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Sterilization, toxicity, biocompatibility and clinical applications of polylactic acid/polyglycolic acid copolymers

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This is a review of salient studies of sterilization, toxicity, biocompatibility, clinical applications and current work in the field of orthopaedics, using implants made of polylactic acid (PLA), polyglycolic acid (PGA) and their copolymers. The intrinsic nature of these biomaterials renders them suitable for applications where temporally slow releases of bioactive agents *in situ* may be required. They are also desirable as fixation devices of bone, because they can virtually eliminate osteopenia associated with stress shielding or additional surgery. The majority of currently available sterilization techniques are not suitable for these thermoplastic materials and it may be desirable to develop new sterilization standards, which can account for the special character of PLA–PGA materials. Biocompatibility and toxicity studies suggest that, overall, PLA–PGA biomaterials may be suitable for orthopaedic applications, although certain problems, especially pertaining to reduction in cell proliferation, have been reported. Clinical applications are also promising, albeit not without problems usually associated with transient tissue inflammation. The future of these materials appears bright, especially in soft tissues. They may be used to address the exceedingly complex problem of osteochondral repair, but also as a means to enhance fixation and repair processes in tendons and ligaments.

Keywords: Polylactic acid, polyglycolic acid, toxicity

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Current trends in orthopaedic practice and research suggest that polylactic acid (PLA), polyglycolic acid (PGA) (*Figure 1*) and their copolymers may enjoy widespread application in the future. Potential applications include bone fixation devices—such as plates, screws, pins and nails—but also scaffolds for soft and hard tissue repair. These biomaterials degrade *in vivo* by hydrolysis into lactic acid and glycolic acid, which are then incorporated into the tricarboxylic acid cycle and excreted. Degradation denotes mass loss due to resorption or dissolution of the material, precipitated or accompanied by a reduction in molecular weight, changes in the implant's structural configuration, and changes in mechanical properties such as reduction in strength and stiffness. In this paper, the term 'biodegradable' will be taken to be tantamount to 'bioresorbable'. Some of the many factors which influence *in vivo* degradation of PLA–PGA include the material's physical and geometric characteristics, host tissue haemodynamic conditions, enzymes (especially with esterase activity) and functional loading. In this paper, methods employed in sterilization of PLA–PGA are presented, followed by a comprehensive review of issues related to toxicity and biocompatibility. Such a review may be timely, especially in light of recent studies questioning the *in vivo* suitability of PLA–PGA biomaterials. A synopsis of salient clinical studies where these polymeric materials have been used, mainly in a European centre, will also be discussed, followed by current experimental applications and projected uses of these versatile materials.

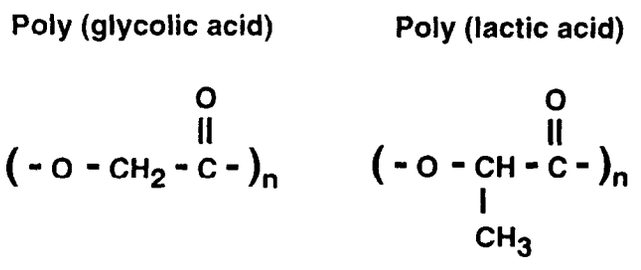

Figure 1 Structural formulae of polylactic acid and polyglycolic acid.

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STERILIZATION

It is necessary to sterilize all medical implants after fabrication and prior to their surgical placement to reduce the risk of infections and associated complications. The most commonly used sterilization techniques utilize heat, steam, radiation or a combination of these methods. *Table 1* gives an overview of sterilization techniques used for PLA–PGA biomaterials and lists their advantages and disadvantages. PLA–PGA polymers, in addition to being susceptible to damage by moisture and radiation, are heat sensitive because of their thermoplastic nature. Thus, the selection of the correct sterilization technique for PLA–PGA implants is crucial to their physical and mechanical properties, and hence to their performance *in vivo*.

Hospital steam sterilization techniques commonly use high moisture and temperatures in excess of 100°C. Such temperatures can approach or exceed the thermal transition temperatures of PLA–PGA polymers and potentially alter their physical and mechanical properties. In a study examining the effects of seven different steam sterilization techniques on L-PLA, it was determined that all the evaluated techniques significantly changed at least one material property of the polymer[1]. The molecular weight decreased in all cases, although in most cases the elastic modulus tended to increase. The authors reported that a sterilization regimen using a temperature of 129°C for 60 s resulted in minimal change in tensile properties of the test L-PLA. However, this method resulted in a significant decrease in the molecular weight, which would affect the degradation kinetics of the polymer.

γ-Radiation sterilization is known to cause chain scission in PLA–PGA polymers. At doses of 2.5 Mrad, ^{60}Co γ-radiation causes deterioration of Dexon® and Vicryl® sutures[2]. In addition, there is a rapid decrease in molecular weight of PGA sutures with increasing doses of γ-radiation[2]. It was determined that the rate of decrease was more pronounced for M_n (number-average molecular weight) compared with M_w (weight-average molecular weight), which indicates that random chain scission was not the primary mechanism. A faster decrease in M_n implies that the impact of radiation treatment was greater on short molecular chains. The authors suggested that the main mechanism was probably unzipping of the chains. The same study also determined that although the initial tensile strength of the sutures remained unchanged immediately post-radiation, it decreased to zero 10 days post-implantation. Other studies have also reported a decrease in the tensile strength of PLA–PGA polymers upon γ-radiation[3,4]. Under *in vivo* conditions, γ-irradiated PGA sutures have been shown to degrade faster than unirradiated samples[5]. This difference might be related to a decrease in the molecular weight of the irradiated specimens. Thus, it is important to bear in mind that the properties and useful lifetime of PLA–PGA implants can be significantly affected by radiation, even though there might be no immediate visual changes.

Chemical sterilization by gases such as ethylene oxide (EO) is often used for polymers that are sensitive to heat and moisture. This is particularly true for PLA–PGA polymers that are thermoplastic in nature and biodegrade by hydrolysis. However, chemical sterilization can potentially leave residues in harmful quantities on the surface and within the polymer. The amount of gas adsorbed into the polymer depends on the equilibrium absorption and diffusion coefficient[6]. These physical parameters depend on the type of polymer as well as the sterilization parameters. It is crucial that polymeric implants are subjected to adequate degassing or aeration subsequent to EO sterilization so that the concentration of residual EO is reduced to acceptable levels[7]. It has been reported that the aeration process is significantly improved if the polymers are subjected to microwave radiation, because such radiation reduces to half the activation energy for diffusion[7]. Using techniques such as infrared spectroscopy, the amount of EO residue can be quantified[8]. Verheyen *et al.*[9] determined that the flexural strength of hydroxyapatite–PLA composites was reduced upon EO gas sterilization. However, detrimental effects of chemical sterilization on the mechanical properties of the PLA–PGA polymers have rarely been reported in the literature.

Sterilization techniques can significantly affect the mechanical and physical properties of PLA–PGA devices. In addition, they can leave harmful residues on these materials, causing them to fail *in vivo*. The specific effects of different techniques are determined by the sterilization parameters, the method used for fabrication, as well as the polymeric material itself. Thus, it is imperative that choice of a particular sterilization regimen be made only subsequent to a careful study. It is essential that a new standard for sterilizing PLA–PGA devices be designed and established.

Table 1 Standard sterilization techniques and their applicability to PLA–PGA

Sterilization technique	Advantages	Disadvantages
Steam sterilization (high steam pressure, 120–135°C)	No toxic residues	Deformation/degradation due to water attack, limited usage for PLA–PGA
Dry heat sterilization (160–190°C)	No toxic residues	Melting and softening of polymer, not usable for PLA–PGA
Radiation (ionizing or γ)	High penetration, low chemical reactivity, quick effect	Instability and deterioration, cross-linking/ breakage of polymer chains
Gas sterilization (ethylene oxide)	Low temperature range	Lengthy process due to degassing, residues are toxic

TOXICITY/BIOCOMPATIBILITY

To perform adequately during many years of service, implants in general must not cause abnormal responses in local tissues and should not produce toxic or carcinogenic effects, either locally or systemically. Biodegradable implants in particular should serve their intended function while releasing products of degradation that are biocompatible and non-toxic, and without interfering with tissue healing. *Table 2* provides a chronological list of salient studies examining biocompatibility characteristics of PLA–PGA biomaterials. In general, PLA–PGA biomaterials have demonstrated satisfactory biocompatibility and absence of significant toxicity, although some reduction in cell proliferation has been reported. The following is a brief review of some *in vitro* and *in vivo* studies examining toxicity and biocompatibility of PLA–PGA biomaterials.

Cell proliferation was studied on polylactides of varying molecular weights using rat epithelial cells, human fibroblasts and osteosarcoma cells under culture conditions[10,11]. Overall, it was determined that satisfactory biocompatibility was exhibited, although some cell inhibition was also noted. In another study, hepatocytes cultured on mesh membranes made of PGA fibres were noted to attach and significantly interact with these transplantation devices[12]. In a more recent study, however, it was reported that both PLA and PGA produce toxic solutions *in vitro*, probably as a result of the acidic degradation products[13]. A bioluminescence toxicity assay was used to test accumulated degradation products of several biodegradable polymers, which were incubated at 37°C in buffer. Obviously, such 'closed' incubation tests do not emulate *in vivo* and *in situ* conditions, because they cannot account for physiological buffering and hydrodynamic evacuation of byproducts.

Numerous other studies have demonstrated successful *in vivo* biocompatibility characteristics of these biomaterials. Owing to the fact that PLA–PGA polymers have enjoyed successful clinical use in the form of sutures, researchers from many centres have theorized that these materials can also be used as fixation devices or replacement implants in musculoskeletal tissues. Indeed, a plethora of innovative designs and concepts have been developed, and in subsequent studies both PLA and PGA were found to exhibit sufficient biocompatibility with bone[14,15]. In some cases, however, inflammatory responses have been noted. For example, L-PLA was used in meniscal reconstruction in the dog and although some success was noted, symptoms related to chronic inflammation (presence of macrophages, fibroblasts, giant cells and lymphocytes) were observed[16]. Biocompatibility may be compromised once degradation is in full progress and the small polymeric particles released promote a foreign body inflammatory reaction, as described in a study where L-PLA was implanted in canine femora[17]. In a study examining implant materials in the goat femoral diaphysis, macrophage-like cells and small L-PLA particles were found in lymph nodes[18]. In contrast, good tissue biocompatibility was observed when PLA was used as a plug in the femoral canal of sheep to increase cement concentration in total hip replacement through intramedullary plugging[14]. Similarly, no inflammatory or foreign body reaction was observed in the medullary cavity of rabbit femora in response to ultra-high strength L-PLA rods for up to 1 year[15].

PLA–PGA copolymers have also been frequently used in bone repair applications and have been found to be biocompatible, non-toxic and non-inflammatory[19–22]. Implants made of these materials have been shown to accelerate bone healing in the rat tibia[20] and induce higher bone formation than untreated controls in cranial defects[21]. Similarly, biocompatibility and absence of infection or inflammation have been observed in studies to promote articular healing in osteochondral defects in the rabbit[23–25].

PGA has also been considered to be immunologically inert, following cytological analysis of materials aspirated from malleolar fracture repair effusions developed around PGA implants, although inflammatory monocytes were observed[26]. No evidence of infection or symptomatic foreign body reaction were observed in another study where self-reinforced PGA rods were used[27]. In a series of European clinical studies of PGA, used for fracture fixation in the foot, foreign body reactions were often reported[28–30]. In some of this group's studies, osteolytic reactions were noted to result from PGA degradation products for 10 weeks following fixation of malleolar fractures[28,29]. In a study of fracture fixation of transverse distal femoral osteotomies in rabbits, variable tissue response and healing were observed in response to PGA[31]. Using a similar model, inflammatory response to either self-reinforced PGA or L-PLA screws for fixation of transverse distal femoral osteotomies in rabbits was observed to be insignificant[32]. Good clinical results were also obtained in paediatric patients requiring internal fracture fixation with PLA pins[33]. It was thus speculated that other physico-chemical factors were responsible for the inflammation observed in this group's previous clinical studies. In a recent, comprehensive, clinical study involving 155 patients with ankle fractures, treated with either PGA or stainless-steel screws, no differences between the two groups were found and no complications related to PGA were noted[34].

All of the above *in vivo* studies involved applications in bone, articular cartilage and the meniscus. It should nevertheless be noted that a significant number of other studies have been performed *in situ* in muscle or other soft tissues. Again, the results of all of these studies appear to support the *in vivo* use of PLA–PGA biomaterials, although inflammatory responses have been observed in some cases. In a study examining both *in vivo* and *in vitro* degradation characteristics of L-PLA implants for up to 39 weeks in rats, the material was found to be well tolerated with no chronic inflammation[35]. PLA membranes, placed transcutaneously in rats, were shown to have sufficient biocompatibility[36]. In contrast, in another study in rats, subcutaneously implanted pre-degraded L-PLA elicited fibrous encapsulation, with macrophages and giant cells covering the smaller particles[37]. Similar histological observations were reported in another study where

Table 2 Biocompatibility/toxicity testing of PGA–PLA in animals, humans and *in vitro*, presented in chronological order

Year	Reference	Application	Material	Results
Animal testing				
1966	Kulkarni *et al.*[52]	Sutures in guinea-pigs and rats	PLA	Non-toxic and non-tissue reactive
1970	Postlethwait[47]	Sutures in rabbits	PGA	Less reaction than catgut, silk or Dacron
1971	Frazza and Schmitt[48]	Sutures in rabbits	PGA	Less inflammation than catgut
1971	Cutright and Hunsuck[50]	Sutures in rat muscle	PLA	Degraded suture induced giant cell reaction
1971	Cutright *et al.*[53]	Sutures in rabbits	PLA PGA	Acceptable soft tissue reactions
1971	Cutright *et al.*[54]	Sutures in monkeys	PLA	Minimal inflammatory response
1971	Kulkarni *et al.*[51]	Sutures in monkeys	D-PLA	Tissue response similar to controls
1973	Brady *et al.*[86]	Soft tissue/rat abdomen	PLA PGA	High degree of biocompatibility
1976	Schwope *et al.*[42]	Soft tissue/mice	PLA PGA	No foreign body reaction
1977	Nelson *et al.*[19]	Bone repair of rat tibia	PLA PGA	Very tissue tolerant, little foreign body reaction
1977	Miller *et al.*[87]	Soft tissue/rats	PLA PGA	High degree of biocompatibility
1981	Varma *et al.*[88]	Sutures in dogs	PGA	Initial reaction intense, chronically mild
1981	Walter *et al.*[89]	Sutures in pigs	PGA	Negligible inflammation
1982	Christel *et al.*[90]	Fracture fixation of rat tibia	L-PLA PGA	Promising results
1983	Christel *et al.*[14]	Bone repair of sheep femur	PLA	Satisfactory tissue compatibility
1983	Hollinger[20]	Bone repair of rat tibia	PLA PGA	No adverse tissue host responses
1983	Salthouse[91]	Sutures in rat muscle	PGA PLA (Vicryl)	Mild reaction
1986	Higashi *et al.*[92]	Bone repair in rats	PLA HA	PLA/hydroxyapatite composite encouraged new bone formation
1986	Visscher *et al.*[39]	Soft tissue/rat muscle	PLA PGA	Slight reaction after 480 days
1987	Leenslag *et al.*[93]	Fracture fixation in dogs, sheep	L-PLA	Well tolerated, increased cellular activity
1988	Schakenraad *et al.*[40]	Drug release in rat soft tissue	L-PLA	Very moderate foreign body tissue reaction
1988	Schmitz and Hollinger[78]	Bone repair of rabbit calvarium	PLA PGA	No adverse host tissue responses
1989	Schakenraad *et al.*[94]	Subcutaneous implants in rats	DL-PLA	Mild foreign body reaction
1990	Schakenraad *et al.*[41]	Drug release in rat soft tissue	L-PLA	L-PLA is tissue compatible
1991	Cooper *et al.*[95]	Rat dermis	PGA PLA	No inflammation
1991	Devereux *et al.*[44]	Abdominal wall of rats	PGA	No intrinsic bacteriocidal or bacteriostatic activity
1991	Galgut *et al.*[36]	Soft tissue of rats	PLA	Sufficient biocompatibility well tolerated
1991	Klompmaker *et al.*[16]	Meniscal repair in dogs	L-PLA	Chronic inflammation
1991	Majola *et al.*[74]	Bone fixation in rat	L-PLA, LD-PLA	No inflammation or foreign body reaction
1991	von Schroeder *et al.*[23]	Articular defects in rabbit	PLA	Well tolerated, minimal inflammatory response
1992	Athanasiou *et al.*[24]	Articular defects in rabbit	PLA PGA	Good long-term compatibility
1992	Böstman *et al.*[31]	Fracture fixation in rabbit	PGA	Variable tissue response
1992	Böstman *et al.*[96]	Fracture fixation of rabbit femur	PGA	No contraindications for clinical application of PGA
1992	Kobayashi *et al.*[97]	Soft tissue/rabbit cornea	PLA PGA	PLA non-toxic and safe PGA some toxicity
1992	Matsusue *et al.*[15]	Bone repair of rabbit femur	L-PLA	No inflammatory or foreign body reaction
1992	Rozema *et al.*[37]	Soft tissue/rats	L-PLA	Some cellular reaction
1993	Athanasiou *et al.*[25]	Articular defects in rabbits	PLA PGA	No infection or inflammatory cells
1993	Lam *et al.*[38]	Soft tissue/mice	L-PLA	L-PLA particles cause cell damage and lesion
1993	Päivärinta *et al.*[32]	Fracture fixation of rabbit femur	PLA PGA L-PLA	Insignificant inflammatory response
1993	Robert *et al.*[98]	Soft tissue/rat abdomen	PLA	Excellent biocompatibility of PLA, larger reaction of PGA
1993	Suganuma and Alexander[17]	Bone repair of dog femur	L-LA	L-PLA particles induce foreign body reaction
1993	Verheyen *et al.*[18]	Bone repair of goat femur	L-PLA	L-PLA debris found in lymph nodes
Human applications				
1974	Horton *et al.*[46]	Suture in subcutaneous skin	PGA PLA (Vicryl)	Vicryl tissue reaction not appreciable
1978	Racey *et al.*[49]	Suture for oral tissue	PGA PLA (Vicryl)	Vicryl response similar to silk

Table 2—*contd.*

Year	Reference	Application	Material	Results
1990	Santavirta *et al.*[26]	Cytological aspiration from fracture repair wound ankle (malleolar) fracture	PGA	Immunologically inert biomaterial
1991	Böstman[28]	Ankle (malleolar) fracture fixation	PGA	Foreign body osteolytic reaction
1991	Devereux *et al.*[45]	Intestinal sling	PGA	Well tolerated
1991	Hope *et al.*[27]	Paediatric elbow fracture fixation	PGA	No infection or foreign body reaction
1991	Wetter *et al.*[99]	Suture for appendix wound	PGA	PGA less infection than nylon
1992	Böstman[29]	Fixation devices for ankle fractures	PGA	Non-bacterial inflammatory reaction seen
1992	Böstman *et al.*[30]	Fixation screws for ankle (malleolar) fractures	PGA	Local non-bacterial reactions observed
1992	Fraser and Cole[100]	Paediatric elbow (humeral) fracture fixation	PGA	Osteolysis present, no foreign body reaction
1993	Böstman *et al.*[33]	Paediatric elbow (humeral) fracture fixation	PGA	No adverse clinical effects
1994	Bucholz *et al.*[34]	Ankle fracture fixation	PLA	Found safe and effective, no complications
In vitro/*cellular response testing*				
1976	Schwope *et al.*[42]	*In vitro* toxicity	PLA PGA	No foreign body reaction
1987	Leenslag *et al.*[93]	*In vitro* degradation	L-PLA	Well tolerated, increased cellular activity
1990	van Sliedregt *et al.*[10]	Fibroblast, osteosarcoma and epithelial cell response	PLA	No reduction in cell proliferation
1992	Daniels *et al.*[70]	*In vitro* toxicity	PLA PGA	Can produce toxic solutions
1992	Matsusue *et al.*[15]	*In vitro* degradation	L-PLA	No inflammatory or foreign body reaction
1992	van Sliedregt *et al.*[11]	Osteosarcoma and epithelial cell response	PLA	Satisfactory biocompatibility
1993	Mikos *et al.*[76]	Rat hepatocyte response	PGA	Hepatocytes attach to PGA mesh
1994	Taylor *et al.*[13]	*In vitro* degradation	PLA PGA	Toxic solutions are produced

L-PLA particles were injected intraperitoneally in mice[38]. In other studies where L-PLA was used for drug delivery, good tissue compatibility was reported[39–41]. Using carriers made of lactide and glycolide polymers either implanted subcutaneously in mice or examined *in vitro*, the absence of foreign body reaction to the implants was noted along with an excellent correlation between *in vitro* and *in vivo* results[42]. In a study examining various PLA–PGA materials, it was determined that as the material degrades the small particles that break off are phagocytosed by macrophages and multinucleated giant cells[43]. It was also suggested that no adverse biological responses occur, especially if the material volume is relatively small[43]. PGA, implanted in the peritoneal cavity of rats, was observed not to have bacteriocidal or bacteriostatic activity and to stimulate inflammatory response[44]. In a subsequent study, a PGA mesh, used in an intestinal procedure, was found to be well tolerated and did not cause infections[45].

CLINICAL APPLICATIONS

In the 1960s and 1970s, research on absorbable suture materials such as Dexon® (100% PGA) and Vicryl® (90% PGA–10% PLA) indicated good tissue compatibility and opened the door to the use of biodegradable polymer implants for other clinical applications[46–54]. These clinical applications of PLA and PGA have been predominantly for fracture fixation in both lower and upper extremities. In lower extremities, PLA–PGA biomaterials are most commonly used in malleolar fractures of the ankle. In 1985, repair of displaced malleolar fractures in 56 patients with ASIF screws and plates was compared with rods made of PLA–PGA[55,56]. No major differences were observed during a 1 year follow-up, indicating that PLA–PGA devices show promising results and are a clinically acceptable alternative to metal fixation devices.

Even though PGA devices for fracture fixation show a high rate of union with no apparent adverse effect on fracture healing, several studies have reported complications using PGA rods and screws for internal fixation of ankle fractures[57–60]. The complications described in these studies included minor displacements of fracture (0–15%), inflammatory sinus (6–8%) and fixation failure (5%). Even though Böstman found discharging inflammatory foreign body reaction adjacent to PGA fixation devices in 25% of the cases of malleolar fractures, normal bone structure was restored after 1 year[28]. Complications occurring with PGA pins prompted a medical centre to cease using them[61]. A clinical reaction occurred in 10.2% of the patients and appeared to be related to patient age, i.e. the younger age group had little risk of complication,

whereas reactions appeared in patients who were over 40 years old[61].

For the upper extremities, PGA implants have been used for intra-articular fractures surrounding the elbow joint. In 1988, a 29 patient study using PGA rods for intra-articular fixation of elbow joints reported fixture failure (3%), slight fracture redisplacement (14%) and late non-infectious inflammatory reaction (14%)[62]. Similarly, PGA pins used for displaced fractures of the distal part of the radius resulted in an inflammatory reaction 47–145 days after insertion in 23% of the patients, requiring debridement of the inflamed tissue[63]. Comparing biodegradable PGA rods with Kirschner wires for fixation of wrist fracture, it was reported that better functional results were achieved with Kirschner wires and, as a result, fixation of distal radial fractures using PGA rods was not recommended[64].

The studies reviewed above were all performed on adults; however, physeal fractures across the growth plate in children have also been repaired using PGA pins[65]. An initial study (six patients) and a subsequent follow-up study (19 patients) showed promising preliminary results leading to further application of these devices. A comparison of PGA pins with standard Kirschner wires to fix displaced elbow fractures in children indicated that the PGA pins provided good fixation and did not require hardware removal, as was the case with the Kirschner wires[27]. Self-reinforced PGA pins have also been used for internal fixation of displaced physeal or non-physeal fractures in 71 children[33]. Severe redisplacement was found in 4% of the patients; however, preliminary results were satisfactory and the absence of the need for hardware removal eliminated the psychological stress associated with a second surgical procedure.

Relatively few reports on the clinical use of PLA have been published, mainly in applications of craniofacial fractures and ankle fixation. Unstable zygomatic fractures repaired with L-PLA and PLA plates and screws were found to be effectively stabilized[66,67]. However, another study using resorbable L-PLA for the fixation of zygomatic fractures documented 60% of the patients had intermittent swelling at the implantation site[68]. The explanted material showed remnants of degraded L-PLA surrounded by a dense fibrous capsule which indicated a non-specific foreign body reaction. Recently, a study compared fixation of ankle fractures with PLA screws and stainless steel screws in 155 patients[34]. After 37 months the radiographic and functional results were similar in the two groups, although patients observed less tenderness in fractures fixated with the PLA. This study confirmed that PLA is a safe and effective alternative to stainless steel for zygomatic fracture fixation. It was further concluded that PLA does not provide the same degree of interfragmental compression as metal, but it avoids hardware prominence and removal[34].

In summary, although PLA–PGA biomaterials are generally biocompatible and non-toxic, several studies have reported inflammatory reactions with the polylactide or polyglycolide implants, usually occurring 7–20 weeks after placement in the body. Bacterial cultures to determine the source of the reaction have been negative, and the problem usually subsides within weeks. It has been suggested that the frequency of occurrences may depend on the anatomical region, since more complications (25%) are observed in the distal radius and scaphoid than in the ankle (5–8%)[69]. The reported complications may be attributed to degradation products draining from the implantation site once polymer hydrolysis has commenced. Furthermore, response may be age related[61], determined by local tissue tolerance, the capacity of bone to clear the degradation products[69], or the volume of polymer implanted[34].

CURRENT AND FUTURE APPLICATIONS

In recent years, the experimental and clinical uses of PLA–PGA polymers in the field of orthopaedics have seen tremendous growth, especially as fracture fixation devices and scaffolds for tissue ingrowth. The biodegradable and biocompatible nature of these polymers as well as their suitable mechanical properties have made them potential candidates for a variety of orthopaedic applications such as bone fixation, repair of osteochondral defects, ligament and tendon reconstructions, and bone substitutes.

The concept of biodegradable fracture fixation devices is particularly attractive because such constructs can reduce problems arising from stress shielding of bone. Daniels *et al.*[70] have presented an extensive review of these devices. Because the mechanical properties of long bones usually exceed those of PLA–PGA materials, it is often necessary to reinforce these polymers with fibres which have higher stiffness and strength, such as carbon fibres or fibres of the copolymer itself[71]. The use of self-reinforced PLA–PGA and PGA rods has also been reported in other studies[3,59,72,73]. Sometimes, the self-reinforced devices are fabricated by sintering together sutures of PLA–PGA materials. For instance, Törmälä *et al.*[74] fabricated self-reinforced PGA rods by sintering together bundles of PGA sutures (Dexon®) at temperatures of 205–232°C under high pressure. As described elsewhere in this paper, PGA and PLA–PGA copolymer rods have been used adequately for the repair of malleolar fractures[56–58]. However, in a significant number of cases an aseptic sinus formation or an inflammatory response was detected at the site of implantation[29,60,69]. The majority of these complications were transient in nature and resolved with time or with minimal intervention. It is conceivable that adverse responses may be better controlled in the future through better quality control of the stock material to reduce impurities and free monomers. Better manipulation of the implant's structural and other physical characteristics through novel manufacturing methodologies may also aid in reducing clinical problems.

The repair of articular cartilage is perhaps one of the most challenging problems in orthopaedics. Self-reinforced PGA rods were used to assist in the repair of cartilage in rabbit perichondrium but the results were unsatisfactory due to a foreign body reaction[72]. In 1991, von Schroeder *et al.*[23] reported the use of a PLA

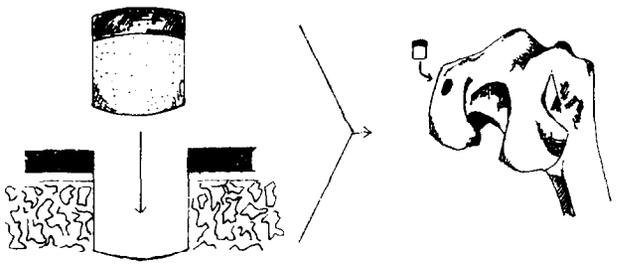

Figure 2 Artist's rendition of osteochondral implant and its placement in the femoral condyle. The two-phase PLA–PGA implant abuts against articular cartilage and bone and can be used either as scaffold or as a carrier of bioactive agents and/or cells.

matrix with and without periosteal grafts in the rabbit knee. Athanasiou *et al.*[24,25] have used implants fabricated from a 50:50 copolymer of PLA–PGA to deliver growth factors to sites of osteochondral defects in rabbit knees in an attempt to regenerate cartilage and the underlying bone (*Figure 2*). They have reported satisfactory results. These devices function not only as controlled release systems for the delivery of proteins over a period of time but also as scaffolds for the growth of neo-tissue. An *in vitro* study of this implant has shown that the protein is released in a sigmoidal fashion over a period of 10 weeks and the implant is fully degraded by this time[75]. PLA–PGA polymers have also been used to fabricate scaffolds on which cells can be cultured *in vitro* prior to implantation to regenerate tissue. Mikos *et al.*[12,76] have developed three-dimensional foams and fibre scaffolds for the purpose of creating polymer–cell grafts. Freed *et al.*[77] used similar scaffolds to develop polymer–chondrocyte grafts for the regeneration of cartilage. *In vitro*, the cell growth rate on the scaffold was twice as high on PGA compared to L-PLA. These grafts were implanted subcutaneously in rats for up to 6 months. At the end of this period, the extracellular matrix maintained the shape of the original scaffolds and histologically resembled cartilage.

The use of osteogenic proteins to induce new bone growth has received considerable attention. Hollinger and Schmitz[78] combined allogenic demineralized freeze-dried bone with a copolymer of PLA–PGA and implanted it in 15 mm calvarial defects in rabbits for periods up to 24 weeks. The control animals did not receive any implants. The results indicated that defects, which were repaired with the implant, displayed a significantly greater volume of trabecular bone in the absence of any adverse tissue responses. The same research team also investigated the use of a PLA–PGA implant for delivering an acidic phospholipid to discontinuities in canine mandibles[79]. To regenerate and guide cranial bone, Levy *et al.*[22] placed PLA films above and below cranial defects to prevent prolapse of soft tissue into the defects, which resulted in significantly more bone formation in the PLA-treated defects than in untreated defects. Heckman *et al.*[80] used a PLA implant with bone morphogenetic protein (BMP) to treat non-unions in canines with satisfactory results. Agrawal *et al.*[81,82] have developed a microporous implant with BMP for the same purpose. The efficacy of incorporating an osteoconductive protein in a copolymer of PLA–PGA and using it as a bone graft to treat large cranial defects in a rabbit model has also been investigated[83]. The treated groups exhibited a significantly greater amount of bone ingrowth. More recently, Kenley *et al.*[84] have reported on achieving osseous regeneration in calvarial defects in rats with the help of an implant comprising recombinant human BMP, microparticles of a PLA–PGA copolymer and a variety of biopolymers including autologous blood clot and hydroxypropyl methylcellulose. At 21 days, all defects treated with BMP exhibited radio-opacity and the copolymer was significantly absorbed. Using a very similar construct, Lee *et al.*[85] treated large segmental defects in rat tibia and reported that such devices effectively aided in defect healing.

Based on these studies, it is envisioned that PLA–PGA biomaterials can be used in the future in clinical practice as neo-tissue scaffolds, delivery vehicles for growth factors, carriers of cells and extracellular matrix, or as means to deliver both growth factors and cells to aid repair processes of musculoskeletal tissues, such as osteochondral defects in diarthrodial joints. Such implants can also contain other purely synthetic, inorganic materials, which may prove to be both inductive and conductive for tissue regeneration. For example, such additives may assist in developing appropriate pathways for the migration of mesenchymal stem cells, which may differentiate according to their environments into articular chondrocytes or osteoblasts, which, in turn, may assist in biological resurfacing of the osteochondral defect. Along the same lines, it is conceivable that such techniques may be applied in tendons and ligaments (both mid-substance and avulsion tears) as well, although the delivery vehicles may have to be redesigned to account for the mainly tensile environment of such tissues.

In conclusion, the future of PLA–PGA polymers in the field of orthopaedics appears to be promising. The use of biodegradable materials will grow as new technologies are developed to supplement traditional treatments. There is increasing research addressing the use of bioactive agents to regenerate tissue and solve previously untreatable problems of the musculoskeletal system. In conjunction with these developments, the use of PLA–PGA polymers as delivery vehicles for these agents is also likely to increase. Because of their thermoplastic nature and their solubility in several organic solvents, these polymers can be readily processed into a variety of shapes and forms. In addition, they have been extensively studied since the 1960s and their properties and behaviour are fairly well understood. These factors, coupled with the biodegradable nature of these materials, render them attractive for formulating delivery vehicles, grafts and scaffolds for neo-tissue growth. As biological cascades of tissue regeneration are further elucidated with future research, the properties of the present generation of PLA–PGA implants can be modulated to better suit the new requirements. PLA–PGA polymers are also likely to find increased applications in the form of fibres and composites to aid in the normal healing of tendons, ligaments and bone. In the future, however,

techniques will have to be developed to reduce the amount of extraneous materials in the polymers and to control the pH of the *in vivo* environment surrounding the degrading implants. These factors may play a crucial role in the response and healing of muscoskeletal tissue and the future application of PLA–PGA materials.

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