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...
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. Intra-operatively, 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
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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. 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

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**Fig. 1.** — Schematic representation of *in vivo* degradation routes of commonly used polyhydroxyacids (3, 13)
mechanical properties attenuation. Afterwards polymer degradation leads to oligomers and monomers that follow the routes presented in the schematic presentation above. The final products (CO₂ and H₂O 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.

### 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.
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
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 crystalline 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.

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**Table III. — Studies in which PLLA has been used**

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Patient Number</th>
<th>Procedure</th>
<th>SR</th>
<th>Follow-up</th>
<th>Reactions Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999 Ward et al (72)</td>
<td>10</td>
<td>ACL reconstruction</td>
<td>No</td>
<td>24 w</td>
<td>1</td>
</tr>
<tr>
<td>2000 Bostman et al (17)</td>
<td>491</td>
<td>Various</td>
<td>No</td>
<td>&gt;4 y</td>
<td>1+3b</td>
</tr>
<tr>
<td>2001 Voutilainen et al (71)</td>
<td>18</td>
<td>Arthrodesis due to RA</td>
<td>Yes</td>
<td>5.4 y</td>
<td>–</td>
</tr>
<tr>
<td>2001 Serlo et al (60)</td>
<td>13</td>
<td>Craniofacial</td>
<td>Yes</td>
<td>32 m</td>
<td>1</td>
</tr>
<tr>
<td>2002 Juutilainen et al (30)</td>
<td>1043</td>
<td>Orthopaedics &amp; Trauma</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2002 Yerit et al (76)</td>
<td>22</td>
<td>Mandibular fractures</td>
<td>Yes</td>
<td>49.1 w</td>
<td>1</td>
</tr>
<tr>
<td>2003 Barber et al (10)</td>
<td>57</td>
<td>Bankart procedure</td>
<td>No</td>
<td>24 m</td>
<td>–</td>
</tr>
<tr>
<td>2003 Arata et al (5)</td>
<td>16</td>
<td>DPP arthrodesis</td>
<td>No</td>
<td>10.6 m</td>
<td>2</td>
</tr>
<tr>
<td>2003-4 Arata et al (4)</td>
<td>26</td>
<td>Hand surgery</td>
<td>No</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2004 Kujala et al (37)</td>
<td>6</td>
<td>Scaphoid fractures</td>
<td>Yes</td>
<td>17 m</td>
<td>–</td>
</tr>
<tr>
<td>2005 Kaeding et al (31)</td>
<td>48</td>
<td>ACL reconstruction</td>
<td>No</td>
<td>2 y</td>
<td>6c</td>
</tr>
<tr>
<td>2005 Kaukonen et al (34)</td>
<td>20</td>
<td>Ankle ligament lesions</td>
<td>No</td>
<td>26 w</td>
<td>3</td>
</tr>
<tr>
<td>2005 Kallela et al (32)</td>
<td>40</td>
<td>Mandibular osteotomies</td>
<td>Yes</td>
<td>2.2 y</td>
<td>2</td>
</tr>
</tbody>
</table>

* 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.
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 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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