant in 57.4% of the cases. Tissue reaction to absorbable materials can also present with synovitis (*17, 25*). The effect of the adverse reactions on the outcome of each procedure is usually minor but may lead to important and permanent adverse results. Treatment options of patients who present with tissue reactions due to materials are the following : a) Healing without treatment (*5, 23*), b) Aspiration and/or surgical debridement (*18*), c) Implant removal (*18, 41*) (especially when combined with material failure), d) Arthrodesis in the case of severe osteoarthritis (*15*). When rapid material degradation cannot be compensated for by the debris removal rate, then fluid is accumulated. Therefore, material scientists have focused on the degradation behaviour of implants, optimisation of their properties and development of new materials in order to avoid such adverse reactions.

Clinical studies

The use of PGA is now limited, since materials and copolymers with better degradation properties have become available. This is the case for most of the unalloyed materials. Most recently published studies regarding PGA materials have been extensively reviewed by Bostman *et al* (*17*) and Ambrose *et al* (*2*). A total of 2037 and 1879 patients were included in studies conducted by Bostman *et al* (*17*) and Tuompo *et al* (*66*) respectively. Adverse reactions occurred with various rates ranging from 2.8% in a series of paediatric fractures, to 60% in a wrist fractures series. Tissue reactions included fluid accumulation, sinus formation and osteolysis that was apparent 2 to 17 months postoperatively.

As previously stated, PLLA has a low degradation rate. This is why adverse reactions tend to appear late, even 4-5 years postoperatively. This renders many studies weak regarding the presentation of true adverse reaction rate in procedures where PLLA implants have been used, since the follow-up of these studies is shorter than the complete absorption time of the material. A review of the first clinical trials where PLLA implants were used (*17*) presents 14 series that were performed from 1990 to 1996. A wide variety of reaction rates

Table III. — Studies in which PLLA has been used

Study	Patient number	Procedure	SR	Follow-up	Reactions[a]
1999 Warden *et al* (*72*)	10	ACL reconstruction	No	24 w	1
2000 Bostman *et al* (*17*)	491	Various	No	> 4 y	1 + 3[b]
2001 Voutilainen *et al* (*71*)	18	Arthrodesis due to RA	Yes	5,4 y	–
2001 Serlo *et al* (*60*)	13	Craniofacial	Yes	32 m	1
2002 Juutilainen *et al* (*30*)	1043	Orthopaedics & Trauma	Yes		3
2002 Yerit *et al* (*76*)	22	Mandibular fractures	Yes	49,1 w	1
2003 Barber *et al* (*10*)	57	Bankart procedure	No	24 m	–
2003 Arata *et al* (*5*)	16	DPP arthrodesis	No	10,6 m	2
2003-β Arata *et al* (*4*)	26	Hand surgery	No		1
2004 Kujala *et al* (*37*)	6	Scaphoid fractures	Yes	17 m	–
2005 Kaeding *et al* (*31*)	48	ACL reconstruction	No	2 y	6[c]
2005 Kaukonen *et al* (*34*)	20	Ankle ligament lesions	No	26 w	3
2005 Kallela *et al* (*32*)	40	Mandibular osteotomies	Yes	2,2 y	2

[a] Reactions caused by tissue reaction to the material
[b] One reaction and three screw parts removal
[c] Without statistically important difference from titanium group.

was reported, from no adverse reactions to swelling in 47% of the patients. Advances in material science, such as self-reinforcement technique and elimination of factors that were considered responsible for reaction (e.g. dyes and older sterilisation techniques), have changed PLLA implants' behaviour. In table III, a review of the modern literature is presented in order to underline significant changes concerning tissue reactions.

Enantiomeric isomers of PLA were mixed to develop a material less crystallic and more hydrophilic than PLLA, in order to accelerate the degradation process and avoid late tissue reactions. SR technique was introduced later and resulted in better mechanical properties of implants. Table IV demonstrates a number of clinical studies about P(L/D)LA implants in oral and maxillofacial surgery and other procedures.

Copolymers made of PGA and PLA have also been optimised over time. Self-reinforcement technique and new polymer proportions have been used. Cyst formation with or without sinus (*7, 23*) and osteolysis (*7, 40*) (table V), are examples of adverse reactions that were reported after the use of PGA implants.

Latjai *et al* (*42*) used P(L/D)LA – PGA copolymer screws in ACL reconstruction procedures. No material-related tissue reactions were reported in the 28 patients that were included in the study. Mean follow-up was 5.2 years.

Ambrose *et al* (*2*) also reviewed clinical studies where non popular materials or materials not currently in use, were included. Polyglyconate (PGA and trimethylene carbonate copolymer) is reported in three studies from 2000 to 2002. The reaction rate ranges from 7% to 60%. Adverse reactions due to PLLA were reported to range from 7% to 47% (1999-2003 series).

Future Prospects

Bioabsorbable material used in Orthopaedic Surgery represent a field with continuous evolution and considerable potential. Some of the upcoming applications are presented. Bioabsorbable materials are already used in paediatric orthopaedic surgery.

Table IV. — Studies in which P(L/D)LA has been used

Study	Patient number	Procedure	SR	Rate	Follow-up	Reactions[a]
2001 Serlo *et al* (*60*)	2	Craniofacial Surgery	Yes	70/30	10-17 m	–
2004 Ylikontiola *et al* (*78*)	10	Mandibular fractures	Yes	70/30	> 6 m	–
2006 Bell *et al* (*11*)	59	Facial fractures	No	70/30	3 w-3 y	3
2005 Yerit *et al* (*77*)	13	Mandibular fractures	Yes	70/30	26,4 m	–
2005 Kumar *et al* (*40*)	3 case	Children neurosurgery	No	70/30	8 m-2 y	3
2006 Turvey *et al* (*67*)	34	Mandibular osteotomies	Yes	70/30	1 y	–
2005 Barber (*9*)	61	ACL reconstruction	No	98/2	24 m	–
2006 Al-Sukhun *et al* (*1*)	13	Orbital wall defects	No	70/30	36 w	–
2004 Mazzonetto *et al* (*48*)	30	Orthognathic Surgery	Yes	70/30	6 m	–
2004 Couture *et al* (*19*)	27	Posterior spinal fusion (bioabsorbable cage)	No	70/30	26 m	2
2002 Voutilainen *et al* (*70*)	8	MTP arthrodesis	Yes	70/30	20-28 m	–
2005 Enislidis *et al* (*22*)	25	Zygomatic fractures	Yes	70/30	12 m	–
2004 Cheung *et al* (*18*)	30	Orthognathic Surgery	Yes	70/30	1,2 y	2[b]

[a] Reactions caused by tissue reaction to the material
[b] Without statistically important difference from titanium group.

Table V. — Studies in which PLA-PGA copolymers have been used

Study	Patient number	Procedure	SR	PLA/PGA Rate	Follow-up	Reactions[a]
2004 Eppley *et al* (*23*)	1883	Child Craniofacial surgery	No	82/18		12
2004 Ashammakhi *et al* (*7*)	165	Craniofacial surgery	Yes	80/20	1,5 y	5
2005 Kumar *et al* (*40*)	1 case	Child neurosurgery	No	82/18	6 m	1
2005 Larsen *et al* (*44*)	7	Osteochondritis dissecans	No	82/18	25-37 m	–

[a] Reactions caused by tissue reaction to the material.

Waris *et al* (*74*) showed that transphyseal SR PLGA 80/20 screws caused only temporary growth retardation in rabbits thus indicating that screws could possibly be used transphyseally in humans as well.

Another upcoming use of bioabsorbable materials is their application as a carrier for various substances, such as growth factors and antibiotics. Antibiotic released from materials such as PLA, can be of great help in patients with osteomyelitis, as the antibiotic is released gradually in the area of concern while the material itself secures the osteofixation (*26, 58*). Although this kind of implants is currently in use, larger studies are to follow in order to optimise results.

Additionally, bioabsorbable materials are used as carriers for growth factors, mainly for human recombinant bone morphogenetic protein (rhBMP-2 and rhBMP-7) (*33, 43, 58*). The rhBMP is released locally, and enhances the fracture healing process in cases of pseudarthrosis and osteoporotic bones (*58*). Bioabsorbable materials used as growth factor carriers appear to find a suitable application in spine surgery. When rhBMP is released locally, the odds of a successful fusion increase (*43, 68*).

Another use of these materials is the augmentation of the bone healing procedure in cases with a bone deficit created by autogenous bone harvesting from the iliac crest (*27, 68*). P(L/D)LA can also be used for coating of non-absorbable implants, such as external fixation pins and screws. Although this does not prevent osseous destruction and severe bacterial colonisation along pin tracks, it can improve osseous integration in the absence of infection (*53*).

A promising report regarding osteoarthritis was presented in 2005 by Tamai *et al* (*63*). Full thickness articular cartilage repair was achieved after subchondral implantation of a composite of interconnected porous hydroxyapatite, synthetic polymer (PLA-PEG) and human recombinant bone morphogenetic protein-2 (rhBMP-2) in rabbits. Existing materials show no osteoconductive properties, as they are not replaced by normal trabecular bone after total absorption (*16*). Therefore considerable effort has been done to give materials this property by adding hydroxyapatite crystals to materials like PLLA (*45, 52, 61*). In order to improve biocompatibility and osteoconduction of materials, researchers tried to add tri-calcium phosphate (TCP), a highly biocompatible and osteoconductive material, to P(L/D)LA, but no significant improvement from P(L/D)LA alone was evident (*55, 56*). Another attempt was made to moderate tissue reaction to materials by blocking parts of the inflammation pathway (*35*). Although this approach was not widely accepted, material scientists continuously strive to produce new biocompatible materials (*24, 50, 57*).

CONCLUSIONS

In recent decades there has been increasing emphasis on the broad field of bioabsorbable materials and their use in Orthopaedic Surgery. Having reviewed the literature, one might come to conclusion that bioabsorbable materials are not widely applied. Adverse tissue reactions along with poor mechanical properties, do not allow the widespread use of these materials. Nevertheless enlightened by the knowledge of these reactions and the pathological processes behind them, material scientists managed to eliminate many of these problems and give a new prospective to bioabsorbable materials use in Orthopaedics.

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