

An Introduction to Biodegradable Polymers as Implant Materials



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Introduction

Historically, metal has been the most popular material for fracture fixation and, whilst it has excellent results, it is not without its problems. Biodegradable materials have been attractive for many years but their use has previously been linked to tissue reactions. A new generation of biodegradable polymer is now available which overcomes these concerns. The current trend from metal to biodegradable can therefore be attributed to the increasing sophistication of biodegradable implants overcoming the inherent disadvantages of metal implants (Rokkanen et al. 2000, Toro et al. 2005).

The main attraction of a biodegradable device, to both surgeons and patients, is that it provides the correct amount of strength when necessary and harmlessly degrades over time, until the load can be safely transferred to the healed bone. This means that there is no need for an additional, removal operation - as there would frequently be if a metal device were used - reducing the total treatment and rehabilitation time of the patient.

As well as the benefits to patients and surgeons, there are obvious economical advantages to avoiding an expensive removal operation.

Background

Titanium is currently the most widely used metal for fracture fixation. Other metals commonly used include stainless steel and cobalt chrome. Whilst metal has the high strength and rigidity to allow the healing process to begin, this can also have negative effects. Metal implants have the potential to cause stress shielding (see box 1) (Brodke et al. 2001, Kennady et al. 1989¹, Kennady et al. 1989², Uhthoff et al. 1983, Uhthoff et al. 1994).

Box 1. Stress shielding.

Stress shielding is a condition that emerges when a metal implant removes all load from the bone. To regenerate bone needs function and without this loading or stimulation, atrophy and weakness of the underlying bone can ultimately occur.

Further disadvantages to having metal plates, pins, mesh or other metallic implants inside the body include:

- Accumulation of metals in tissues (Jorgenson et al. 1997, Katou et al. 1996, Kim et al. 1997, Rosenberg et al. 1993, Schliephake et al. 1993)
- Hypersensitivity to titanium (Hunt et al. 1994, Katou et al. 1996, Lalor et al. 1991)
- Growth restriction (Yaremchuk 1994)
- Pain (Alpert and Seligson 1996, Schmidt et al. 1998)
- Corrosion (Agins et al. 1998)
- Implant migration (Cohen et al. 2001, Fearon et al. 1995, Goldberg et al. 1995, Honig et al. 1995, Stendel et al. 2001, Yu et al. 1996)
- Imaging and radiotherapy interference (Castillo 1988, Sullivan et al. 1994)

The operation to remove the implant is often required once the healing process is complete or due to any of the complications above.

Patient Choice

In a recent publication, 91% of patients who participated in a questionnaire saw the removal operation as the most negative aspect of a metal implant (Mittal et al. 2005). A further operation increases treatment and rehabilitation time, which can have a significant impact on patients' lives. Additionally, patients often experience temperature sensitivity with metal implants (Orringer et al 1998) and may be uncomfortable being able to see and feel the metal under the skin. They may also be apprehensive of metal-detecting security systems.

In the publication mentioned above, 95% of patients appreciated the features of biodegradable implants and responded that they would prefer to have their fracture stabilised with a biodegradable implant (Mittal et al. 2005).

Polymer background

By definition, biodegradable refers to a biologically assisted degradation process. Within orthopaedics, terms such as bioabsorbable and resorbable refer to the use of biodegradable materials.

A number of biodegradable polymers have been approved for safe internal use and have been used in surgical applications for the past 35 years, initially as suture materials:

- Dexon - Polyglycolide (PGA) suture
- Vicryl - PGA/Poly lactide (PLA) 90:10 suture
- PDS - Polydioxanone (PDS)
- Maxon - PGA/Tri-Methylene Carbonate (TMC)

In the last two decades the use of biodegradable materials has expanded to include fixation applications. They now have more than 20 years clinical history, with successful documented use in pins, screws, plates, membranes, anchors, dowels, rods, drug delivery devices and supportive scaffolds.

Some of the earlier biodegradable implants caused problems as they were typically created from a single type of polymer. Some degraded too quickly causing tissue reactions or took too long to degrade offering no real advantages over metal (Andriano et al. 1994).

The most common biodegradable polymers previously used in orthopaedics were created from L lactide, D lactide and Glycolide. In the literature the terminology can vary; for example, L lactide (the monomer) can also be referred to as L lactic acid and the homopolymer as poly L lactic acid, PLLA or LPLA.

L lactide, D lactide, Glycolide and Tri-Methylene Carbonate (TMC) are single units - known as monomers (figure 1).

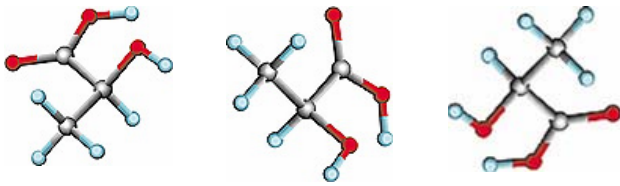


Figure 1. Examples of monomer units.

These monomers can be formed into chains called polymers (figure 2). For example, L lactide monomers can join to form the polymer Poly L Lactide (PLLA).

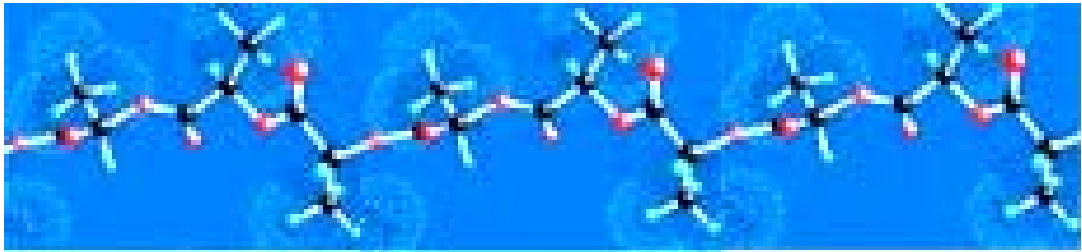


Figure 2. Monomers joined to form a polymer.

A polymer can consist of a single type of monomer, creating a homopolymer (figure 3).



Figure 3. Representation of a homopolymer chain with only one monomer repeated.

Or a polymer can consist of two or more types of monomer, creating a copolymer (figure 4).



Figure 4. Representation of a copolymer chain using two different monomers.

Inion OPTIMA™

To create the next generation of biodegradable polymers, Inion has perfected the process of blending materials to allow the creation of polymers with appropriate strength, excellent flexibility and tailored degradation rates – suitable for each specific application - producing the most advanced biodegradable implants available.

The Inion OPTIMA™ family of materials is created using a combination of the safe and biocompatible (Böstman and Pihlajamäki 2000, Middleton and Tipton 2000, Rokkanen et al. 2000) monomers; L lactide, D lactide, TMC and occasionally also Glycolide when particularly fast degradation is required. By blending, Inion has been able to establish a 'library' of materials from which to select ones of the appropriate strength, toughness, malleability and degradation to meet specific clinical requirements.

For example, the material used in screws is selected to give optimal torque resistance and shear strength. For plates, different polymer combinations are used to give optimal flexibility and tensile strength.

The presence of TMC increases the toughness and contributes to the product's ease-of-use. There are additional practical benefits to Inion OPTIMA™ that may make operational procedures easier to perform:

- Screws, plates and mesh can be cut to size
- Plates and mesh can be moulded to shape

Polymer degradation

Degradation characteristics depend on many factors including:

- Microstructure
- Molecular structure
- Copolymer ratio
- Processing conditions
- Shape of the implant
- Implantation site

The microstructure of a polymer refers to whether it is amorphous or crystalline (figure 5). An amorphous structure means that the polymer chains are randomly oriented. The chains are loosely packed and can slip past each other relatively easily. Crystalline polymers have regions in which the chains lie parallel and in close proximity to each other.

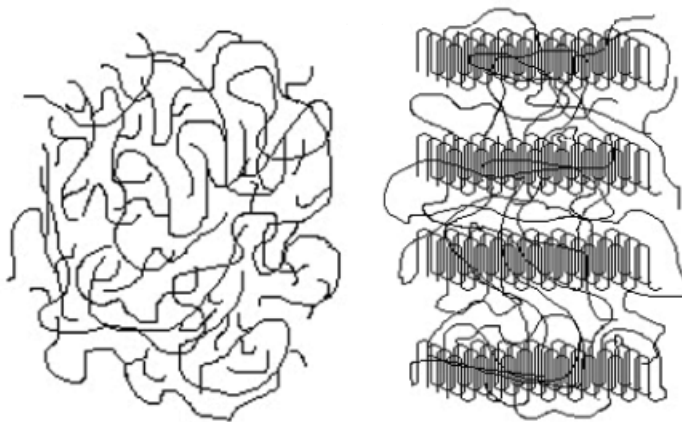


Figure 5. Polymer microstructures: amorphous (left) and semi-crystalline polymer with crystalline and amorphous regions (modified from Pietrzak et al. 1997).

Homopolymer chains tend to form *more* ordered structures which are therefore more crystalline. Copolymers tend to form *less* ordered structures which are therefore usually amorphous. However, even crystalline homopolymers are never completely crystalline. Rather, a crystalline polymer will always contain both crystalline and amorphous regions and is best termed semi-crystalline (figure 5).

Crystalline polymers have a regular internal structure and because of the orderly arrangement are slow to degrade. Amorphous polymers have a random structure and are completely and more easily degraded. Semi-crystalline polymers have crystalline and amorphous regions. Breakdown of the implant begins in the amorphous area leaving the more slowly degrading crystalline debris.

During the first phase of degradation, water penetrates the biodegradable device, initially cutting the chemical bonds and converting the long polymer chains into shorter and shorter fragments (hydrolysis).

In the second phase, the fragments are degraded into natural monomeric acids found in the body, such as lactic acid.

These acids enter the Krebs's (citric acid) cycle and are metabolised into carbon dioxide and water which are then exhaled and excreted in phase three.

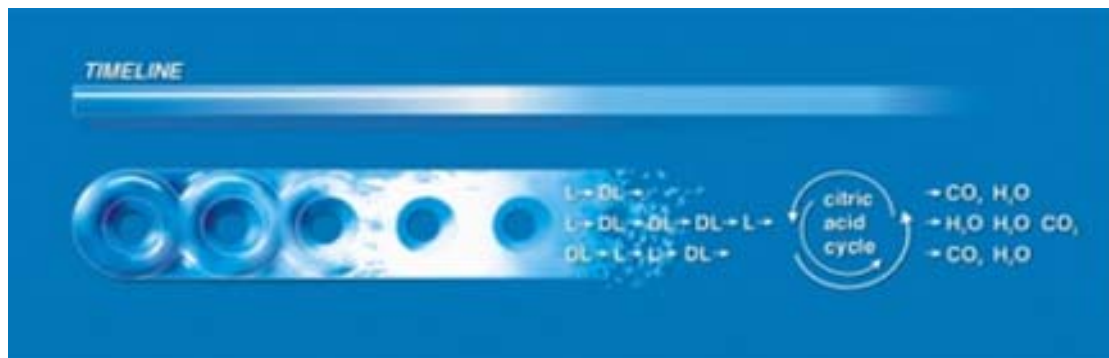


Figure 6. Illustration of the degradation process of a biodegradable polymer.

The polymers PLLA and PGA exhibit distinctly different degradation behaviour (Wu et al. 2003). PGA is hydrophilic and degrades very quickly (Andriano et al. 1994), losing virtually all strength within one month and all mass within 6-12 months. During this phase of rapid degradation, large quantities of the Glycolide monomer are released.

PLLA has a much slower rate of absorption (Andriano et al. 1994). This homopolymer of L lactide is highly crystalline due to the ordered pattern of the monomers and has been documented to take more than 5 years to absorb (Bergsma et al. 1995).

Biodegradable implants do induce a non-symptomatic but histopathologically recognisable tissue response; it seems to be a phenomenon inherent in the

degradation and absorption processes (Rokkanen et al. 2000). This is expected and normal as long as it does not cause any clinical signs.

However, incidence of adverse tissue reactions to implants made of PGA (faster degradation) has been reported from 2.0 to 46.7% (Böstman and Pihlajamäki 2000, Pietrzak et al. 1997). Adverse reactions can occur if the rate of degradation exceeds the limit of tissue tolerance (Böstman and Pihlajamäki 2000) as can be the case with PGA (Andriano et al. 1994). Local accumulation of released monomers may lower the local pH of the tissue (Ambrose and Clanton 2004). This drop in the local pH in turn can lead to increased osmotic pressure, which may lead to a temporary expansion of the implant cavity or to a local sterile fluid accumulation. The patient would notice this reaction as swelling and pain (Böstman and Pihlajamäki 2000) and would typically be prescribed anti-inflammatory drugs and rest.

Conversely, in studies investigating PLA-based implants (slower degradation), the incidence of adverse tissue reaction is much lower; from 0 to 1% (Böstman and Pihlajamäki 2000).

The ideal biodegradable material provides appropriate strength whilst degrading in a predictable fashion throughout the healing process, without causing adverse reactions (Peltoniemi 2000).

Inion OPTIMA™ materials live up to this ideal.

The polymers within the OPTIMA library of blends get their physical properties from varying proportions of its composite monomers:

- L Lactide
 - Provides strength to implants
 - Hydrophobic - degrades slowly
- D Lactide
 - Disrupts crystallinity
 - Flexibility

- Glycolide
 - Hydrophilic - degrades quickly
- TMC
 - Glass transition temperature is subzero; it is rubbery at room temperature
 - Provides enhanced malleability and toughness

Because Inion OPTIMA™ materials consist of several monomer types, they are amorphous and degrade completely. The implants also remain amorphous after manufacturing due to Inion's carefully controlled production processes (some other copolymers become semicrystalline during manufacture). In comparing the degradation of Inion OPTIMA™ to PLLA and PGA: PLLA degrades slowly with crystalline debris usually remaining. PGA degrades completely but too quickly (Andriano et al. 1994). OPTIMA™ degrades completely and within the appropriate length of time for each application.

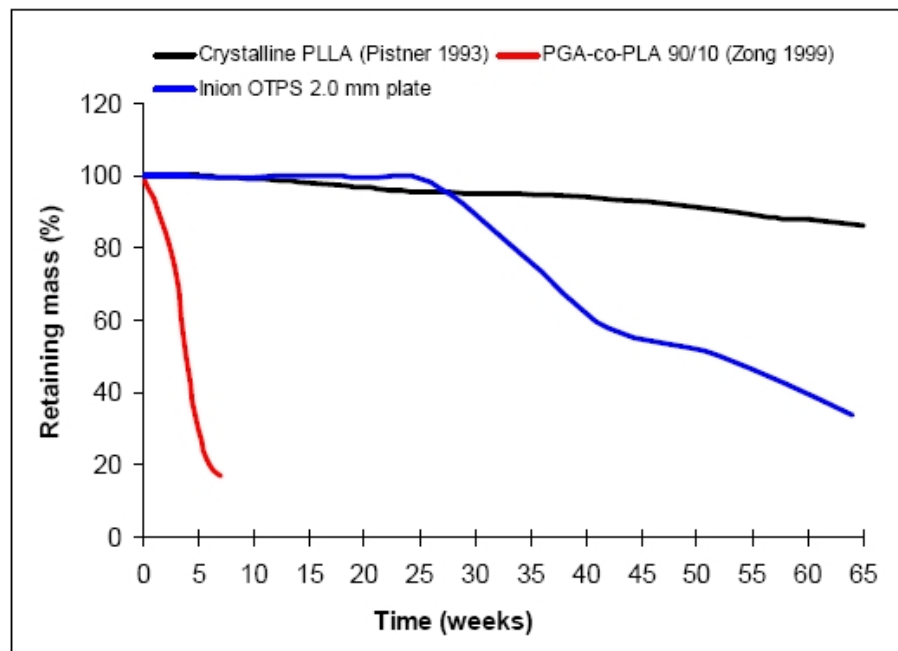


Figure 7. Mass loss rate of fast degrading PGA-co-PLA 90/10 copolymer and slowly degrading crystalline PLLA in comparison to Inion OTPS™ 2.0 mm plate material.

The tailored degradation rate of Inion OPTIMA™ progressively transfers load to healing bone so that the material degrades to coincide with the rate of bone healing (Figure 8).

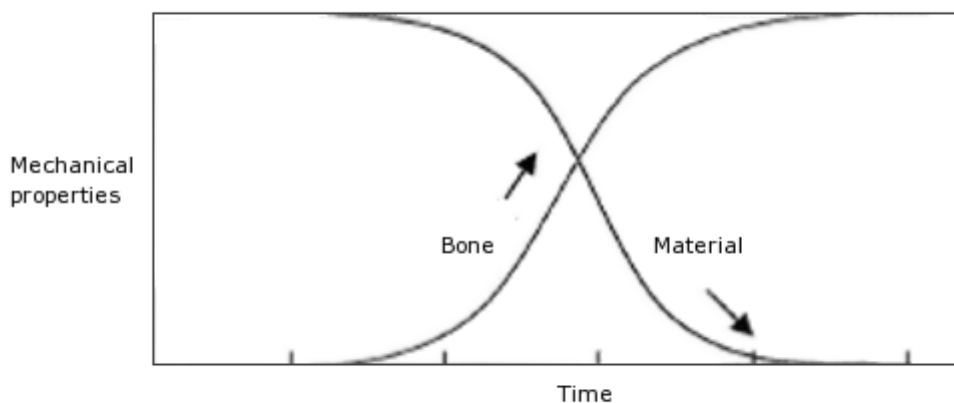


Figure 8. The material's mechanical properties decrease as it degrades.

Typically, Inion OPTIMA™ materials decrease to 70% of their initial strength 9-14 weeks after implantation (6-9 weeks for paediatric implants) then disappear completely over a period of 2-4 years *in vitro*.

Due to the blending process, the overall degradation of Inion OPTIMA™ does not have the extreme degradation peaks sometimes seen in products made from one type of polymer. The likelihood of degradation-related inflammatory reactions is therefore usually lower than fast-degrading homopolymers (Inion data on file. 2005) and very low levels of adverse tissue reaction (~0.1%) have been reported to Inion – compared to incidences of up to 46% seen in other materials (Böstman and Pihlajamäki 2000).

Summary

Many agree that biodegradable implants offer clear advantages over the traditional metal implants. They retain their strength long enough to support a healing bone, then gradually and harmlessly disintegrate in the patient's body (Gourville 2005).

Inion OPTIMA™ biodegradable implants have many advantages over metal implants, specifically for:

- Patients
 - No additional surgery required for implant removal
 - No permanent implant in the body
 - Safe and biocompatible material, no risk of metal allergic reactions
 - Reduced trauma
 - No long-term implant palpability
 - No implant temperature sensitivity

- Clinicians
 - Compatible with Magnetic Resonance Imaging (MRI) for post-operative diagnosis
 - Reduced radiographic scatter/obstruction
 - Minimised risk of obstruction during any follow-up surgery
 - Increased patient satisfaction

- Additional benefits
 - Predictable degradation to provide progressive bone loading, preventing stress shielding to aid better bone healing
 - Reduced total cost - no removal operation
 - Provided sterile reducing risk of cross infection
 - No growth disturbances in children
 - Allows micro-movement to aid fracture healing

The predictable and tailored degradation profile of Inion OPTIMA™ materials in addition to the structural benefits of the polymer blend, afford the advantage over first-generation biodegradable devices.

The use of biodegradable polymers in the field of orthopaedic surgery has gained increased popularity (El-Amin et al. 2002) and many clinicians are predicting more widespread application of biodegradable materials (Liu et al. 2002). The use of biodegradable materials is also well-accepted by patients, with 95% of patients who participated in a recent study responding that they would prefer to have their fracture stabilised with a biodegradable implant (Mittal et al. 2005).

Future developments

As the use of biodegradable orthopaedic implants increases, the ability to carry osteoconductive compounds (that promote bone formation) can be further investigated. Their release over the course of the degradation can stimulate enhanced fracture healing (Bessho et al. 2002, Raschke and Schmidmaier 2004, Saito et al. 2005, Wildemann et al. 2005).

References

Agins HJ, Alcock NW, Bansal M, Salvati EA, Wilson PD Jr, Pellicci PM, Bullough PG. Metallic wear in failed titanium-alloy total hip replacements. A histological and quantitative analysis. *J Bone Joint Surg Am* 1988;70(3):347-56.

Alpert B, Seligson D. Removal of asymptomatic bone plates used for orthognathic surgery and facial fractures. *Journal Oral Maxillofacial Surgery* 1996;54(5):618-21.

Ambrose CG, Clanton TO. Bioabsorbable implants: Review of clinical experience in orthopedic surgery. *Annals of Biomedical Engineering* 2004;32:171-177.

Andriano KP, Pohjonen T, Tormala P. Processing and characterization of absorbable polylactide polymers for use in surgical implants. *J Appl Biomater* 1994;5(2):133-40.

Bergsma JE, de Bruijn WC, Rozema FR, Bos RRM, Boering G. Late Degradation Tissue Response to Poly(L-Lactide) Bone Plates and Screws. *Biomaterials* 1995;16:25-31.

Bessho K, Carnes DL, Cavin R, Ong JL. Experimental studies on bone induction using low-molecular-weight poly (DL-lactide-co-glycolide) as a carrier for recombinant human bone morphogenetic protein-2. *J Biomed Mater Res* 2002;61(1):61-5.

Böstman O, Pihlajamäki H. Clinical biocompatibility of biodegradable orthopaedic implants for internal fixation: a review. *Biomaterials* 2000;21:2615-2621.

Brodke DS, Gollogly S, Alexander Mohr R, Nguyen BK, Dailey AT, Bachus aK. Dynamic cervical plates: biomechanical evaluation of load sharing and stiffness. *Spine* 2001;26(12):1324-9.

Castillo MH, Button TM, Doerr R, Homs MI, Pruett CW, Pearce JI. Effects of radiotherapy on mandibular reconstruction plates. *Am J Surg* 1988;156(4):261-3.

Cohen SR, Holmes RE, Amis P, Fitchner H, Shusterman EM. Tacks: a new technique for craniofacial fixation. *J Craniofac Surg* 2001;12(6):596-602.

El-Amin SF, Attawia M, Lu HH, Shah AK, Chang R, Hickok NJ, Tuan RS, Laurencin CT. Integrin expression by human osteoblasts cultured on degradable polymeric materials applicable for tissue engineered bone. *J Orthop Res* 2002;20(1):20-8.

Fearon JA, Munro IR, Bruce DA. Observations on the use of rigid fixation for craniofacial deformities in infants and young children. *Plast Reconstr Surg* 1995;95(4):634-7; discussion 638.

Goldberg DS, Bartlett S, Yu JC, Hunter JV, Whitaker LA. Critical review of microfixation in pediatric cranio-facial surgery. *J Craniofac Surg* 1995;6:301-7; discussion 308.

Gourville JT. Holding fast. *Harv Bus Rev* 2005 Jun;83(6):35-8,40,42 passim.

Honig JF, Merten HA, Luhr HG. Passive and active intracranial translocation of osteosynthesis plates in adolescent minipigs. *J Craniofac Surg* 1995;6:292-8; discussion 299-300.

Hunt JA, Williams DF, Ungersbock A, Perrin S. The Effect of Titanium Debris on Soft-Tissue Response. *Journal of Materials Science: Materials in Medicine* 1994;5:381-383.

Inion data on file. White paper. Enhancing Biocompatibility: Second Generation Biodegradable Implants. 2005.

Jorgenson DS, Mayer MH, Ellenbogen RG, Centeno JA, Johnson FB, Mullick FG, Manson PN. Detection of titanium in human tissues after craniofacial surgery. *Plast Reconstr Surg* 1997;99:976-9; discussion 980-1.

Katou F, Andoh N, Motegi K, Nagura HJ. Immuno-inflammatory responses in the tissue adjacent to titanium miniplates used in the treatment of mandibular fractures. *Craniofac Surg* 1996;24(3):155-62.

Kim YK, Yeo HH, Lim SC. Tissue response to titanium plates: a transmitted electron microscopic study. *J Oral Maxillofac Surg.* 1997;55(4):322-6.

1. Kennady MC, Tucker MR, Lester GE, Buckley MJ. histomorphometric evaluation of stress shielding in mandibular continuity defects treated with rigid fixation plates and bone grafts. *Int J Oral Maxillofac Surg* 1989;18(3):170-4.

2. Kennady MC, Tucker MR, Lester GE, Buckley MJ. Stress shielding effect of rigid internal fixation plates on mandibular bone grafts. A photon absorption densitometry and quantitative computerized tomographic evaluation. *Int J Oral Maxillofac Surg* 1989;18(5):307-10.

Lalor PA, Revell PA, Gray AB et al. Sensitivity to titanium. A Cause of Implant Failure? *Journal Bone Joint Surgery* 1991;73B:25.

Liu JG, Ma WH, Xu XX. [Orthopaedic applications for biodegradable and absorbable internal fixation of fractures] *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi* 2002;16(3):209-11.

Middleton JC, Tipton AJ. Synthetic biodegradable polymers as orthopaedic devices. *Biomaterials* 2000;21:2335-2346.

Mittal R, Morley J, Dinopoulos H, Drakoulakis EG, Vermani E, Giannoudis PV. Use of bio-resorbable implants for stabilisation of distal radius fractures: the United Kingdom patients' perspective *Injury.* *Int J Care Injured* 2005;36:333-338.

Orringer JS, Barcelona V, Buchman SR. Reasons for removal of rigid internal fixation devices in craniofacial surgery. *J Craniofac Surg* 1998;9:40-4.

Peltoniemi H. Biocompatibility and fixation properties of absorbable miniplates and screws in growing calvarium. An experimental study in sheep. Helsinki 2000.

Pietrzak WS, Sarver DR, Verstynen ML. Bioabsorbable Polymer Science for the Practicing Surgeon. *The Journal of Craniofacial Surgery* 1997;8(2):87-91.

Pistner H, Bendix DR, Mühling J, Reuther JF: Poly(L-lactide): a long-term degradation study in vivo. Part III Analytical characterization. *Biomaterials* 1993;14(4): 291-298.

Raschke MJ, Schmidmaier G. [Biological coating of implants in trauma and orthopedic surgery] *Unfallchirurg* 2004;107(8):653-63.

Rokkanen PU, Böstman O, Hirvensalo E, Mäkelä EA, Partio EK, Päätiälä H, Vainionpää S, Vihtonen K, Törmälä P. Bioabsorbable fixation in orthopaedic surgery and traumatology. *Biomaterials* 2000;21:2607-2613.

Rosenberg A, Gratz KW, Sailer HF. Should titanium miniplates be removed after bone healing is complete? *Int J Oral Maxillofac Surg* 1993;22:185-188.

Saito N, Murakami N, Takahashi J, Horiuchi H, Ota H, Kato H, Okada T, Nozaki K, Takaoka K. Synthetic biodegradable polymers as drug delivery systems for bone morphogenetic proteins. *Adv Drug Deliv Rev* 2005;57(7):1037-48.

Schliephake H, Reiss G, Urban R, Neukam FW, Guckel S. Metal release from titanium fixtures during placement in the mandible: an experimental study. *Int J Oral Maxillofac Implants* 1993;8(5):502-11.

Schmidt BL, Perrott DH, Mahan D, Kearns G. The removal of plates and screws after Le Fort I osteotomy. *J Oral Maxillofacial Surgery* 1998;56(2):184-8.

Stendel R, Krischek B, Pietila TA. Biodegradable implants in neurosurgery. *Acta Neurochir (Wien)* 2001;143(3):237-43.

Sullivan PK, Smith JF, Rozzelle, AA. Cranio-orbital reconstruction: safety and image quality of metallic implants on CT and MRI scanning. *Plast Reconstr Surg* 1994;94:589-96.

Toro C, Robiony M, Zerman N, Politi M. Resorbable plates in maxillary fixation. A 5-year experience. *Minerva Stomatol* 2005;54(4):199-206.

Uhthoff HK, Finnegan M. The effects of metal plates on post-traumatic remodelling and bone mass. *J Bone Joint Surg Br* 1983;65(1):66-71.

Uhthoff HK, Boisvert D, Finnegan M. Cortical porosis under plates. Reaction to unloading or to necrosis? *J Bone Joint Surg Am* 1994;76(10):1507-12.

Wildemann B, Sander A, Schwabe P, Lucke M, Stockle U, Raschke M, Haas NP, Schmidmaier G. Short term in vivo biocompatibility testing of biodegradable poly(D,L-lactide)--growth factor coating for orthopaedic implants. *Biomaterials* 2005;26(18):4035-40.

Wu HC, Shen FW, Hong X, Chang WV, Winet H. Monitoring the degradation process of biopolymers by ultrasonic longitudinal wave pulse-echo technique. *Biomaterials* 2003;24(22):3871-6.

Yaremchuk MJ, Fiala TG, Barker F, Ragland R. The effects of rigid fixation on craniofacial growth of rhesus monkeys. *Plast Reconstr Surg*. 1994;93(1):1-10; discussion 11-5.

Yu JC, Bartlett SP, Goldberg DS, Gannon F, Hunter J, Habecker P, Whitaker LA. An experimental study of the effects of craniofacial growth on the long-term positional stability of microfixation. *J Craniofac Surg* 1996;7:64-8.

Zong X, Wang Z, Hsiao BS, Chu B, Zhou JJ, Jamiolkowski DD, Muse E, Dormier E. Structure and Morphology Changes in Absorbable Poly(glycolide) and Poly(glycolide-co-lactide) during in Vitro Degradation. *Macromolecules* 1999;32(24):8107-8114.